Priority Medicines for Europe and the World 2013 Update

Background Paper 6 - Priority diseases and reasons for inclusion

From BP 6.1 to 6.12

BP 6.1 - Antimicrobial resistance
BP 6.2 - Pandemic Influenza
BP 6.3 - Ischaemic heart disease
BP 6.4 - Diabetes
BP 6.5 - Cancer and cancer therapeutics
BP 6.6 - Ischaemic and haemorrhagic stroke
BP 6.7 - Human immunodeficiency virus (HIV)/Acquired immune deficiency syndromes (AIDS)
BP 6.8 - Tuberculosis
BP 6.9 - Neglected tropical diseases
BP 6.10 - Malaria
BP 6.11 - Alzheimer disease and other dementias
BP 6.12 - Osteoarthritis

BP 6.13 to 6.24
BP 6.13 - Chronic obstructive pulmonary disease (COPD)
BP 6.14 - Harmful use of Alcohol, Alcohol use disorders: alcoholic liver diseases
BP 6.15 - Depression
BP 6.16 - Postpartum haemorrhage
BP 6.17 - Tobacco use cessation therapies
BP 6.18 - Obesity
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Background Paper 6.1
Antimicrobial resistance

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## Acronyms

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<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMR</td>
<td>Antimicrobial resistance</td>
</tr>
<tr>
<td>CGD</td>
<td>Centre for Global Development</td>
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<tr>
<td>CDC</td>
<td>US Centers for Disease Control and Prevention</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>EARS-NET-Net</td>
<td>European Antimicrobial Resistance Surveillance System Network</td>
</tr>
<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>EARS-NET</td>
<td>European Centre for Disease Prevention and Control</td>
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<tr>
<td>EEA</td>
<td>European economic area</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>ESBL</td>
<td>Extended-spectrum beta-lactamase</td>
</tr>
<tr>
<td>ESPID</td>
<td>European Society for Paediatric Infectious Diseases</td>
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<tr>
<td>EPRUMA</td>
<td>European Platform for the Responsible Use of Medicines in Animals</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<td>FDA</td>
<td>US Food and Drug Agency</td>
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<tr>
<td>GAIN</td>
<td>Generating antibiotic incentives now</td>
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<tr>
<td>GBS</td>
<td>Group B streptococcal septicemia</td>
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<td>HAI</td>
<td>Hospital acquired infection</td>
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<tr>
<td>IDSA</td>
<td>Infectious Diseases Society of America</td>
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<td>IMI</td>
<td>Innovative Medicines Initiative</td>
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<tr>
<td>LOS</td>
<td>Length of stay</td>
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<tr>
<td>MDR TB</td>
<td>Multidrug – resistant tuberculosis</td>
</tr>
<tr>
<td>MRSA</td>
<td>Meticillin – resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>NDM – 1</td>
<td>New Delhi metallo-lactamase 1</td>
</tr>
<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
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<tr>
<td>OSDD</td>
<td>Open source drug discovery</td>
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<tr>
<td>PDCO</td>
<td>Paediatric Committee</td>
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<td>PDUFA</td>
<td>Prescription Drug User Fee Act</td>
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<tr>
<td>PPP</td>
<td>Public private partnerships</td>
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<tr>
<td>R &amp; D</td>
<td>Research and development</td>
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<tr>
<td>ReAct</td>
<td>Action on Antibiotic Resistance</td>
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<td>TATFAR</td>
<td>Transatlantic Taskforce on Antimicrobial Resistance</td>
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<tr>
<td>USA</td>
<td>United States of America</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1. **Introduction**

The increasing prevalence of antimicrobial resistance (AMR) coupled with the dry antimicrobial development pipeline threatens the success and continuation of clinical medicine as we know it. This threat decreases the ability to successfully treat numerous infectious diseases while simultaneously increasing health risks for vulnerable patients. Medical procedures, such as hip replacements, organ transplants, chemotherapy, hemodialysis and care for preterm infants may become too risky or impossible due to untreatable community-acquired (“nosocomial”) infections. Common infectious diseases may once again result in death.¹

The increased public health threats caused the World Health Organization (WHO) to declare AMR to be one of the three greatest threats to human health as reported for World Health Day 2011.² In 2004, when the *Priority Medicines for Europe and the World* report was published, AMR was given great attention.³ This review together with annexes identifies what has occurred since 2004 to address this continuing challenge.⁴,⁵,⁶,⁷,⁸,⁹

Overall, there have also been a number of success stories since 2004:

- Surveillance programmes have been initiated at local, national and international levels.¹⁰
- Successful programmes have led to better interventions aimed at assessing AMR and ensuring more appropriate antibiotic prescribing. The adoption in November 2011 of the Communication from the Commission to the European Parliament and the Council on an Action Plan on Antimicrobial Resistance has significantly strengthened the combat against AMR. (See Section 5.1)
- There have been major improvements in the development of diagnostic tools. Inexpensive and readily available diagnostic tools are now available for a variety of infectious diseases. Some of these tools are able to distinguish between viral and bacterial infections, while others are able to distinguish between bacterial species (see Annex 6.1.7).
- Since 2004, various national and international organizations have responded to the issue of AMR through numerous meetings, task forces, workshops, and publications (see Annex 6.1.1). Several major publications addressing AMR and its public health threat are in print.
- One success in efforts to slow the development of AMR in Europe is the overall decline in the prevalence of meticillin-resistant *Staphylococcus aureus* (MRSA) in this region since 2005 (see Figure 6.1.4).

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¹ The term “antimicrobial” is intended to encompass microorganisms generally, which includes bacteria, viruses and protozoans and typically are unicellular. As most resistance issues deal with bacteria, we shall use “antimicrobial” and “antibacterial” interchangeably in this background paper but the reader should be aware of the distinctions. If we specifically mean one or the other, we shall note this.
2. Why does the problem persist?

Table 6.1.1 has been developed from the CGD report *The Race Against Drug Resistance.* This table aims to summarize the complex interactions related to antimicrobial resistance. Explanations concerning the persistence of AMR include biological, societal, industrial and legislative factors. Each perspective, by itself, is not solely responsible for the persistence of AMR. In order to accurately address this concern, these different perspectives must be appropriately addressed in a holistic manner in order to effectively contain and address the persistence of resistance.

Table 6.1.1: Explaining antimicrobial resistance from different perspectives

<table>
<thead>
<tr>
<th>Biological Explanation (contributing factors)</th>
</tr>
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<tbody>
<tr>
<td>• <strong>Selective pressure:</strong> Bacteria that are not killed by an antimicrobial continue to survive thereby becoming the prevailing type. This results in an imbalance of the ideal microflora at a community and individual level.</td>
</tr>
<tr>
<td>• <strong>Evolution:</strong> To ensure survival in the presence of antibiotics, bacteria develop genetic and biochemical mechanisms such as alterations within the existing genome and gene transfer within and between species.</td>
</tr>
<tr>
<td>• <strong>Transmission:</strong> The transmission of gene sequences encoding for resistance is highly efficacious due to the small number of successful clonal lineages that share genetics related in pathogenicity and antimicrobial resistance.</td>
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<table>
<thead>
<tr>
<th>Societal Explanation (contributing factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Overuse:</strong> Capacious antibiotic use includes use based on the incorrect medical indications, administration route, dose and/or treatment duration. This then creates a selective pressure favoring resistant bacteria.</td>
</tr>
<tr>
<td>• <strong>Transmission:</strong> Factors such as poor hygiene, densely populated settings, international trade, travelling, ecosystem disturbances and the increase of the ageing and immunocompromised populations further promote the propagation of resistant microbes.</td>
</tr>
<tr>
<td>• <strong>Underuse:</strong> An inadequate or adulterated supply of the appropriate antimicrobials to treat an individual perpetuates AMR by creating a selective pressure to favor resistant bacteria.</td>
</tr>
<tr>
<td>• <strong>Hospitals:</strong> Antibiotics are often less expensive than AMR prevention strategies. This often results in many hospitals preferring to provide treatment rather than implement prevention mechanisms.</td>
</tr>
<tr>
<td>• <strong>Behaviors:</strong> Patients may demand antibiotics from their providers thereby resulting in inappropriate antibiotic use. Additionally, providers may feel pressured to engage in inappropriate antibiotic use thereby further discouraging prudent antibiotic use.</td>
</tr>
<tr>
<td>• <strong>Economic:</strong> Many healthcare systems are weak and underfunded. Coupled with the rising costs of healthcare services, pressure on providers to seek economical alternatives is created. Since antibiotics are often inexpensive, providers may feel pressured to distribute them as a hasty alternative. Weak surveillance is also an issue since many surveillance systems cannot be fully and appropriately developed due to lack of funds.</td>
</tr>
</tbody>
</table>
| • **Agriculture:** More than half of all of the antibiotics consumed within the USA are utilized for agriculture. This overuse creates a selective pressure that favors bacteria that are resistant to antimicrobials. The capacious overuse affects the surrounding livestock, surrounding water and soil and public health. The contribution by this animal “reservoir” is not insignificant although nosocomial (i.e. hospital-derived) infections and human-to-
human transfer of bacteria occurs constantly and routinely (sharing meals, aerosolized dissemination of bacteria, and intimate physical contact).

**Industrial Explanation**

- **Diagnostic tools:** Providers may not have the appropriate tools to properly distinguish between a viral and bacterial infection that would benefit from treatment and this may result in a misdiagnosis and inappropriate antimicrobial use. The development of diagnostic tools to distinguish between viral and bacterial infections is critical to appropriately treat the patient while reducing the misuse of antibiotics. Access to existing tools is also required as it is lacking in many low- and middle-income countries.

- **Pharmaceutical industries:** The R & D for antibiotics often lacks the financial incentives that many pharmaceutical companies seek. This results in a lack of innovative antimicrobial therapies against AMR. Further, antimicrobial residues from pharmaceutical industries and hospitals are contaminating water supplies in many parts of the world.

- **Pipeline:** Between 1930 and 1962, more than 20 new classes of antibiotics were developed. Between then and 2011, only two new classes of antibiotics have been marketed for human use. A dearth of new antibiotics results in inability to treat emerging resistance to existing antibiotics, but resistance is an inevitable process.

**Legislative Explanation**

- **Registration:** There have been several antibiotic registration difficulties. These difficulties may present additional costs, time and other resources that may discourage the company to continue the process. These registration difficulties may discourage other companies from entering the antibiotic development pipeline.

- **Requirements:** The FDA has implemented stricter requirements, such as decreased non-inferiority margins. This results in increased costs and clinical trial time which further discourage the development of antibiotics.

- **Legislation against over the counter (OTC) sale is absent or not enforced in many countries.**

Source: Nugent R, Back E, Beith A. The race against drug resistance: Center for Global Development; 2010

Note: * Legislative action or inaction does not per se cause AMR. To the extent legislative barriers discourage innovation of antimicrobials, AMR may be exacerbated.

### 2.1 New variants of resistance have continued to emerge

An important change in resistance prevalence rates has occurred with the shift from Gram-positive to multi-resistant Gram-negative bacteria, for which treatment options are limited or entirely lacking. Particular attention has been drawn to a gene that codes for New Delhi metallo-lactamase 1 (NDM-1) which makes Gram-negative enterobacteria resistant to last line antibiotics, such as carbapenems.\(^\text{12}\) (See Section 3.2.2.) Indeed, this illustrates the AMR problem as there has been a general increase in carbapenemase-producing enterobacteria in Europe and globally as a consequence largely of acquisition of carbapenemase genes.

Other emerging problems during the last decade include multi-or extensively resistant tuberculosis, Neisseria (i.e. gonorrhoea-causing bacteria) resistant to the latest cephalosporins and *Clostridium difficile* causing severe colitis resistant to moxifloxacin. Advancements have, however, been made in understanding the complexities of the reversibility of resistance.\(^\text{13}\)
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Research has revealed that there is a low possibility, if at all, of reversing AMR once it has been established in both community and non-community settings.\(^{14,15}\)

### 2.2 Transmission of antibiotic-resistant bacteria

The exploding emergence of multi-resistance, particularly among Gram-negative bacteria, has drawn attention to the increasing importance of transmission of genetic elements coding for multi-resistance, and also for the potential of zoonotic (animal-based) transmission. New information about the transmissibility of AMR pathogens is exemplified by the "resistome".\(^{16}\)

The resistome is a collection of genes originally found in soil bacteria. It is thought to be responsible for the development of various resistance mechanisms that permit soil bacteria to survive in the presence of antibiotics that are found naturally within the environment.\(^{17}\) It is believed that the genes of the resistome may have the potential to be transferred to non-soil bacteria thereby exacerbating the issues of resistance. Although debatable, research suggests that some resistant bacteria have been more successful in perpetuating extensively and surviving because of the resistome.\(^{18}\)

Misuse of antimicrobials outside of human medicine is a further exacerbating factor in AMR, particularly the emergence of AMR in animals and humans.\(^{19,20,21,22,23}\) Use of antimicrobials in agriculture can create an important source of antimicrobial resistant bacteria that can spread to humans through the food supply when the animals are eaten. This includes non-therapeutic use such as for growth promotion. It also includes use as prophylaxis to try to prevent infections developing in food animals and use as a therapeutic agent to treat sick animals. See previous section.

Agriculture serves as a reservoir of transmission of AMR pathogens both to and from humans.\(^{24,25,26,27}\) Yet it continues remains difficult to correlate antibiotic resistance of foodborne pathogens, antibiotic uses on farms and clinical isolation of a resistant pathogen in humans. That is, the ecosystem interactions amongst humans and agriculture are dynamic so that increased incidence of illness in any given year may or may not parallel increased use of antibiotics potentially selecting for resistant bacteria.

In 1976, it was proven that one could track resistant \(E. \) coli from chickens in an experimental farm plot to the human farmers in close proximity.\(^{28}\) Recently, it has been possible to trace the connections between two farmers in Denmark, each of whom suffered a MRSA infection, and animals on their farms, which lie 28 miles apart.\(^{29}\) More specifically, one farmer who kept two horses and two cows, was diagnosed with a MRSA blood infection. The other had a flock of 10 sheep and the farmer had a wound that had become infected with MRSA. When their cases came to light they were recognized as a new MRSA strain that has been reported in cattle and so Danish researchers went out to check the animals on both farms. One cow on one farm, and three sheep on the other farm were carrying the new strain.

All bacterial samples from both farms and both humans were identical on several different assays and had the same resistance pattern, i.e., susceptible to antibiotics that were not beta-lactams (penicillins and cephalosporins). A whole-genome sequencing was then done (something impossible in 1976) and compared to see how closely all samples really were. The isolates from the farmer and the cow samples were all functionally identical (5 SNPs), and so were the isolates from the other farmer and the majority of the sheep. Across all samples there was a difference of 154 SNPs (single nucleotide polymorphisms — single-letter
“copying errors” in the genetic code). Based on their relatedness, the samples made clusters that corresponded to the two farms: the first farmer and a cow, and the second farmer and the sheep. Thus, phylogenetic analysis revealed two distinct farm-specific clusters comprising isolates from the human case and their own livestock, whereas human and animal isolates from the same farm only differed by a small number of SNPs, which supports the likelihood of zoonotic transmission.

Further analyses identified a number of genes and mutations that may be associated with host interaction and virulence and that these specific mecC-MRSA CC130 isolates are rarely found in humans. The inference is that they were transmitted between animals and humans. However, the challenges of this kind of proof remain. This was not observed experimentally and the sample size was small. It is possible that whatever genetic diversity of the isolates that did exist on a given farm could represent a second introduction of MRSA into the flock, not one introduction followed by dissemination. If that happened, then a human-to-animal transmission might be as likely as a zoonotic one.

The “host range” of species carrying mecC CC130 MRSA is worryingly large and includes not just cows and sheep, but horses, rabbits, cats, dogs, deer, seals, rats and wild birds. Research clearly has supported the hypothesis that modern society has enhanced the opportunity for resistant pathogens to perpetuate and thrive throughout the animal and human ecosystem.\textsuperscript{30,31} The implication of this observation is that as trade increases, the AMR threat will also increase and thus the need to develop new antimicrobial products.

\section*{2.3 Antibiotic misuse continues to be a challenge}

Antibiotic misuse continues to exacerbate AMR issues. Decrease of unwarranted high prescription rates has been proven to be achievable with national activities in several European countries. The prevalence of resistance is still strongly related to consumption of antimicrobials.\textsuperscript{32,33} See Annex 6.1.3. Patterns of antibiotic consumption throughout different regions of the world have changed over time. See Annex 6.1.4.

Furthermore, there are serious cultural and behavioral challenges. For instance, most antibiotics are prescribed by physicians with varying levels of interest and sophistication in thinking about how to use molecular and microbiological data to inform therapeutic choices.\textsuperscript{34} Strategies designed to modify physician antimicrobial-prescribing practices must therefore choose simplicity over complexity and must acknowledge their fundamental ignorance of many of the specifics of antibiotic-microorganism interactions. They must also acknowledge the critical nature of bacterial illnesses in hospitalized patients and the importance of delivering effective antimicrobial therapy early in the illness.\textsuperscript{35}

In short, major challenges still remain with respect to promoting rational use of antimicrobials and measuring and monitoring use.

Unfortunately, this use of antimicrobial agents includes agents defined by the WHO as being “critically important” for human medicine. The World Health Organization (WHO) has developed and applied criteria to rank antimicrobials according to their relative importance in human medicine. Clinicians, regulatory agencies, policy-makers and other stakeholders can use this ranking when developing risk management strategies for the use of antimicrobials in food production animals. The list has subsequently been re-examined and
updated during WHO-AGISAR expert meetings held in Copenhagen in 2009 (second revision) and in Oslo, Norway in 2011 (third revision). The highest priority critically important antimicrobials were identified in this WHO document based on these three criteria:

1. High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few alternatives to treat serious human disease.
2. High frequency of use of the antimicrobial for any indication in human medicine, since usage may favour selection of resistance.
3. Greater degree of confidence that there are non-human sources that result in transmission of resistant bacteria (Campylobacter spp.), or their resistance genes, to humans (high for Salmonella spp., Escherichia coli and Enterococcus spp.).

These “highest priority” antimicrobials are listed below:

**Fluoroquinolones**: These are known to select for fluoroquinolone-resistant Salmonella spp. and E.coli in animals. At the same time, fluoroquinolones are one of few available therapies for serious Salmonella spp. and E.coli infections in humans.

**3rd and 4th generation cephalosporins** are known to select for cephalosporin-resistant Salmonella spp. and E. coli in animals. At the same time, 3rd and 4th generation cephalosporins are one of few available therapies for serious Salmonella and E. coli infections, particularly in children.

**Macrolides** are known to select for macrolide-resistant Campylobacter spp. in animals, especially Campylobacter jejuni in poultry. At the same time, macrolides are one of few available therapies for serious campylobacter infections, particularly in children, in whom quinolones are not recommended for treatment.

**Glycopeptides** are known to select for glycopeptides-resistant Enterococcus spp. in food animals (e.g., when avoparcin was used as a growth promoter, vancomycin resistant enterococcus (VRE) developed in food animals and were transmitted to people). At the same time, glycopeptides are one of the few available therapies for serious enterococcal infections.

### 3. Epidemiological trends

#### 3.1 Increasing levels of Gram-negative resistant bacteria in Europe

Surveillance programmes have been initiated on local, national and international levels. These programmes have demonstrated that the prevalence of AMR is increasing throughout the world resulting in the EARS-net placing AMR as one of the primary work areas. Successful programmes have led to better interventions aimed at assessing AMR and maximize antibiotic prescribing. Continuous and uniform surveillance is still needed to appropriately address the issue of resistance.

However, an important issue is the increasing resistance to antibiotics in Gram-negative bacteria. Gram-negative bacteria cause infections including pneumonia, bloodstream infections, wound or surgical site infections, and meningitis in healthcare settings. The distinctive feature of Gram-negative bacteria is the presence of a double membrane surrounding each bacterial cell. Although all bacteria have an inner cell membrane, Gram-
negative bacteria have a unique outer membrane. This outer membrane excludes certain drugs and antibiotics from penetrating the cell, partially accounting for why Gram-negative bacteria are generally more resistant to antibiotics than are Gram-positive bacteria. Gram-negative bacteria have a great facility for exchanging genetic material (DNA) among strains of the same species and even among different species. Resistance is increasing in Europe for Gram-negative bacteria such as *Escherichia coli* or *Klebsiella pneumonia* collected from normally sterile sites, i.e. blood or cerebrospinal fluid. Also, there have been no novel mechanism agents for Gram-negative organisms for decades.

### 3.1.1 *Escherichia coli*

Predictions of a worrisome increasing trend of resistance to this Gram-negative and extremely common microbe have been confirmed in Europe. Increased prevalence trends over time reveal decreased fluoroquinolone susceptibility (i.e. increasing resistance) as shown in Figure 6.1.1. *E. coli* formerly susceptible to carbapenem and third generation cephalosporins strains exhibit similar trends. (See Annex 6.1.9).

**Figure 6.1.1: Percentage of invasive isolates of *E. coli* that are resistant to fluoroquinolones in participating countries, 2005 (upper) and 2011 (lower)**

Source: EARS-NET – interactive database. 2
3.1.2 Multidrug-resistant *Klebsiella pneumoniae*

Predictions of a worrisome increasing trend of resistance to these Gram-negative bacteria have been confirmed in Europe. Increased prevalence trends over time reveal decreased multiple drug resistance increasing as shown in Figure 6.1.2.

Figure 6.1.2: *Klebsiella pneumoniae* isolates in participating countries in 2005 (left figure) and 2011 (right figure) that are resistant to third-generation cephalosporins, fluoroquinolones and aminoglycosides.

Source: EARS-NET – Net database.

3.1.3 Carbapenem resistance in *Pseudomonas aeruginosa*

*Pseudomonas aeruginosa* carries multiresistance plasmids less often than does *Klebsiella pneumoniae*, develops mutational resistance to cephalosporins less readily than *Enterobacter* species. What nevertheless makes *P. aeruginosa* uniquely problematic is a combination of the following: the species' inherent resistance to many drug classes; its ability to acquire resistance, via mutations, to all relevant treatments; its high and increasing rates of resistance locally; and its frequent role in serious infections. A few isolates of *P. aeruginosa* are resistant to all reliable antibiotics.45

As seen in Figure 6.1.3, the situation with regard to *P. aeruginosa* is mixed, with many (but not all) countries in Eastern Europe showing a decreasing trend in the fraction of all *P. aeruginosa* isolates that are resistant but an increasing trend in some southern European countries such as Italy and Portugal.
3.1.4 *Staphylococcus aureus*

The issue of increased resistance of the Gram-positive meticillin resistant *Staphylococcus aureus* (MRSA) has been ameliorated somewhat (See Figure 6.1.4: France, Eastern European countries, United Kingdom, Scandinavia). **Thus, there has been an overall decreased prevalence of MRSA within Europe** although some European countries continue to exhibit a continued high prevalence of MRSA. See Figure 4 and Annex 6.1.10. Activities to improve compliance to infection control practices have probably decreased transmission in healthcare settings. Instead, community acquired MRSA is now reported to be the dominating problem.

A particular problem has been the emergence of MRSA in livestock. See also above, Section 2.2. In 2005, decades after the discovery of the hospital acquired and community-acquired MRSA, a new MRSA type was isolated from pigs and pig farmers in the Netherlands and was named livestock-associated MRSA or LA-MRSA. Resistance to the antibiotics used in livestock farming such as tetracycline, trimethoprim, aminoglycosides, etc. was found in LA-MRSA isolates. Further, LA-MRSA has been reported worldwide, and is known to colonize humans and livestock animals such as pigs, cattle and chickens.46
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Figure 6.1.4: Proportion of meticillin resistant *Staphylococcus aureus* isolates in participating countries, 2005 and 2010

![Map showing percentage resistance of meticillin resistant *Staphylococcus aureus* isolates in participating countries, 2005 and 2010.]

Source: EARS-NET - Net database.

3.1.5 Emerging carbapenemase-producing bacteria in Europe.

Carbapenems have the broadest antibacterial spectrum compared to penicillins and cephalosporins. In addition, they are generally resistant to the typical bacterial enzyme, β-lactamase, which is one of the principal β-lactam resistance mechanisms of bacteria. Carbapenemases are a group of clinically important enzymes that efficiently inactivate most beta-lactam-type antibiotics such as cephalosporins and penicillins. Resistance to carbapenems (via carbapenamase-production) has emerged and spread among the Enterobacteriaceae family of bacteria worldwide. Resistance is endemic in certain countries. Risk factors include severity of illness, a history of hospitalisation or a stay in an intensive care unit, prior antimicrobial use and immunosuppression. Patient mobility has also recently been highlighted as a risk factor for the acquisition of carbapenamase activity and many reports by Member States discuss the introduction and spread of carbapenemases into healthcare settings as a result of patient transfer, mostly from endemic areas, across borders. EARS-net risk assessment. 2011.

DNA encoding carbapenemases are easily introduced because they are highly transmissible, resulting in colonisation or infection of patients. Thus, dissemination of mobile genetic elements coding for resistance and of epidemic, multidrug-resistant strains has been the cause of many reported outbreaks. Infections with carbapenamase producing bacteria are a threat to patient safety due to their resistance to multiple antimicrobials, meaning that there are very few therapeutic options with which to treat infected patients. Furthermore, human infections are associated with poorer patient outcomes, increased morbidity, mortality and higher hospital costs. The risk for humans becomes greater since therapeutic options are limited because there are very few novel antimicrobial agents in the development pipeline.
3.2 Antibiotic resistance in other regions

3.2.1 The Americas

Resistance within the United States has not changed substantially with the exception of an increased concern about Gram-negative pathogens. Mortality and morbidity rates for MRSA are still high with more than 19,000 deaths and 90,000 infections per year.\(^\text{48,49}\) (Annex 6.1.12). Research has also revealed the USA exhibits seasonal patterns of AMR with antibiotic use as shown in Figure 6.1.5.\(^\text{50}\)

Figure 6.1.5: Mean monthly seasonal variation for trimethoprim / sulfamethoxazole prescriptions and E. coli resistance to trimethoprim / sulfamethoxazole

\[ \text{Source: Sun L, Klein EY, Laxminarayan R. Seasonality and temporal correlation between community antibiotic use and resistance in the United States. Clinical Infectious Diseases: An Official Publication Of The Infectious Diseases Society of America. 2012.}^{50} \]

3.2.2 Asia and the World

High prevalence rates of numerous resistant bacterial pathogens are still commonly reported throughout Asia.\(^\text{12,51}\) In India, rates of antimicrobial resistance are very high. A high prevalence of extended-spectrum β-lactamase (ESBL)–producing bacteria is increasing the prevalence of resistance to carbapenems. More specifically, metallo-beta-lactamase-1 (NDM-1) is an enzyme that makes bacteria resistant to a broad range of beta-lactam antibiotics. NDM-1 was first detected in a Klebsiella pneumoniae isolate from a Swedish patient of Indian origin in 2008. It was later detected in bacteria in India, Pakistan, the United Kingdom, the United States, Canada, and Japan. The most common bacteria that make this enzyme are Gram-negative such as Escherichia coli and Klebsiella pneumoniae, but the gene for NDM-1 can spread from one strain of bacteria to another by horizontal gene transfer. The original organism was found to be resistant to all antimicrobial agents tested except colistin. Molecular examination of the isolate revealed that it contained a novel metallo-beta-
lactamase that readily hydrolyzed penicillins, cephalosporins, and carbapenems (with the exception of aztreonam).\textsuperscript{52}

See also Annex 6.1.13.\textsuperscript{53}

### 4. The disease and economic burdens of antibiotic resistance

Infectious diseases are one of the leading causes of mortality, with an excess of 25,000 additional deaths per year in EU member states alone.\textsuperscript{54} Although surveillance systems have helped, estimating the disease burden of AMR remains a difficult challenge.\textsuperscript{9} This burden greatly increases the duration of hospital length of stay (LOS), complication risks and mortality risks.\textsuperscript{55,56,57}

Recently, using data from the Burden of Resistance and Disease in European Nations project\textsuperscript{58} the European burden of disease associated with meticillin-resistant \textit{S. aureus} and third-generation cephalosporin-resistant \textit{E. coli} blood stream infections was estimated, and expressed as excess number of deaths, excess number of days in hospital, and excess costs.\textsuperscript{55} An estimated 5,503 excess deaths were associated with blood stream infections caused by meticillin-resistant \textit{S. aureus} (with the United Kingdom and France predicted to experience the highest excess mortality), and 2,712 excess deaths with blood stream infections caused by third-generation cephalosporin-resistant \textit{E. coli} (predicted to be the highest in Turkey and the United Kingdom). This study also found that blood stream infections caused by both meticillin-resistant \textit{S. aureus} and third-generation cephalosporin-resistant \textit{E. coli} contributed respective excesses of 255,683 and 120,065 extra bed-days, accounting for an estimated extra cost of 62.0 million euros (92.8 million US dollars).

Excess mortality associated with these infections caused by meticillin-resistant \textit{S. aureus} and third-generation cephalosporin-resistant \textit{E. coli} is high, and the associated prolonged length of stays in hospital imposes a considerable burden on health care systems in Europe. The possible shift in the burden of antibiotic resistance from Gram-positive to Gram-negative infections is of some concern.

Overall, the economic burden associated with AMR is considerable and there is more extensive data than in 2004.\textsuperscript{59} These costs are primarily due to the doubled increase in hospital LOS, additional discharge costs to facilities, extra medical care needed and productivity loss. Societal costs of infections (including productivity losses, extra length of stay, in-patient and out-patient costs) due to various resistant Gram-positive (mostly MRSA and vancomycin-resistant \textit{Enterococcus faecium}) and Gram negative (third-generation cephalosporin-resistant \textit{E. coli} and \textit{K. pneumoniae}, and carbapenem-resistant \textit{P. aeruginosa}) for the EU, Iceland and Norway in 2007 were estimated in excess of €1.5 billion per year.\textsuperscript{9}

A more detailed summary of information is presented within Annex 6.1.14. Table 6.1.2 is a brief summary of the ranges of this burden.
Table 6.1.2: Summary of the economic burden of antimicrobial resistance

<table>
<thead>
<tr>
<th>Country</th>
<th>Additional Costs</th>
<th>Additional Hospital LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>US$ 10 276 – 50 896/patient</td>
<td>4.3 – 16 days/patient</td>
</tr>
<tr>
<td>Spain</td>
<td>€1 205.75 – 5 614/patient</td>
<td>2 – 29 days/patient</td>
</tr>
<tr>
<td>Europe</td>
<td>€1.5 billion total (societal cost)</td>
<td>2.5 million days total</td>
</tr>
<tr>
<td>Israel</td>
<td>US$ 30 093/patient</td>
<td>6 - 10 days/patient</td>
</tr>
</tbody>
</table>

5. What are the current policy initiatives regarding AMR control?

5.1 European Union

Various national and international organizations such as the European Centre for Disease Control and Prevention (EARS-net), the European Medicines Agency (EMA), the European Commission (EC), the Centre for Global Development (CGD), the European Federation of Pharmaceutical Industries and Associations (EFPIA) (Annex 6.1.1).³

Much information on antibiotic use has been collected via international projects. For instance, ESAC-Net (formerly ESAC) is a Europe-wide network of national surveillance systems, providing European reference data on antimicrobial consumption both in the community and in the hospital sector. The collected data are used to provide timely information and feedback to EU countries on indicators of antimicrobial consumption. These indicators provide a basis for monitoring the progress of countries towards prudent use of antimicrobials.⁷³

As another example, from 2009-2011, the European Centre for Disease Prevention and Control (EARS-NET) funded the HALT project (Healthcare Associated infections in Long-Term care facilities). The aim of this project was to develop and implement a protocol for surveillance of antimicrobial use and resistance in European long-term care facilities (i.e., nursing homes and the like) in order to establish baseline rates and identify priorities for improvement. A point prevalence survey was conducted across 25 European countries. An antimicrobial prevalence study will be repeated in mid-2013.⁷⁴

The European Union (EU) has produced major publications addressing AMR and its public health threat include The Race Against Drug Resistance, Extending the Cure, Innovative Incentives for Effective Antibacterials, Recommendations for Future Collaboration between the USA and EU and The Bacteria Challenge: Time to React.⁵⁶⁷⁸⁹ These diverse efforts demonstrate the need for concerted action to address the current and future concerns of AMR.

In brief overview, FP5-7 (1999-2012) has spent about €600 million for projects related to antimicrobial resistance. The priorities included: developing new strategies for prudent/rational antibiotics use in medicine and agriculture; understanding how antimicrobial resistance develops; testing new antimicrobial drugs and alternatives to antibiotics; developing diagnostic tests to determine whether and which antimicrobials to prescribe.
Since 2004, the issue of AMR has been the subject of many initiatives, both educational and scientific. The problem of AMR has been recognized both by the Council and the European Parliament. The Council adopted on 10th June 2008 “Conclusions on AMR” calling upon the EC in accordance with the “health in all policies” approach, to promote cooperation between the EC and Member States against AMR, and on 1 December 2009 the Council adopted conclusions on innovative incentives for effective antibiotics calling upon the Commission to develop a comprehensive action plan concerning incentives to develop new effective antibiotics including ways to secure their rational use.

On 12th May 2011 the European Parliament (EP) adopted a non-legislative resolution on antibiotic resistance in which it stressed that AMR has become a huge issue in recent years. To cope with this growing problem and the consequent treatment failures, the EP called on the Commission to establish an EU-wide plan to combat AMR. The European Parliament subsequently issued a resolution on 27 October 2011 on the public health threat of antimicrobial resistance.

On the same day, the EC presented a recommendation on a Joint Programming Initiative (JPI) entitled ‘The Microbial Challenge - An Emerging Threat to Human Health’. The EC encouraged Member States, amongst other things, to “… develop a common Strategic Research Agenda (SRA) establishing medium to long-term research needs and objectives in the area of antimicrobial resistance. The SRA should be further developed towards an implementation plan, establishing priorities and timelines and specifying the actions, instruments and resources required for its implementation.”

Similarly, in 2011, an “Action plan against the rising threats from Antimicrobial Resistance” was issued from the EC. The EC proposed to put in place a five-year Action Plan to fight against AMR based on 12 key actions. In particular the actions related to research activities promoting public-private collaborative research and development to bring new antibiotics to patients (Action 6) as well as the reinforcing and coordinating research efforts (Action 11) are already well advanced in their implementation. All these actions have strengthened the combat against AMR.

As another example, European Antibiotic Awareness Day is an annual European public health initiative that takes place on 18 November to raise awareness about the threat to public health of antibiotic resistance and prudent antibiotic use.

In addition, the EU has enacted numerous strategies and policies to deal with use outside human medicine. In 2006, the EU banned the feeding of antibiotics to livestock for growth promotion purposes. We note that the US Food and Drug Administration (FDA) is also promoting judicious use with three directives: the Veterinary Feed Directive, Guidance #209 and Guidance #213.

The Innovative Medicines Initiative (IMI) has recently launched research calls for their new theme “NewDrugs4BadBugs” (ND4BB) which aims to bring new antibiotics by funding research in which small and medium-sized enterprises (SMEs) and academics work in close collaboration with large pharmaceutical companies in order to establish a vibrant antimicrobial drug discovery hub.
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

In February 2013, the IMI launched its first two projects under New Drugs for Bad Bugs. The new projects are Combacte (Combating Bacterial Resistance in Europe) and Translocation (Molecular basis of the bacterial cell wall permeability). COMBACTE will last for seven years and will bring together about 20 partners from all over Europe. It is designed to generate innovative trials to facilitate the registration of new anti-bacterial agents, mainly through the creation of a network of experienced investigators. It will also design and validate tests to support the diagnosis of patients, identify the most suitable treatments and monitor the treatment response.\textsuperscript{83}

TRANSLOCATION aims to increase the overall understanding of how to get antibiotics into multi-resistant Gram-negative bacteria such as *Escherichia coli* and *Klebsiella pneumoniae* and how to stop the bacteria from ejecting the drug. In sharing the knowledge and data discovered, TRANSLOCATION will develop guidelines for designing and developing new drugs to tackle antibiotic resistance and create an information centre for pre-existing and ongoing antibacterial research data which will be used to establish best practices for future antibacterial drug discovery efforts.\textsuperscript{84} The EC currently funds numerous projects, under the FP-7 projects programme, to help develop the necessary tools needed to contain AMR (See Research and Innovation Initiatives to support AMR related research in the EU\textsuperscript{85} and Annex 6.1.17. There are numerous national antibiotic stewardship campaigns, although mostly in high-income countries. (Annex 6.1.5). The European Technology Platform on Nanomedicine has also been established to create diagnostic tools to identify a disease at the earliest possible stage to encourage appropriate antibiotic use.\textsuperscript{86} Top Institute (TI) Pharma, a non-profit organization in the Netherlands, has also provided support for projects concerning MRSA and MDR pathogens.\textsuperscript{87}

5.2 World Health Organization

The WHO has been heavily involved with a range of national and global activities concerning AMR and has a long history of engagement in containing AMR. Some of the highlights are listed in Annex 6.1.18.

AMR was chosen as the subject for the World Health Day 2011 under the theme “No action today - no cure tomorrow”.\textsuperscript{88} During this day, a six-point policy package was launched to reaffirm that a multifaceted approach is needed to deal with this complex issue. The points for action are to:

1. Commit to a comprehensive, financed national plan with accountability and civil society engagement (a master plan to combat antimicrobial resistance)
2. Strengthen surveillance and laboratory capacity
3. Ensure uninterrupted access to essential medicines of assured quality
4. Regulate and promote rational use of medicines, including in animal husbandry and ensure proper patient care. Reduce use of antimicrobials in food-producing animals
5. Enhance infection prevention and control
6. Foster innovations and research and development for new tools

On 8 March, 2012, WHO launched a new book "The evolving threat of antimicrobial resistance - Options for action".\textsuperscript{89}

It examines the experiences with interventions which address the growing threat of antimicrobial resistance, describes the lessons learnt along the way and highlights the gaps...
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

still remaining. It draws attention to areas where knowledge is lacking and where urgent action is still needed. A specific objective is therefore to encourage policy-makers and the global community to commit to intensified action against AMR.

In addition to these global actions several of the WHO regional offices have specific activities: WHO Euro has launched a strategic plan\(^9^0\) which has been adopted in the biennial work-plan of some 20 non-EU countries.

A number of key strategic actions are proposed to mitigate, prevent and control antibiotic resistance. These include promoting national coordination to implement national strategic plans of action and develop regulatory functions and guidance; promoting the prudent use of antibiotics across many sectors; strengthening surveillance systems to monitor the use of antibiotics and resistant bacteria; and creating awareness of the prudent use of antibiotics and the fact that new antibiotic drugs are not coming onto the market soon.\(^9^1,9^2\)

WHO-SEARO has released a regional resolution “prevention and containment of antimicrobial resistance”.\(^9^3\)

Through resolutions passed by the World Health Assembly (WHA), WHO Member States have highlighted not only the public health threat of resistant organisms, but also the harm caused by misuse of antimicrobials by patients, prescribers and medicine dispensers. Activities following publication of the 2004 Report are encapsulated in the following WHA Resolutions:

- WHA58.27 – Improving the containment of antimicrobial resistance, 25 May 2005 (see Appendix 1.1).
- WHA60.16 – Progress in the rational use of medicines, 23 May 2007 (see Appendix 1.2).
- WHA62.15 – Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis, 22 May 2009 (see Appendix 1.3).

5.3 World

China’s activities concerning AMR are rather recent but are expanding.\(^9^4,9^5\) In 2004, China created its first AMR surveillance programme and national guidelines for appropriate antibiotic use.\(^9^6,9^7\) Israel has had success with a national campaign promoting prudent antibiotic use.\(^9^8,9^9\) Numerous other countries have also implemented stewardship campaigns and other control strategies.\(^1^0^0\)

The recent ‘Chennai Declaration’ for India is an outgrowth of a meeting of leaders from medical societies, federal and state governments, and representatives from the World Health Organization, that gathered in 2012 in Chennai, India. The Chennai Declaration proposes a plan to create a road map for tackling the challenge of antimicrobial resistance in India.\(^1^0^1\)

Among many recommendations, the declaration calls for regulation of over-the-counter sales of antibiotics, monitoring of in-hospital antibiotic use, and development of a national antimicrobial resistance surveillance system. It also suggests roles for a variety of stakeholders, including the Ministry of Health and Family Welfare, the Medical Council of India (the statutory body regulating medical colleges), and the World Health Organization.
5.4 The Americas

The activities of the USA concerning AMR are extensive and have expanded. The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) have reacted with numerous meetings, task forces, workshops and publications to address this issue. The Transatlantic Taskforce was established between the EU and the USA as “… transatlantic task force on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial medicines in the medical and veterinary communities, prevention of bother healthcare – and community associated medicine-resistant infections and strategies for improving the pipeline of new antimicrobial medicines, which could be better addressed by intensified cooperation between us”. The taskforce’s purpose is to identify issues related to AMR that would be better addressed through collaboration between the EU and the USA. The primary areas of focus of the TATFAR are the appropriate use of antimicrobial medicines in the medical setting and veterinary community, prevention of AMR infections both within the community and hospital settings and fostering the antimicrobial development pipeline. In 2011, the TATFAR published its first report Recommendations for Future Collaboration Between the USA and EU.

An action plan released in March 2011 by the Interagency Task Force on Antimicrobial Resistance, co-chaired by the CDC, FDA, and NIH. The action items are organized into four focus areas: surveillance, prevention and control, research, and product development. In commemoration of World Health Day 2011, The Infectious Diseases Society of America (IDSA) released the official publication "Combating Antimicrobial Resistance: Policy Recommendations to Save Lives,” which summarizes IDSA recommendations about how to address antibiotic resistance. APUA is a strong supporter of IDSA's work to address the dry antibiotic pipeline and the crisis of antibiotic resistance.

The IDSA has an advocacy campaign, the 10x'20 initiative, to address the dry antibiotic pipeline and call for 10 new antibiotics by 2020. 10 x '20 encourages the development of antibiotics and the improvement of diagnostic tests for priority resistant infections, as well as the creation of incentives that stimulate new antibacterial research and development. The IDSA has published a report entitled, Bad Bugs, No Drugs.

On April 13, 2012, the FDA issued a final guidance on the Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals, concluding that the unnecessary or inappropriate use of medically important antimicrobials in food animal production is not beneficial to public health. In agreement with APUA, FDA recommends that antibiotics be used with veterinary oversight. FDA does not consider use for growth promotion or improvement of feed efficiency to be judicious, but does consider antimicrobial use for treatment, control, and prevention of disease to be “necessary for assuring the health of food-producing animals.”

Several actions by Congress have also occurred such as passing the Generating Antibiotic Incentives Now (GAIN) Act. This is an economic incentivization tool to encourage new antibiotic R&D.

In South America there is also the South American Infectious Diseases Initiative to contain AMR. The Pan American Health Organization (PAHO) has conducted for many years a project on surveillance of AMR and has produced an annual report since 2004, although the last report appears to be in 2009.
6. Research into the past and present pharmaceutical interventions: what can be learnt?

6.1 Antibiotic development

The number of new molecular entity FDA approved antibiotics continues to decrease. (Annex 6.1.21). Only 10 antibiotics that are “New Molecular Entities” have been approved by the FDA from 2004 to 2012 whereas 13 were approved between 1996 and 2003.

Figure 6.1.6: FDA Approved New Molecular Entity Antibiotics, 2004 – 2012

![FDA Approved New Molecular Entity Antibiotics, 2004 - 2012](source)


6.2 Are incentives insufficient for the pharmaceutical industry?

The financial incentives for the pharmaceutical industry to bring a new antibiotic compound through the stages of medicine development appear to be insufficient. Linking profits from product sales is exactly the driver of increased sales of antimicrobials that should be discouraged. Of course, this poses a problem for the current R&D business models.

Numerous incentives have been proposed that have attracted industry interest. (Annex 6.1.22.) Examples of these incentives include patent extensions, data exclusivity, market exclusivity, and a special market approval track.
6.3 Public resources for basic and applied research

Public funding for AMR research has greatly increased since 2004. (Annex 6.1.20). Public-private partnerships (PPPs) have shown to be attractive for both the private and public sectors.\footnote{112} Public resources that are used to help stimulate the dry antibiotic development pipeline are commonly utilized within a PPP. Additionally, some private companies are providing funds to public organizations, such as universities, to also stimulate pipeline development.

6.4 What is in the current antibiotic pipeline?

The rather weak antibiotic pipeline discussed in the 2004 Report continues. As of early 2012, only 109 antibiotics are in the pipeline in which 70% are in the early stages of development. Only 31 potential candidates are in Phase 2 and nine candidates in Phase 3. Sixty-six companies are developing these 109 antibiotics in which only nine are large companies while the remaining 57 companies are small/medium enterprises.\footnote{113} Of the 15 large pharmaceutical companies that previously had active antimicrobial programmes, only five remain. Reports reveal that only a few antimicrobials are in the company pipelines and only two candidates target Gram-negative resistant bacteria as shown in Figure 6.1.7.\footnote{114,115} (Annex 6.1.23).

![Antimicrobials in development as of 2011 – Gram–negative versus Gram–positive](image)


Recently, there is renewed interest in research to find new effective antimicrobials, much of it being carried out by small biotechnology companies and academic centres, rather than by large pharmaceutical companies. Antibiotics that are currently in clinical development or at the preclinical stage, including both improved compounds related to approved drugs and new chemical classes as of 2011 are listed in Table 6.1.3.\footnote{117}
### 6.1 Antimicrobial resistance

#### 6.1.3: Antibiotics that are currently in clinical development or at the preclinical stage

<table>
<thead>
<tr>
<th>Compound name</th>
<th>Chemical class</th>
<th>Target</th>
<th>Dev. stage</th>
<th>Route</th>
<th>Developing company</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC-3205</td>
<td>Pleuromutilin</td>
<td>Ribosome</td>
<td>Phase 1</td>
<td>Oral</td>
<td>Nabriva</td>
</tr>
<tr>
<td>BC-7013</td>
<td>Pleuromutilin</td>
<td>Ribosome</td>
<td>Phase 1</td>
<td>Oral</td>
<td>Nabriva</td>
</tr>
<tr>
<td>CG400549</td>
<td>Triclosan</td>
<td>FabI</td>
<td>Phase 1</td>
<td>iv</td>
<td>Crystal Genomics</td>
</tr>
<tr>
<td>AF-1252</td>
<td>New lead</td>
<td>FabI</td>
<td>Phase 1</td>
<td>iv</td>
<td>Affininium</td>
</tr>
<tr>
<td>FAB-001</td>
<td>Triclosan</td>
<td>FabI</td>
<td>Phase 1</td>
<td>iv</td>
<td>FAB Pharma</td>
</tr>
<tr>
<td>Delafloxacin</td>
<td>Fluoroquinolone</td>
<td>gyrase</td>
<td>Phase 2</td>
<td>iv/oral</td>
<td>Rib-X</td>
</tr>
<tr>
<td>TP-434</td>
<td>Tetracycline</td>
<td>Ribosome</td>
<td>Phase 2</td>
<td>iv/oral</td>
<td>Tetraphase</td>
</tr>
<tr>
<td>BC-3781</td>
<td>Pleuromutilin</td>
<td>Ribosome</td>
<td>Phase 2</td>
<td>iv/oral</td>
<td>Nabriva</td>
</tr>
<tr>
<td>Solithromycin</td>
<td>Ketolide</td>
<td>Ribosome</td>
<td>Phase 2</td>
<td>iv/oral</td>
<td>Cempra</td>
</tr>
<tr>
<td>ACHN-490</td>
<td>Aminoglycoside</td>
<td>Ribosome</td>
<td>Phase 2</td>
<td>iv</td>
<td>Achaogen</td>
</tr>
<tr>
<td>CB-183&lt;comma&gt;315</td>
<td>Lipopeptide</td>
<td>Membrane</td>
<td>Phase 2</td>
<td>Oral</td>
<td>Cubist</td>
</tr>
<tr>
<td>Ramoplanin</td>
<td>Lipoglycodepsipeptide</td>
<td>Cell wall</td>
<td>Phase 2</td>
<td>Oral</td>
<td>Nanotherapeutics</td>
</tr>
<tr>
<td>GSK-1322322</td>
<td>New lead</td>
<td>PDF</td>
<td>Phase 2</td>
<td>iv</td>
<td>GSK</td>
</tr>
<tr>
<td>JNJ-Q2</td>
<td>Fluoroquinolone</td>
<td>gyrase</td>
<td>2/3</td>
<td>iv/oral</td>
<td>Furiex</td>
</tr>
<tr>
<td>Nemonoxacin</td>
<td>Quinolone</td>
<td>gyrase</td>
<td>2/3</td>
<td>Oral</td>
<td>TaiGen/ Warner</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>Glycopeptides</td>
<td>Cell wall</td>
<td>Phase 3</td>
<td>iv</td>
<td>The Medicine Co</td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>Glycopeptides</td>
<td>Cell wall</td>
<td>Phase 3</td>
<td>iv</td>
<td>Durata</td>
</tr>
<tr>
<td>Torezolid</td>
<td>Oxazolidinone</td>
<td>Ribosome</td>
<td>Phase 3</td>
<td>iv/oral</td>
<td>Trius</td>
</tr>
<tr>
<td>Radezolid</td>
<td>Oxazolidinone</td>
<td>Ribosome</td>
<td>Phase 3</td>
<td>iv/oral</td>
<td>Rib-X</td>
</tr>
<tr>
<td>Amadacycline</td>
<td>Tetracycline</td>
<td>Ribosome</td>
<td>Phase 3</td>
<td>iv/oral</td>
<td>Paratek</td>
</tr>
<tr>
<td>Cethromycin</td>
<td>Ketolide</td>
<td>Ribosome</td>
<td>Phase 3</td>
<td>Oral</td>
<td>Advanced Life Sciences</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Source: Daniela Jabes, The antibiotic R&D pipeline: an update *Current Opinion in Microbiology* Volume 14, Issue 5, October 2011, Pages 564–569

Considering the attrition rate for antibiotics in development and commercial considerations, only a small number of the compounds listed in Table 6.1.3 are expected to reach the marketplace.

### 6.5 Optimization of antibiotic dosing regimens

Optimization of antimicrobial dosing regimens have made progress. Pharmacokinetic/pharmacodynamic parameters are not fully understood although there is research underway. Additionally, innovative ways to use old antibiotics to combat the issue of AMR is also being addressed, mostly through combination regimens but also through shortened treatment duration.
7. **What are the gaps between current research and potential research issues which could make a difference?**

### 7.1 Need for Rapid and inexpensive diagnostics

Diagnostic tools have made major advancements although the cost still remains high for many of these tests. Diagnostic tools to detect *S. pyogenes*, urinary tract infections and bacterial and viral bronchitis are currently available although they are not always used by practitioners. Efforts to reduce these costs have been made, most notably with the Xpert MTB/RIF diagnostic test and its concessional pricing methods. Even though there are many obstacles preventing the development of AMR diagnostic tools, numerous initiatives have been developed by organizations such as the IMI. See Chapter 2.

Improvements have been made regarding diagnostic tools but in low- and middle-income countries (LMIC), there are still few useful and context-appropriate diagnostics. Inexpensive and readily available diagnostic tools are now available for a variety of infectious diseases, the best known being rapid diagnostic tests for malaria.

Some tools are able to distinguish between viral and bacterial infections while others are able to distinguish between bacterial species. (See Annex 6.1.7). However, point-of-care diagnostics remain an unmet need.

The development and validation of new diagnostic tests can in principle help determine whether antibiotics should be prescribed at all and, if they are prescribed, such tools can help determine which antibiotics should be prescribed. Further, rapid diagnostics can help control the spread of infections if an infection is diagnosed early enough. Certainly, rapid diagnostics are being developed to determine the presence of resistant strains of clinically important bacteria.

There is no doubt rapid diagnostics can be developed but there will be regulatory and other challenges to creating inexpensive diagnostics, particularly for use in low and middle income countries. The business environment poses both opportunity and challenge. From a business model, a diagnostic company will typically look at the total market; product value, project growth rates, the projected manufacturer market share, the competition, and alignment with overall strategy to determine if they want to pursue a particular diagnostic for a particular indication. For low- and middle-income countries, the issues of “market failure” (great patient need but inability to pay), as in pharmaceuticals, will be a key consideration.

**The widespread use of improved and cost effective diagnostic tools to identify bacterial infections which will benefit from treatment is still needed to reduce antibiotic misuse.** More research may be needed to identify how these diagnostic products can most effectively be used to reduce inappropriate antimicrobial prescriptions.

### 7.2 Identifying the most urgent needs for new antibiotics

Efforts attempting to identify the most urgent needs for new antibiotics continue. A greater proportion of infections are caused by Gram–positive pathogens although prevalence of Gram–negative infections is steadily increasing as shown in Figure 6.1.8. Surveillance has
revealed that the total burden of AMR Gram-positive pathogens is less than that for Gram-negative pathogens.9 This means that priority should be given to the development of Gram-negative antibiotics.

Figure 6.1.8: Population-weighted, average percentage of resistant isolates among bacteria from bloodstream infections, EU, Iceland and Norway, 2002-2010

Numerous incentives for medicine development have been proposed and implemented.97 See Annex 6.1.22. The United States passed the Prescription Drug User Fee Act (PDUFA) V Act in July 2012 along with the controversial GAIN Act. The GAIN act will provide five additional years of market exclusivity, priority review and fast track status for antimicrobials targeted towards the most serious AMR pathogens.131 Priority review vouchers have been proposed to stimulate the antibiotic development pipeline, similar to those distributed by the FDA for neglected tropical diseases.132

Scientific opportunities for medicine development have been proposed. Open source innovations have been recommended by WHO and various other stakeholders.133

7.3 New therapeutic approaches

7.3.1 Alternatives to antimicrobials: Antivirulence medicines

Progress during the last five years is being made toward one alternative, the development of antivirulence drugs focusing on bacterial secretion systems. Secretion systems translocate macromolecules across the envelope of bacterial cells and in many cases directly into the host where these effectors modulate the defense response and thereby facilitate survival of the
pathogen. Antivirulence drugs would not kill but rather deprive bacteria of their virulence functions so that they can be eliminated by the immune system. Since antivirulence drugs would not impact vital cell functions it is believed that the development of resistance will be slow. Therefore, they would constitute a valuable alternative to antibiotics. Also, they may be used in combination therapies to augment the potency of antibiotics or to slow down the development of resistance.\textsuperscript{134, 135}

### 7.3.2 Host-pathogen interactions

The production of cationic antimicrobial peptides (CAMPs) by an animal host is widespread.\textsuperscript{136} Significantly, these CAMPs are still highly effective against pathogens after millions of years of co-evolution. Antibiotics are usually designed to function at low concentrations through a defined high-affinity antimicrobial target — a set of circumstances that makes it comparatively easy for bacteria to develop resistance. By contrast, CAMPs are released precisely at infected sites and are usually active at much higher concentrations than antibiotics. Moreover, many CAMPs have multiple antimicrobial activities. In theory, it can be argued that the evolution of the innate host defense systems has favored the design of antimicrobials that disturb many biological functions with low potency rather than blocking a specific high-affinity target such as enzymes for building bacterial cell walls. Such properties enable the host to control a much wider range of potential pathogens without creating the selection pressure for high-level resistance that is observed with potent, high-affinity antibiotics. Considering the high concentrations that are required for antimicrobial activity, it is thought that CAMPs might exhibit greater toxicity compared with the therapeutic antibiotics currently in use.

CAMPs have a number of potential advantages as future therapeutics; in addition to their broad spectrum antimicrobial activity and rapid killing of microbes, they are unaffected by classical antibiotic resistance mechanisms. Moreover, CAMPs do not appear to induce antibiotic resistance. CAMPs currently are being widely used as blueprints for the development of innovative therapeutic agents that may be used as antimicrobials, modifiers of inflammation, or in cancer therapy.\textsuperscript{137, 138}

### 7.3.3 Non-antibiotics

Most clinical isolates that exhibit a multi-drug resistant phenotype owe that resistance to over-expressed efflux pumps. Compounds that are efflux pump inhibitors (EPIs) reduce or reverse resistance to antibiotics to which the bacterial strain is initially resistant. Recent work has evaluated non-antibiotics to reduce resistance of commonly encountered bacterial pathogens to antibiotics. Non-antibiotics such as phytochemical flavonoids (galangin, quercetin and baicalein) and other compounds such as chlorpromazine, amitryptiline and trans-chlorprothixene were shown to reduce or reverse resistance of a variety of bacteria to antibiotics.\textsuperscript{139, 140}

### 7.3.4 Use of Phage and Phage Therapy

Another alternative approach was recently demonstrated in a proof-of-concept trial in which bacteriophages were genetically engineered to reverse a pathogen's drug resistance, thereby restoring its sensitivity to antibiotics.\textsuperscript{141}
Another use of ‘phage therapy’ would be use phage to directly kill specific bacteria and eliminate an individual patient’s infection without affecting the body’s communities of beneficial bacteria. Because phages attack bacteria by attaching to receptors on the bacterial cell surface that are often bacterial virulence factors, phage-resistant bacterial mutants (which lack these receptors) are often less pathogenic than phage-susceptible bacteria. Further, the development of phage-resistance can be forestalled altogether if phages are used in cocktails (preparations containing multiple types of phages) and/or in conjunction with antibiotics. An improved understanding of phages’ in vivo pharmacokinetics would also increase phages’ therapeutic value. For phage therapy to be useful in clinical settings, a patient’s specific etiological agent would need to be rapidly identified and matched to the relevant phage(s) in a comprehensive pre-existing database. New and interdisciplinary thinking involving bioinformaticists, health care professionals, and phage researchers, among others, would be required to make phage therapy practicable on a large-scale. Phage therapy has been extremely effective at treating a number of bacterial infections in controlled animal studies. In 2009, a double-blind Phase II clinical study showed phages to be safe and effective at treating chronic drug-resistant ear infections.\textsuperscript{142}

### 7.3.5 Vaccines: Primary prevention of resistance

Several FDA approved vaccines addressing bacterial pathogens have been released. (Annex 6.1.24). Vaccines would be an ideal approach and there are several suggestive examples.\textsuperscript{143} The vaccine pipeline is extensive although many fail in the early stages. Currently, several vaccines are undergoing clinical trials.\textsuperscript{144} The possibility of targeting vaccines towards therapeutics remains a challenge. See also Section 9.1. It is interesting that the effect of vaccines leading to substitution of one resistant microbe with another of increasing resistance clones has been debated in relation to pneumococcal vaccines. Clearly, conjugate vaccines have had a major effect in reducing the absolute incidence of drug-resistant \textit{Streptococcus pneumoniae} (DRSP) not only in immunised children, but also in their contacts. However, continued antibiotic exposure of pneumococci lacking a response to pneumococcal conjugate vaccines PCV has led to increasing resistance among these strains, which has reduced the overall impact of these vaccines.\textsuperscript{145} Thus, serotype replacement as observed for pneumococcal strains can undermine vaccine effectiveness.

Nonetheless, it is possible to make vaccines virtually against any pathogen. The presence of antibiotics in the environment and host imposes a strong selective filter of resistances acquired through horizontal gene transfer (HGT) of plasmids, transposons and/or integrons or through mutations. Although antigenic variation could potentially be the mechanism behind the emergence of vaccine resistant strains, vaccines harbor several unique features that make them virtually resilient to resistance phenomena. First, protein-based vaccines usually contain multiple immunogenic epitopes implying that many mutations should accumulate before resistant strains rise.

Vaccine-resistant bacteria have never been reported. By preventing infections, vaccines do not allow bacteria to replicate in the host, limiting the selection process of variants to the initial phases of the infection.

By targeting bacterial pathogens, vaccines directly reduce the need for the use of antibiotics. Vaccines also contribute to the reduction of antibiotic usage through the establishment of herd immunity by halting the levels of transmission of pathogenic bacteria to potentially
Antimicrobial resistance

susceptible individuals and therefore limiting the numbers of infections in the overall population. However, no vaccines yet exist for the most important multi-drug resistant strains. There are several ongoing preclinical and clinical research programs on antibiotic resistant pathogens (Table 6.1.4). Development of novel vaccines against bacterial pathogens for which antibiotic therapies are still efficacious, including veterinary infections, would also contribute substantially to further prevent the emergence of antibiotic resistant strains.\(^\text{146}\)

Table 6.1.4: Status of vaccine development against relevant nosocomial antibiotic resistant pathogenic bacteria

<table>
<thead>
<tr>
<th>Bacterial pathogen</th>
<th>Disease</th>
<th>Vaccines status and references</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>Skin and soft tissue infections, endocarditis, pneumonia, bacteremia, osteomyelitis, toxic shock syndrome</td>
<td>Clinical trials(^\text{147})</td>
</tr>
<tr>
<td><em>C. difficile</em></td>
<td>Antibiotics associated diarrhea and colitis</td>
<td>Clinical trials(^\text{148})</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Chronic pulmonary infections in immunocompromised and cystic fibrosis patients, pneumonia, urinary tract infections (UTIs)</td>
<td>Clinical trials(^\text{149})</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>Respiratory tract infections, bacteremia, meningitis, epiglottitis</td>
<td>Licensed vaccine and Clinical trials(^\text{150})</td>
</tr>
<tr>
<td>Pathogenic <em>E. coli</em></td>
<td>UTIs, diarrhea, hemolytic-uremic syndrome</td>
<td>Research and Clinical trials(^\text{151})</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>Pneumonia (bronchopneumonia and bronchitis), UTIs</td>
<td>Research reported</td>
</tr>
<tr>
<td><em>E. faecium</em></td>
<td>Neonatal meningitis, UTIs, endocarditis, bacteremia</td>
<td>Research reported</td>
</tr>
<tr>
<td><em>A. baumannii</em></td>
<td>Pneumonia, UTIs, bacteremia</td>
<td>Research reported</td>
</tr>
</tbody>
</table>

8. Conclusion

Collaborative, global and more concerted efforts are needed to address the public health threat that AMR poses. The EU should continue its extensive contributions and collaborations in this regard and can provide leadership in the following areas:

**Diagnostic and therapeutic tools:**
- Development and use of cost-effective and point of care diagnostic tools to encourage prudent and appropriate antibiotic use.
- Priority development of antibiotics against Gram- negative bacteria.
- Replenishment of the antibiotic development pipeline, possibly using new business models for R&D, in order to develop new products with novel mechanisms of action to address the already heavy burden of AMR.
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Health systems:
- Establishment and implementation of a multi-faceted approach using standardized surveillance coupled with appropriate antimicrobial stewardship campaigns at country level.
- Allocation of public funding to continue providing evidence/data on antimicrobial resistance to treatment for vaccine-preventable diseases in order to assess the potential impact of comprehensive vaccination policies in reducing antimicrobial resistance.
- Exploration of further possibilities for extending global cooperation.

Prescription interventions:
- Promotion of strategies designed to modify physician antimicrobial-prescribing practices towards an approach based on simplicity rather than complexity. These strategies should take into account physicians’ limited knowledge of many of the specifics of the complex interaction between antibiotics and microbes.
- Approaches to encourage improved adherence to veterinary “judicious use” guidelines.
- Promotion of investment in research and development of future innovative vaccines capable of targeting and preventing antibiotic-resistant bacteria.

References


28 Levy SB, Fitzgerald GB, Macone A. 1976 Spread of antibiotic-resistant plasmids from chicken to chicken and from chicken to man Nature 260, 40 - 42 (04 March 1976); doi:10.1038/260040a0

29 [Harrison EM, Peterson GK, Holden MTG et al. Whole genome sequencing identifies zoonotic transmission of MRSA isolates with the novel mecA homologue mecC. EMBO Molecular Medicine published online 25 MAR 2013. DOI: 10.1002/emmm.201202413]


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Risk assessment on the spread of carbapenemase-producing Enterobacteriaceae (CPE) through patient transfer between healthcare facilities, with special emphasis on cross-border transfer. Stockholm: European Centre for Disease Prevention and Control (EARS-NET).

EARS-NET, 2011.


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83 The Innovative Medicines Initiative - Combatting Bacterial Resistance in Europe (COMBACTE); 2013 [accessed 23 April 2013] Available at: http://www.imi.europa.eu/content/combacte

84 The Innovative Medicines Initiative - Translocation; 2013 [accessed on 23 April 2013] Available at: http://www.imi.europa.eu/content/translocation


90 European strategic action plan on antibiotic resistance; 2012 [accessed 23 April 2013] Available at: (http://www.euro.who.int/__data/assets/pdf_file/0008/147734/wd14E_AntibioticResistance_111380.pdf)


93 Resolution for the WHO regional committee for South-East Asia: PREVENTION AND CONTAINMENT OF ANTIMICROBIAL RESISTANCE; 2010 [accessed 23 April 2013] Available at: (http://repository.searo.who.int/bitstream/123456789/15013/1/sea-rc63-r4.pdf).


104 http://www.tufts.edu/med/apua/policy/other_initiatives_2_765224796.pdf


113 PR Newswire. The antibiotic development pipeline and strategies to combat antibiotic resistance. [News Article]: United Business Media (UBM); 2012 [updated 18 January 2012; cited 20 July 2012];
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Malaria Rapid Diagnostic Tests; 2005 [accessed 24 April 2013] Available at: http://www.wpro.who.int/malaria/sites/rdt/


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143 Zhou F et al. Pediatrics 2008; 121:253-260 (heptavalent pneumococcal conjugate vaccines (PCV7) against drug-resistant streptococcus pneumoniae (DRSP) led to a drop in antibiotic prescriptions); Whitney C. et al Seminars in Pediatric Infectious Diseases, Vol 15, No 2 (April), 2004: pp 86-93 (pneumococcal conjugate vaccine effective in preventing disease in young children and may be reducing the rate of disease in adults); Haddy et al. The Pediatric Infectious Disease Journal Volume 24, Number 4, April 2005 (case rates for invasive S. pneumoniae disease among children decreased significantly in the 2-year period after introduction of the heptavalent S. pneumonia protein conjugate vaccine).


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Annex 6.1.18: Activity Review of the WHO and Antimicrobial Resistance
Annex 6.1.19: Examples of Concerted Action Addressing Antimicrobial Resistance in Europe
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Annex 6.1.22: Incentives to Encourage Antimicrobial Research and Development
Annex 6.1.1: Examples of Global Activities and Publications Addressing Antimicrobial Resistance

This table presents several examples of global activities and actions concerning AMR. This is a brief overview of actions and is not inclusive of all of the efforts that have occurred since 2004.

<table>
<thead>
<tr>
<th>Organization</th>
<th>Location</th>
<th>Activity (Year)</th>
<th>Purpose / Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO¹</td>
<td>World</td>
<td>Published: Priority Medicines for Europe and the World (2004)</td>
<td>Identify AMR as the greatest infectious disease to public health if the appropriate drugs were not developed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Formulate suggestions for future activities conducted at the EMA</td>
</tr>
<tr>
<td>ECDC³</td>
<td>Europe</td>
<td>Visited: Several countries within Europe (2006 – 2011)</td>
<td>Discuss implementation of EC recommendations from 2001</td>
</tr>
<tr>
<td>EU⁴</td>
<td>Europe</td>
<td>Legislated: Ban antibiotics in poultry farming (2006)</td>
<td>Ban the use of antibiotics in poultry farming</td>
</tr>
<tr>
<td>ECDC</td>
<td>Europe</td>
<td>Meeting: Develop the ECDC / EMA Joint Working Group (2007)</td>
<td>Discuss, plan and develop a group to formally produce a report concerning AMR and the gaps in antimicrobial R &amp; D</td>
</tr>
<tr>
<td>EMA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ReAct⁵</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Foster prudent antimicrobial use</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Organization</th>
<th>Location</th>
<th>Activity (Year)</th>
<th>Purpose / Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU⁷</td>
<td>Europe</td>
<td>Legislated: AMR surveillance in pigs (2008)</td>
<td>Implement AMR surveillance and reporting strategies for Salmonella, Campylobacter and MRSA within pigs</td>
</tr>
<tr>
<td>EMA</td>
<td>Europe</td>
<td>Integrated: Suggestions by Think-Tank Group (2008)</td>
<td>Plan to bolster the EU scientific network</td>
</tr>
<tr>
<td>Scientific Committees²</td>
<td>Europe</td>
<td></td>
<td>Encourage international communication concerning antimicrobial R &amp; D</td>
</tr>
<tr>
<td>EC⁸,⁹</td>
<td>Europe</td>
<td>Legislated: Suggestions for antibiotic use (2008 / 2010)</td>
<td>AMR and its relationship with antibiotics within animals</td>
</tr>
<tr>
<td>EPRUMA¹⁰</td>
<td>Europe</td>
<td>Published: Best - practice framework for the use of antimicrobials in food-producing animals (2008)</td>
<td>Encourage prudent use of antibiotics in animals within the EU</td>
</tr>
<tr>
<td>CHMP¹¹, PDCO, ECDC, EMA, ReAct</td>
<td>Europe</td>
<td>Published: The bacterial challenge: time to react - A call to narrow the gap between multidrug - resistant bacteria in the EU and the development of new antibacterial agents (2009)</td>
<td>Produce a report concerning gaps in antimicrobial drug R &amp; D and the increasing prevalence of antimicrobial resistant bacteria</td>
</tr>
<tr>
<td>Numerous AMR experts (Hosted by Swedish EU Presidency)¹²</td>
<td>Europe</td>
<td>Conference: Innovative incentives for effective antibacterials (2009)</td>
<td>Develop and discuss incentives to stimulate antimicrobial drug R &amp; D</td>
</tr>
<tr>
<td>EC¹²</td>
<td>Europe</td>
<td>Presented: Suggestions for patient safety (2009)</td>
<td>Propose strategies to prevent AMR in HAIs</td>
</tr>
<tr>
<td>EU United States¹³</td>
<td>Europe / US</td>
<td>Annual summit: EU – United States presidencies</td>
<td>Discuss the human public health threats of AMR</td>
</tr>
</tbody>
</table>

⁷ EU, ⁸ EC, ⁹ EMA, ¹⁰ EPRUMA, ¹¹ CHMP, ¹² EC, PDCO, EMA, ReAct, ¹³ United States
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<table>
<thead>
<tr>
<th>Organization</th>
<th>Location</th>
<th>Activity (Year)</th>
<th>Purpose / Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Europe</td>
<td>Published: Road map to 2015 (2010)</td>
<td>Discuss past, current and future actions of the EMA about the gaps in industry and antimicrobial R &amp; D</td>
</tr>
<tr>
<td>Numerous AMR experts (Hosted by ReAct)&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Europe</td>
<td>Conference: The global need for effective antibiotics-moving towards concerted action (2010)</td>
<td>Further elaborate findings and discussions pertaining to those at the 2009 conference Innovative Incentives for Effective Antibacterials</td>
</tr>
<tr>
<td>Ministry of Health&lt;sup&gt;16&lt;/sup&gt;</td>
<td>China</td>
<td>Legislated: Separate physician salary and drug sales at primary care level (2010)</td>
<td>To discourage inappropriate use of antibiotics • Part of the national campaign that was implemented in 2004</td>
</tr>
<tr>
<td>Numerous AMR experts (Hosted by ReAct)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Europe</td>
<td>Conference: Collaboration for innovation – the urgent need for new antibiotics (2011)</td>
<td>Discuss the need to develop the appropriate medicines to combat AMR • Contribute ideas to the EU’s official plan against AMR</td>
</tr>
<tr>
<td>TATFAR</td>
<td>Europe / US</td>
<td>Published: Recommendations for future collaboration between the US and EU (2011)</td>
<td>Issue 17 recommendations that could be implemented with opportunities for collaboration concerning AMR • Provide a platform to potentially stimulate the antimicrobial development pipeline</td>
</tr>
<tr>
<td>Numerous AMR experts (Hosted by the Australian Society for Infectious Diseases and the Australian Society for Antimicrobials)&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Australia</td>
<td>Conference: Antimicrobial Resistance Summit - defining the problem - an international perspective (2011)</td>
<td>Discuss: • Control strategies • National surveillance • Antibiotic stewardship • Antibiotic use in food production • Research needs</td>
</tr>
<tr>
<td>FDA</td>
<td>United States</td>
<td>Legislated: Guidance for antibiotics and use in animals</td>
<td>Offers recommendations that would limit antibiotic use in animals</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Organization</th>
<th>Location</th>
<th>Activity (Year)</th>
<th>Purpose / Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>United States</td>
<td>Legislated: PDUFA – V GAIN Act (2012)</td>
<td>Offer incentives to stimulate the R &amp; D pipeline for new innovative antimicrobials</td>
</tr>
<tr>
<td>Industry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ministry of Health(^2)</td>
<td>China</td>
<td>Legislated: Administrative Measures on Clinical Application of Antimicrobial Drugs (2012)</td>
<td>Stricter regulations concerning the prescription of antimicrobials</td>
</tr>
<tr>
<td>Others(^3)</td>
<td></td>
<td></td>
<td>Promote prudent antimicrobial use</td>
</tr>
</tbody>
</table>

### Sources:


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Annex 6.1.2: Correlation between Antibiotic Consumption and Resistance in Europe

This figure confirms the 2004 report’s assentation that resistance is directly proportional to antibiotic consumption. This figure provides an example within Europe in which the consumption of fluoroquinolones and penicillins is related to resistant *E. coli* and *S. pneumonia* strains, respectively.

Occurrence of fluoroquinolone resistant *Escherichia coli* against outpatient fluoroquinolone use in 17 European countries (with 95% confidence intervals)

Occurrence of penicillin resistant *Streptococcus pneumonia* against outpatient penicillin use in 17 European countries (with 95% confidence intervals)

Annex 6.1.3: Correlation between Antibiotic Consumption and Resistance in the World

This figure shows the positive relationship between several antibiotic prescription rates and resistant Gram–negative infection rates in several Singapore hospitals. These findings suggest that antimicrobial usage may be directly related to resistance.

Annex 6.1.4: Outpatient Antibiotic Consumption

These figures represent various outpatient antibiotic use in several European countries and Latin America. Figure 1 offers a comparison of several European countries’ outpatient antibiotic use in 2002 and 2009. Figure 2 shows antibiotic consumption in eight Latin American countries in 2007.

Figure 1

Total outpatient antibiotic use in 26 European countries in 2002

Total outpatient antibiotic use in 28 European countries in 2009

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*For Cyprus and Lithuania, total consumption (both community and hospital sector)
**For Spain, reimbursement data that do not include over-the-counter sales without a prescription.
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Figure 2
Antibiotic utilization in eight Latin American countries, by therapeutic class, 2007

Sources:
Annex 6.1.5: Examples of Campaigns Addressing the Issue of Antimicrobial Resistance

This table offers several examples of campaigns addressing the issue of AMR. These campaigns differ from one another in their target audience, budgets, locations and intervention strategy used. Some of these campaigns run several times throughout the year while others run periodically. This table is not inclusive of all of the campaigns that have occurred since 2004.

<table>
<thead>
<tr>
<th>Location</th>
<th>Organization</th>
<th>Name of Campaign</th>
<th>Intervention Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>• Belgian Antibiotic Policy Coordination Committee¹</td>
<td>Antibiotics are ineffective for the common cold, acute bronchitis and flu</td>
<td>Numerous interventions targeting wide demographics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Various media types</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Seminars</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Academic workshops</td>
</tr>
<tr>
<td></td>
<td>(2000 – Current)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>• Private organization²</td>
<td>Informational campaign on antibiotic resistance</td>
<td>• Distributes herbal remedies</td>
</tr>
<tr>
<td></td>
<td>(2007 – Current)</td>
<td></td>
<td>• Website</td>
</tr>
<tr>
<td>Greece</td>
<td>• Government - Department of Health</td>
<td>For the prudent use of antibiotics</td>
<td>Numerous interventions targeting wide demographics</td>
</tr>
<tr>
<td></td>
<td>(2001 – 2003)</td>
<td></td>
<td>• Various media types</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Seminars</td>
</tr>
<tr>
<td>Luxemburg</td>
<td>• Government - Department of Health²</td>
<td>Awareness campaign for the appropriate use of antibiotics</td>
<td>Numerous interventions targeting wide demographics</td>
</tr>
<tr>
<td></td>
<td>(2004 -2009)</td>
<td></td>
<td>• Various media types</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Seminars</td>
</tr>
<tr>
<td>Portugal</td>
<td>• Department of Health</td>
<td>Antibiotics, use them in an adequate way</td>
<td>Numerous interventions targeting wide demographics</td>
</tr>
<tr>
<td></td>
<td>• Numerous professional societies</td>
<td></td>
<td>• Various media types</td>
</tr>
<tr>
<td></td>
<td>• Industry (Pfizer)²</td>
<td></td>
<td>• Seminars</td>
</tr>
<tr>
<td></td>
<td>(2004 – 2007)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>• French Social Insurance System³</td>
<td>Antibiotics are not automatic</td>
<td>Numerous interventions targeting wide demographics</td>
</tr>
<tr>
<td></td>
<td>(2002 – Current)</td>
<td></td>
<td>• Various media types</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Seminars</td>
</tr>
</tbody>
</table>
## Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

<table>
<thead>
<tr>
<th>Location (Year)</th>
<th>Organization</th>
<th>Name of Campaign (Budget)*</th>
<th>Intervention Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>England (2001 – Current)</td>
<td>Government - Department of Health</td>
<td>Antibiotic campaign (£600 000/year)</td>
<td>Numerous interventions targeting wide demographics, Various media types</td>
</tr>
<tr>
<td>Europe (2008 – Current)</td>
<td>EC, WHO, Others</td>
<td>European antibiotic awareness day (€3 000/2009)</td>
<td>Numerous interventions targeting wide demographics, Various media types</td>
</tr>
<tr>
<td>United States (2003 – Current)</td>
<td>CDC</td>
<td>Get smart: know when antibiotics work (US$ 1.6 million/2003)</td>
<td>Numerous interventions targeting wide demographics, Various media types</td>
</tr>
<tr>
<td>United States: Arkansas (2000 – Current)</td>
<td>Government - Department of Health, Private sponsor</td>
<td>Save the antibiotic — don’t use it when you don’t need it! (US$ 30 000/year)</td>
<td>Academic programme</td>
</tr>
<tr>
<td>Canada: British Columbia (2005 – Current)</td>
<td>Government - Department of Health</td>
<td>Do bugs need drugs? (CA$ 460 000/year)</td>
<td>Numerous interventions targeting wide demographics, Various media types, Seminars</td>
</tr>
</tbody>
</table>
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

<table>
<thead>
<tr>
<th>Location (Year)</th>
<th>Organization</th>
<th>Name of Campaign (Budget)*</th>
<th>Intervention Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia (2000 - 2008)</td>
<td>• Agency of the department of health⁹</td>
<td>Common colds need common sense, not antibiotics (AU$ 800 000/2007)</td>
<td>Numerous interventions targeting wide demographics • Various media types • Academic workshops</td>
</tr>
<tr>
<td>Israel (2001, 03, &amp; 06)</td>
<td>• Health Organization • Government¹⁰</td>
<td>Antibiotic campaign</td>
<td>Numerous interventions targeting wide demographics • Various media types</td>
</tr>
</tbody>
</table>

* Budget costs are not current PPP adjusted. Budget costs are current year indicated within the parenthesis.

Sources:
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance


Annex 6.1.6: Successful Campaigns for Prudent and Appropriate Antibiotic Use

The table presented below is a brief overview of campaigns targeted against AMR. The outcomes of these campaigns were considered successful if antibiotic consumption, antibiotic prescription, and or prevalence rates decreased.

<table>
<thead>
<tr>
<th>Name of Campaign</th>
<th>Location</th>
<th>Year</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic management teams¹</td>
<td>Belgium</td>
<td>2002 – Current</td>
<td>Successful implementation of AMR control strategies</td>
</tr>
<tr>
<td>Assistance Publique-Hôpitaux de Paris’ MRSA control programme²</td>
<td>France</td>
<td>1993 - Current</td>
<td>Reduced MRSA rates</td>
</tr>
<tr>
<td>Keep Antibiotics Working³</td>
<td>France</td>
<td>2001 - Current</td>
<td>Reduced antibiotic consumption</td>
</tr>
<tr>
<td>Antibiotics are not automatic anymore⁴</td>
<td>France</td>
<td>2001 - Current</td>
<td>Reduced antibiotic prescription</td>
</tr>
<tr>
<td>For the prudent use of antibiotics⁵</td>
<td>Greece</td>
<td>2001 - 2003</td>
<td>Decreased antibiotic prescription</td>
</tr>
<tr>
<td>Awareness campaign for the appropriate use of antibiotics⁵</td>
<td>Luxembourg</td>
<td>2004 - 2009</td>
<td>Decreased antibiotic use</td>
</tr>
<tr>
<td>Wise use of antibiotics⁵</td>
<td>New Zealand</td>
<td>1999 - 2009</td>
<td>Decreased antibiotic prescription</td>
</tr>
<tr>
<td>Antibiotics, use them in an adequate way⁵</td>
<td>Portugal</td>
<td>2004 - 2007</td>
<td>Decreased antibiotic consumption</td>
</tr>
<tr>
<td>Campaign for the responsible use of antibiotics⁵</td>
<td>Spain</td>
<td>2006 - 2008</td>
<td>Decreased antibiotic consumption</td>
</tr>
<tr>
<td>Campaign for the appropriate antibiotic use in the community⁵</td>
<td>United States</td>
<td>1995 - 2002</td>
<td>Decreased antibiotic prescription</td>
</tr>
<tr>
<td>Get smart: know when antibiotics work⁵</td>
<td>United States</td>
<td>2003 - Current</td>
<td>Decreased antibiotic prescription</td>
</tr>
<tr>
<td>Task force on antimicrobial resistance and infection control⁵</td>
<td>Israel</td>
<td>2007 - Current</td>
<td>Decreased antibiotic prescription</td>
</tr>
</tbody>
</table>

Sources:


Annex 6.1.7: Examples of Diagnostics for Containing Antimicrobial Resistance

The table presented below offers a brief overview of several diagnostic tools. These tools may detect a specific pathogen, a specific strain or strains of a pathogen or distinguish between a viral and bacterial infection. This list is not comprehensive of all of the diagnostic tools currently available.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer</th>
<th>Pathogen(s) of Interest</th>
<th>Turn Around Time</th>
<th>Cost* (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeneXpert System (Xpert MRSA)</td>
<td>Cepheid</td>
<td>• MRSA</td>
<td>66 minutes or less¹,²</td>
<td>€69.62 / test³ (2010)</td>
</tr>
<tr>
<td>GeneXpert System (Xpert GBS)</td>
<td>Cepheid</td>
<td>• S. agalactiae (GBS)</td>
<td>30 minutes⁴</td>
<td>US$ 45.00 / assay⁵ (2006)</td>
</tr>
<tr>
<td>GeneXpert System (Xpert C. difficile)</td>
<td>Cepheid</td>
<td>• C. difficile</td>
<td>45 minutes⁶</td>
<td>US$ 37.50 / test⁷ (2011)</td>
</tr>
<tr>
<td>SmartCycler System (Smart GBS)</td>
<td>Cepheid</td>
<td>• S. agalactiae (GBS)</td>
<td>26 hours⁹</td>
<td>£29.95 / test¹⁰ (2009)</td>
</tr>
<tr>
<td>AMPLIFIED MTD Test (Mycobacterium Tuberculosis Direct)</td>
<td>Gen - Probe Inc.</td>
<td>• M. tuberculosis complex</td>
<td>3.5 hours¹¹</td>
<td>US$ 47.37 / test¹² (2008)</td>
</tr>
<tr>
<td>AccuProbe MYCOBACTERIUM TUBERCULOSIS Complex Culture Identification Test</td>
<td>Gen - Probe Inc.</td>
<td>• M. tuberculosis complex</td>
<td>50 minutes¹³</td>
<td>US$ 35.00 / test¹⁴ (2002)</td>
</tr>
<tr>
<td>AccuProbe MYCOBACTERIUM AVIUM Complex Culture Identification Test</td>
<td>Gen - Probe Inc.</td>
<td>• M. avium</td>
<td>50 minutes¹³</td>
<td>US$ 35 / test¹⁴ (2002)</td>
</tr>
<tr>
<td>AccuProbe MYCOBACTERIUM GORDONAE Culture Identification Test</td>
<td>Gen - Probe Inc.</td>
<td>• M. gordonae</td>
<td>50 minutes¹³</td>
<td>US$ 35 / test¹⁴ (2002)</td>
</tr>
<tr>
<td>AccuProbe MYCOBACTERIUM KANSASII Culture Identification Test</td>
<td>Gen - Probe Inc.</td>
<td>• M. kansasii</td>
<td>50 minutes¹³</td>
<td>US$ 35 / test¹⁴ (2002)</td>
</tr>
</tbody>
</table>
## Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer</th>
<th>Pathogen(s) of Interest</th>
<th>Turn Around Time</th>
<th>Cost* (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AccuProbe GROUP B STREPTOCOCCUS Culture Identification Test</td>
<td>Gen - Probe Inc.</td>
<td>• <em>S. agalactiae</em> (GBS)</td>
<td>50 minutes⁴</td>
<td>US$ 19.71 / specimen (2002)</td>
</tr>
<tr>
<td>ProGastro Cd Detection Kit</td>
<td>Gen - Probe Inc.</td>
<td>• <em>C. difficile</em></td>
<td>3 hours³</td>
<td>US$ 25.00 / test (2011)</td>
</tr>
<tr>
<td>BD GeneOhm MRSA ACP Assay</td>
<td>Becton -Dickinson</td>
<td>• MRSA</td>
<td>2 hours¹⁶</td>
<td>€56.22 / test (2010)</td>
</tr>
<tr>
<td>BD GeneOhm Cdiff Assay</td>
<td>Becton-Dickinson</td>
<td>• <em>C. difficile</em> • <em>C. difficile</em> toxin B</td>
<td>1 hour¹⁷</td>
<td>US$ 27.00 / test (2011)</td>
</tr>
<tr>
<td>BD GeneOhm StaphSR Assay</td>
<td>Becton-Dickinson</td>
<td>• <em>S. aureus</em> • MRSA</td>
<td>2 hours¹⁸</td>
<td>US$ 35.00 / test¹⁹ (2008)</td>
</tr>
<tr>
<td>Phoenix Automated Microbiology System</td>
<td>Becton-Dickinson</td>
<td>• Several bacterial and viral pathogens</td>
<td>12 hours²⁰</td>
<td>€12.65 / test²¹ (2008)</td>
</tr>
<tr>
<td>BD ProbeTec ET System</td>
<td>Becton-Dickinson</td>
<td>• <em>C. trachomatis</em> • <em>N. gonorrhoeae</em></td>
<td>2 hours²²</td>
<td>US$ 21.50 / test²³ (2010)</td>
</tr>
<tr>
<td>BD GeneOhm StrepB Assay</td>
<td>Becton-Dickinson</td>
<td>• <em>S. agalactiae</em> (GBS)</td>
<td>1 hour²⁴</td>
<td>US$ 26.00 / test²⁵ (2010)</td>
</tr>
<tr>
<td>Vitek</td>
<td>bioMérieux</td>
<td>• Several bacterial and viral pathogens</td>
<td>5 – 8 hours²¹</td>
<td>€12.71 / test²¹ (2008)</td>
</tr>
<tr>
<td>Chromogenic agar (MRSA-ID)</td>
<td>bioMérieux</td>
<td>• MRSA</td>
<td>18 hours²⁶</td>
<td>€2.08 / test³ (2010)</td>
</tr>
<tr>
<td>API system identification</td>
<td>bioMérieux</td>
<td>• Several bacterial pathogens</td>
<td>24 hours²⁷</td>
<td>€6.00 / test²¹ (2008)</td>
</tr>
<tr>
<td>LightCycler SeptiFast Test</td>
<td>Roche</td>
<td>• Several bacterial and viral pathogens</td>
<td>6 hours²⁸</td>
<td>€150-200 / test²⁹ (2012)</td>
</tr>
<tr>
<td>MagNA Pure</td>
<td>Roche</td>
<td>• Several bacterial and viral pathogens</td>
<td>5.5 hours³⁰</td>
<td>€4.04 / sample³¹ (2005)</td>
</tr>
</tbody>
</table>
## Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer</th>
<th>Pathogen(s) of Interest</th>
<th>Turn Around Time</th>
<th>Cost* (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alere BinaxNOW Legionella Urinary Antigen Card</td>
<td>Alere Inc.</td>
<td>• <em>L. pneumophila</em></td>
<td>15 minutes(^{32})</td>
<td>US$ 29.00 / test(^{32}) (2012)</td>
</tr>
<tr>
<td>Alere PBP2a Test</td>
<td>Alere Inc.</td>
<td>• <em>S. aureus</em></td>
<td>24 hours(^{32})</td>
<td>US$ 9.00 / test(^{32}) (2012)</td>
</tr>
<tr>
<td>BinaxNOW S. aureus Test</td>
<td>Alere Inc.</td>
<td>• <em>S. aureus</em></td>
<td>30 minutes(^{32})</td>
<td>US$ 10.00 / test(^{32}) (2012)</td>
</tr>
<tr>
<td>C. DIFF QUIK CHEK COMPLETE</td>
<td>Alere Inc.</td>
<td>• <em>C. difficile</em> toxins A &amp; B</td>
<td>30 minutes(^{32})</td>
<td>US$ 13.00 / test(^{32}) (2012)</td>
</tr>
<tr>
<td>Alere BinaxNOW <em>S. pneumoniae</em> Antigen Card</td>
<td>Alere Inc.</td>
<td>• <em>S. pneumoniae</em></td>
<td>15 minutes(^{32})</td>
<td>US$ 17.00 / test(^{32}) (2012)</td>
</tr>
<tr>
<td>Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry</td>
<td>Bruker Daltonik GmbH</td>
<td>• Several bacterial pathogens</td>
<td>6 minutes / 1 isolate(^{21})</td>
<td>€1.43 / test(^{21}) (2008)</td>
</tr>
<tr>
<td>GenoType Mycobacterium CM/AS</td>
<td>GenoType</td>
<td>• <em>M. tuberculosis</em> complex • 30 most common non-Tuberculosis mycobacteria species</td>
<td>5 hours(^{33})</td>
<td>US$ 35.00 / test(^{34}) (2011)</td>
</tr>
<tr>
<td>Hyplex TBC PCR Test</td>
<td>BAG Health Care GmbH</td>
<td>• <em>M. tuberculosis</em> complex</td>
<td>6 hours(^{35})</td>
<td>€12.00 / test(^{35}) (2010)</td>
</tr>
<tr>
<td>Easy-Plex Assay</td>
<td>AusDiagnostics</td>
<td>• 12 Gram - positive pathogens</td>
<td>3 hours(^{36})</td>
<td>US$ 25.00 / test(^{36}) (2011)</td>
</tr>
<tr>
<td>BacLite Rapid MRSA</td>
<td>3M</td>
<td>• MRSA</td>
<td>5 hours(^{37})</td>
<td>€15.00 / test(^{37}) (2011)</td>
</tr>
<tr>
<td>MicroScan 40 SI</td>
<td>Siemens</td>
<td>• Several bacterial and viral pathogens</td>
<td>48 hours(^{38})</td>
<td>US$ 14.46 / test(^{38}) (2010)</td>
</tr>
<tr>
<td>MicroSeq 500 System</td>
<td>Applied Biosystems</td>
<td>• Several bacterial and viral pathogens</td>
<td>1 - 2 days(^{39})</td>
<td>US$ 54 / test(^{14}) (2002)</td>
</tr>
<tr>
<td>Verigene GP Blood Culture Nucleic Acid Test (BC-GP)</td>
<td>Nanosphere</td>
<td>• Several various Gram - positive pathogens</td>
<td>4 hours(^{40})</td>
<td>US$ 45.00 / test(^{41}) (2012)</td>
</tr>
</tbody>
</table>
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

*Costs are not current PPP adjusted. Costs are current year indicated within the parenthesis.*

Sources:
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance


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Annex 6.1.8: Antibiotic Resistant Streptococcus pneumoniae trends in Europe, 2005 and 2010

These figures represent the burden of antimicrobial resistant *S. pneumoniae* trends in Europe in 2005 and 2010.

**Figure 1**

Proportion of penicillins (R+I) resistant *Streptococcus pneumoniae* isolates in participating countries

This report has been generated from data submitted to TESSy, The European Surveillance System on 2012-07-04. Page: 1 of 1. The report reflects the state of submissions in TESSy as of 2012-07-04 at 16:00. ([www.rivm.nl/earss](http://www.rivm.nl/earss))
Figure 2
Proportion of macrolides (R+I) resistant *Streptococcus pneumoniae* isolates in participating countries

This report has been generated from data submitted to TESSy, The European Surveillance System on 2012-07-04. Page: 1 of 1. The report reflects the state of submissions in TESSy as of 2012-07-04 at 16:00. ([www.rivm.nl/earss](http://www.rivm.nl/earss))


These figures represent the burden of antimicrobial resistant *E. coli* trends in Europe in 2005 and 2010.

**Figure 1**

Proportion of fluoroquinolones (R+I) resistant *Escherichia coli* isolates in participating countries, 2005 and 2010

This report has been generated from data submitted to TESSy, The European Surveillance System on 2012-07-09. Page: 1 of 1. The report reflects the state of submissions in TESSy as of 2012-07-09 at 16:00
Figure 2

Proportion of carbapenem (R+I) resistant *Escherichia coli* isolates in participating countries, 2005 and 2010

This report has been generated from data submitted to TESSy, The European Surveillance System on 2012-07-09. Page: 1 of 1. The report reflects the state of submissions in TESSy as of 2012-07-09 at 16:00
Figure 3

Proportion of third generation cephalosporins (R+I) resistant *Escherichia coli* isolates in participating countries in 2005 and 2010

This report has been generated from data submitted to TESSy, The European Surveillance System on 2012-07-09. Page: 1 of 1. The report reflects the state of submissions in TESSy as of 2012-07-09 at 16:00
Figure 4
Proportion of resistant *Escherichia coli* isolates to third generation cephalosporins in participating countries in 2005 versus 2010

This report has been generated from data submitted to TESSy, The European Surveillance System on 2012-07-04. Page: 1 of 1. The report reflects the state of submissions in TESSy as of 2012-07-04 at 16:00. (www.rivm.nl/earss)

Annex 6.1.10: Meticillin Resistant Staphylococcus aureus trends in Europe, 2005 and 2010

These figures represent the burden of antimicrobial resistant *S. aureus* trends in Europe in 2005 and 2010.

Figure 1

Proportion of meticillin resistant *Staphylococcus aureus* isolates in participating countries, 2005 and 2010

This report has been generated from data submitted to TESSy, The European Surveillance System on 2012-07-04. Page: 1 of 1. The report reflects the state of submissions in TESSy as of 2012-07-04 at 16:00. (www.rivm.nl/earss)
Figure 2

Proportion of meticillin resistant *Staphylococcus aureus* isolates in participating countries in 2005 versus 2010

This report has been generated from data submitted to TESSy, The European Surveillance System on 2012-07-04. Page: 1 of 1. The report reflects the state of submissions in TESSy as of 2012-07-04 at 16:00. (www.rivm.nl/earss)
Figure 3

Trends in the proportion of meticillin resistant *Staphylococcus aureus* in Europe*1*

*Only countries reporting 500 cases or more per year were included.*


These figures represent the burden of antimicrobial resistant *E. faecium* trends in Europe in 2005 and 2010.

Figure 1

Proportion of vancomycin resistant *Enterococcus faecium* isolates in participating countries, 2005 and 2010

This report has been generated from data submitted to TESSy, The European Surveillance System on 2012-07-11. Page: 1 of 1. The report reflects the state of submissions in TESSy as of 2012-07-11 at 16:00.
Figure 2

Proportion of high level gentamicin resistant *Enterococcus faecium* isolates in participating countries, 2005 and 2010

This report has been generated from data submitted to TESSy, The European Surveillance System on 2012-07-11. Page: 1 of 1. The report reflects the state of submissions in TESSy as of 2012-07-11 at 16:00
Figure 3

Proportion of aminopenicillins (R+I) resistant *Enterococcus faecium* isolates in participating countries, 2005 and 2010.

This report has been generated from data submitted to TESSy, The European Surveillance System on 2012-07-11. Page: 1 of 1. The report reflects the state of submissions in TESSy as of 2012-07-11 at 16:00.

Annex 6.1.12: Epidemiological Trends in the USA

These figures represent epidemiological trends of resistant bacterial pathogens and their respective antibiotics throughout the United States. The table provided provides a brief summary of AMR pathogens and their trends in the United States.

Figure 1
Resistance of meticillin-resistant *Staphylococcus aureus* isolates to clindamycin, ciprofloxacin, gentamicin and sulfamethoxazole / trimethoprim in outpatient areas of hospitals, United States, 1999–2006.
Figure 2

*S. aureus* isolates resistant to meticillin
*K. pneumoniae* isolates resistant to ceftazidime or ceftriaxone
*A. baumannii* resistant to imipenem
*P. aeruginosa* resistant to piperacillin
Table 1
Epidemiological Trends in Multidrug – Resistant Organisms in the United States

<table>
<thead>
<tr>
<th>Pathogen(s) of Interest</th>
<th>Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive MRSA</td>
<td>• Increasing proportion of CA-MRSA strain USA300&lt;sup&gt;4, 5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Decreasing rate of bloodstream infections for adults&lt;sup&gt;6, 7&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• No change in rate of bloodstream infections for children&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Overall rate of MRSA infection increasing for children&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vancomycin resistant <em>Enterococcus</em></td>
<td>• Increasing prevalence among patients with inflammatory bowel disease for adults&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Outbreaks in pediatric ICUs with prevalence similar to that of adult ICUs for children&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>C. difficile</td>
<td>• Increasing incidence of healthcare-associated CDI for adults&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Increasing incidence of hospitalizations for children&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gram-negative bacilli ESBL producers</td>
<td>• Increasing prevalence of community-associated clone ST131 for adults&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td><em>K. pneumoniae</em> carbapenemase producers</td>
<td>• Endemic to northeastern U.S.A but incidence increasing nationwide for adults&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>NDM-1 producers</td>
<td>• Five U.S.A cases have been reported to the CDC, all linked to travel or hospitalization in South Asia for adults</td>
</tr>
<tr>
<td></td>
<td>• First case in a pediatric patient reported in Los Angeles in April 2011&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Sources


These figures present the epidemiological trends of various antimicrobial resistant bacterial pathogens throughout various countries and regions in the world.

Figure 1
Rates of extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae* strains amongst Asian countries

![Figure 1](image)

Figure 2*
Trends in the incidence of penicillin-resistant and penicillin-intermediate *S. pneumoniae*, 2000 -2009

*PISP: penicillin-intermediate *S. pneumoniae*
Figure 3**

Trends in the prevalence of the predominant antimicrobial resistant bacteria in China, 2000 to 2009 (a) Gram-positive bacteria; (b) Gram-negative bacteria

**MRSA**: meticillin-resistant *S. aureus*; VRE: vancomycin-resistant enterococcus; PNSP: penicillin non-susceptible *S. pneumoniae*; ESBL (+) EC: extended-spectrum β-lactamase-producing E. coli; CPR-REC: ciprofloxacin-resistant E. coli; IMI-R PA: imipenem-resistant *P. aeruginosa*; IMI-R AB: imipenem-resistant *A. baumannii*.
Figure 4
Prevalence of antimicrobial resistance among respective bacterial pathogen and antibiotics in South Africa

Antibiotic Tested

Antibiotics Tested

Antibiotics Tested
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

Sources:


Annex 6.1.14: Examples of the Economic Impact of Antimicrobial Resistance

This table presents a brief summary of the economic impact of AMR. The economic impact of AMR may be attributed to direct costs, increased labor costs, increased hospital length of stay, additional treatment and or other factors.

<table>
<thead>
<tr>
<th>Study</th>
<th>Pathogen of Interest Description</th>
<th>Treatment costs* (Year)</th>
<th>Hospital LOS</th>
<th>Treatment costs* (Year)</th>
<th>Hospital LOS</th>
<th>Treatment costs* (% change)</th>
<th>Hospital LOS (% change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States¹</td>
<td>Non-AMR versus AMR Several AMR pathogens</td>
<td>US$ 15 104 per patient (2007)</td>
<td>4.7 days per patient</td>
<td>US$ 25 380 per patient (2007)</td>
<td>9 days per patient</td>
<td>US$ 10 276 per patient (+ 40%)</td>
<td>4.3 days per patient (+ 47%)</td>
</tr>
<tr>
<td>United States², Review</td>
<td>MSSA versus MRSA</td>
<td>US$ 15 923 per patient (2004 – 2006)</td>
<td>5 days per patient</td>
<td>US$ 34 657 per patient (2004 – 2006)</td>
<td>15 days per patient</td>
<td>US$ 18 734 per patient (+ 54%)</td>
<td>10 days per patient (+ 66%)</td>
</tr>
<tr>
<td>United States³, Primary</td>
<td>Non-AMR versus AMR Infections</td>
<td>US$ 24 794 per patient (2009)</td>
<td>12.8 days per patient</td>
<td>US$ 53 863 per patient (2009)</td>
<td>23.8 days per patient</td>
<td>US$ 29 069 per patient (+ 54%)</td>
<td>11 days per patient (+ 46%)</td>
</tr>
<tr>
<td>United States⁴, Primary</td>
<td>MSSA versus MRSA Surgical Site Infections</td>
<td>US$ 75 353 per patient (2003)</td>
<td>18.1 days per patient</td>
<td>US$ 99 466 per patient (2003)</td>
<td>23.7 days per patient</td>
<td>US$ 24 113 per patient (+ 25%)</td>
<td>5.6 days per patient (+ 23.6%)</td>
</tr>
<tr>
<td>United States⁵, Primary</td>
<td>Susceptible Gram-negative versus Resistant Gram-negative HAI</td>
<td>US$ 106 293 per patient (2008)</td>
<td>31 days per patient</td>
<td>US$ 144 414 per patient (2008)</td>
<td>36 days per patient</td>
<td>US$ 38 121 per patient (+ 29.3%)**</td>
<td>5 days per patient (+ 23.8%)**</td>
</tr>
<tr>
<td>Location Description</td>
<td>Pathogen of Interest Description</td>
<td>Study</td>
<td>Control</td>
<td>AMR</td>
<td>Additional Burden</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>United States&lt;sup&gt;6&lt;/sup&gt; Primary</td>
<td>Non-AMR versus Vancomycin resistant (Enterococci)</td>
<td>Non-AMR versus Vancomycin resistant (Enterococci)</td>
<td>US$ 31,915 per patient (1993 – 1997)</td>
<td>8.5 days per patient</td>
<td>US$ 52,449 per patient (1993 – 1997)</td>
<td>14.7 days per patient</td>
<td>US$ 20,534 per patient (1993 – 1997)</td>
</tr>
<tr>
<td>Spain&lt;sup&gt;8&lt;/sup&gt; Primary</td>
<td>Non-AMR versus AMR P. aeruginosa</td>
<td>Non-AMR versus AMR P. aeruginosa</td>
<td>€3,983 per patient (2005 – 2006)</td>
<td>25.1 days per patient</td>
<td>€9,597 per patient (2005 – 2006)</td>
<td>39 days per patient</td>
<td>€5,614 per patient (2005 – 2006)</td>
</tr>
<tr>
<td>Spain&lt;sup&gt;9&lt;/sup&gt; Primary</td>
<td>MSSA versus MRSA</td>
<td>MSSA versus MRSA</td>
<td>€9,839.25 per patient (2006)</td>
<td>22.88 days per patient</td>
<td>€11,045 per patient (2006)</td>
<td>24.88 days per patient</td>
<td>€1,205.75 per patient (2006)</td>
</tr>
<tr>
<td>Spain&lt;sup&gt;10&lt;/sup&gt; Primary</td>
<td>Non-AMR versus AMR K. pneumoniae</td>
<td>Non-AMR versus AMR K. pneumoniae</td>
<td>Unavailable</td>
<td>7 days per patient (2009)</td>
<td>Unavailable</td>
<td>36 days per patient (2009)</td>
<td>Unavailable</td>
</tr>
<tr>
<td>United Kingdom Primary</td>
<td>MRSA Outbreak in 32 hospitals</td>
<td>MRSA Outbreak in 32 hospitals</td>
<td>Unavailable</td>
<td>Unavailable</td>
<td>£500,000 total costs (1991 – 1993)</td>
<td>Unavailable</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Europe&lt;sup&gt;12&lt;/sup&gt; Primary</td>
<td>MRSA</td>
<td>MRSA</td>
<td>Unavailable</td>
<td>Unavailable</td>
<td>€44 million total (2007)</td>
<td>255,683 days total</td>
<td>Unavailable</td>
</tr>
</tbody>
</table>
**Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance**

<table>
<thead>
<tr>
<th>Location Description</th>
<th>Pathogen of Interest Description</th>
<th>Treatment costs* (Year)</th>
<th>Hospital LOS</th>
<th>Treatment costs* (Year)</th>
<th>Hospital LOS</th>
<th>Treatment costs* (% change)</th>
<th>Hospital LOS (% change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe&lt;sup&gt;12&lt;/sup&gt; Primary</td>
<td>Cephalosporin-resistant <em>E. coli</em> Third-generation</td>
<td>Unavailable</td>
<td>Unavailable</td>
<td>€18.1 million total (2007)</td>
<td>120 065 days total</td>
<td>Unavailable</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Europe&lt;sup&gt;13&lt;/sup&gt; Surveillance Data</td>
<td>Several AMR pathogens</td>
<td>Unavailable</td>
<td>Unavailable</td>
<td>Unavailable</td>
<td>Unavailable</td>
<td>€910 million per year (2007)</td>
<td>2.5 million days total</td>
</tr>
<tr>
<td>South Africa&lt;sup&gt;14&lt;/sup&gt; &amp; United States Simulation</td>
<td>Non-MDR TB versus MDR TB (Conventional therapy)</td>
<td>US$ 13 000 - 30 000 per patient (1998)</td>
<td>Unavailable</td>
<td>US$ 26 000-60 000 per patient (1998)</td>
<td>Unavailable</td>
<td>US$ 13 000 – 30 000 per patient (+ 50%)</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Israel&lt;sup&gt;15&lt;/sup&gt; Primary</td>
<td>Non-ESBL versus ESBL (Enterobacteriaceae)</td>
<td>US$ 16 877 per patient (2000 – 2003)</td>
<td>5 days per patient</td>
<td>US$ 46 970 per patient (2000 – 2003)</td>
<td>11 days per patient</td>
<td>US$ 30 093 per patient (+ 57%)</td>
<td>6 days per patient (+ 56%)</td>
</tr>
<tr>
<td>Israel&lt;sup&gt;16&lt;/sup&gt; Primary</td>
<td>Non-MDR versus MDR (<em>P. aeruginosa</em>)</td>
<td>Unavailable</td>
<td>10 days per patient (2005)</td>
<td>Unavailable</td>
<td>20 days per patient (2005)</td>
<td>Unavailable</td>
<td>10 days per patient (+ 50%)</td>
</tr>
</tbody>
</table>

* Costs are not current PPP adjusted. Costs are current year indicated within the parenthesis.

** Multivariate analysis
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

Sources:


Annex 6.1.15: Activity Review of the European Commission on Antimicrobial Resistance

This table presents a review of the European Commission’s activities concerning AMR. Activities include projects, publications, consultations, general communication, Eurobarometers, press documents, conferences and collaborative efforts.

<table>
<thead>
<tr>
<th>Projects</th>
<th>Project Title</th>
<th>Years Funded / EC Contribution*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>European Surveillance of Antimicrobial Consumption (ESAC I)²</td>
<td>2001 – 2004 / €533 440</td>
</tr>
<tr>
<td></td>
<td>European Antimicrobial Resistance Surveillance System (EARSS)³</td>
<td>2003 – 2006 / €734 142</td>
</tr>
<tr>
<td></td>
<td>European Committee on Antimicrobial Susceptibility Testing (EUCAST)⁴</td>
<td>2004 -2007 / €355 680</td>
</tr>
<tr>
<td></td>
<td>Antibiotic Resistance and Prescribing in European Children (ARPEC)⁵</td>
<td>2009 – 2012 / €698 994</td>
</tr>
<tr>
<td></td>
<td>European Surveillance of Antimicrobial Consumption (ESAC II)⁶</td>
<td>2004 – 2007 / €880 606</td>
</tr>
<tr>
<td></td>
<td>Improving Patient Safety in Europe (IPSE)⁸</td>
<td>2005 – 2008 / €1 006 916</td>
</tr>
<tr>
<td></td>
<td>Burden of Disease and Resistance in European Nations⁹</td>
<td>2007 – 2010 / €1 139 412</td>
</tr>
<tr>
<td></td>
<td>Development and Dissemination of a School Antibiotic and Hygiene Education Pack and website across Europe (EBUG PACK)⁹</td>
<td>2005 – 2008 / €1 865 358</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Publications</th>
<th>Publication Title</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The European Community Strategy Against Antimicrobial Resistance¹⁰</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td>Research strategy to address the knowledge gaps on the antimicrobial resistance effects of biocides¹¹</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>2nd report from the Commission to the Council on the implementation of the Council Recommendation (2002/77/EC) on the prudent use of antimicrobial agents in human medicine¹²</td>
<td>2010</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consultations</th>
<th>Consultation Title</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stakeholder Consultation on the Transatlantic Task Force on antimicrobial resistance¹⁵</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>Public Consultation on the SCENIHR preliminary report on Effects of the Active Substances in Biocidal Products on Antibiotic Resistance¹⁶</td>
<td>2008</td>
</tr>
<tr>
<td></td>
<td>Call for information on assessment of the Antibiotic Resistance Effects of Biocides¹⁷</td>
<td>2008</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General Communication</th>
<th>Title of Communication</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Communication from the Commission to the European Parliament and the Council - Action plan against the rising threats from Antimicrobial Resistance¹⁸</td>
<td>2011</td>
</tr>
<tr>
<td></td>
<td>Video message from Commissioner Dalli - Conference: combatting Antimicrobial Resistance - Time for joint action¹⁹</td>
<td>2012</td>
</tr>
</tbody>
</table>

6.1-90
### Eurobarometers

<table>
<thead>
<tr>
<th>Title of Eurobarometer</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Les antibiotiques: EUROBAROMETER 58.2&lt;sup&gt;30&lt;/sup&gt;</td>
<td>2003</td>
</tr>
<tr>
<td>Antimicrobial Resistance: EUROBAROMETER 72.5&lt;sup&gt;31&lt;/sup&gt;</td>
<td>2010</td>
</tr>
</tbody>
</table>

### Press Documents

<table>
<thead>
<tr>
<th>Title of Press Release</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU acts to combat resistance to antibiotics&lt;sup&gt;22&lt;/sup&gt;</td>
<td>2006</td>
</tr>
<tr>
<td>Employment, Social Policy, Health and Consumer Affairs Council&lt;sup&gt;23&lt;/sup&gt;</td>
<td>2008</td>
</tr>
<tr>
<td>Androulla Vassiliou, Member of the European Commission, responsible for Health, Europe for Patients, Launch for the &quot;Europe for Patients&quot; Campaign&lt;sup&gt;24&lt;/sup&gt;</td>
<td>2008</td>
</tr>
<tr>
<td>Androulla Vassiliou, Member of the European Commission, responsible for Health, Speech at the launch of the European Antibiotic Awareness Day&lt;sup&gt;25&lt;/sup&gt;</td>
<td>2008</td>
</tr>
<tr>
<td>EU Health Prize for Journalists&lt;sup&gt;26&lt;/sup&gt;</td>
<td>2009</td>
</tr>
<tr>
<td>Launching the first EU health prize for journalists, part of the Europe for Patients campaign&lt;sup&gt;27&lt;/sup&gt;</td>
<td>2009</td>
</tr>
<tr>
<td>Winners of the EU Health Journalism Prize announced at an award ceremony in Brussels&lt;sup&gt;28&lt;/sup&gt;</td>
<td>2009</td>
</tr>
<tr>
<td>Commission paper lays foundations of discussion to tackle the problem of antimicrobial resistance&lt;sup&gt;29&lt;/sup&gt;</td>
<td>2009</td>
</tr>
<tr>
<td>Employment, Social Policy, Health and Consumer Affairs Council&lt;sup&gt;30&lt;/sup&gt;</td>
<td>2009</td>
</tr>
<tr>
<td>Almost 40% of Europeans are aware of the issue of overuse of antibiotics, says a survey&lt;sup&gt;31&lt;/sup&gt;</td>
<td>2009</td>
</tr>
<tr>
<td>World Health Day: fight against antimicrobial resistance must continue on a global scale&lt;sup&gt;32&lt;/sup&gt;</td>
<td>2011</td>
</tr>
<tr>
<td>Action Plan against antimicrobial resistance: Commission unveils 12 concrete actions for the next five years&lt;sup&gt;33&lt;/sup&gt;</td>
<td>2011</td>
</tr>
<tr>
<td>Preparation of Agriculture and Fisheries Council, 18 June 2012 - Antimicrobial Resistance and human health to be discussed&lt;sup&gt;34&lt;/sup&gt;</td>
<td>2012</td>
</tr>
<tr>
<td>EU Health Prize for Journalists - Ben Hirschler and Kate Kelland won 1st prize for their article on antimicrobial resistance. &quot;When the drugs don't work&quot;&lt;sup&gt;35&lt;/sup&gt;</td>
<td>2012</td>
</tr>
</tbody>
</table>

### Conferences

<table>
<thead>
<tr>
<th>Title of Conference</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Microbial Threat to Patient Safety in Europe&lt;sup&gt;36&lt;/sup&gt;</td>
<td>2009</td>
</tr>
<tr>
<td>Conference on Antimicrobial resistance&lt;sup&gt;37&lt;/sup&gt;</td>
<td>2010</td>
</tr>
<tr>
<td>Combating Antimicrobial Resistance - Time for Joint Action&lt;sup&gt;38&lt;/sup&gt;</td>
<td>2012</td>
</tr>
</tbody>
</table>

### Collaborative Efforts

<table>
<thead>
<tr>
<th>Name of Organization</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transatlantic task force on urgent antimicrobial resistance - TATFAR&lt;sup&gt;39&lt;/sup&gt;</td>
<td>2010</td>
</tr>
<tr>
<td>European Centre for Disease Prevention and Control&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Several Efforts</td>
</tr>
<tr>
<td>European Food Safety Authority&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Several Efforts</td>
</tr>
</tbody>
</table>

* EC contributions are not current PPP adjusted. EC contributions are current year as indicated.

**Sources:**


3. European Commission (EC). EARSS - The European antimicrobial resistance surveillance system. [Web Page] [updated 1 March 2012; cited 11 July 2012]; Available from:
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance


## 6.1 Antimicrobial resistance


Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

Annex 6.1.16: Press Release of IMI’s €223.7 Programme to Combat Antibiotic Resistance

This is the press release that describes the launch of IMI’s €223.7 million programme against AMR.

For immediate release

PRESS RELEASE

UNITING EUROPEAN RESEARCHERS IN THE FIGHT AGAINST ANTIMICROBIAL RESISTANCE

IMI LAUNCHES €223.7 MILLION PROGRAMME FOR COMBATING ANTIMICROBIAL RESISTANCE

- Major threat of antibiotic-resistant bacteria causes 25 000 deaths in EU every year.
- IMI offers historic opportunity to speed up research for new antibiotics.
- IMI calls public and private research teams to collaborate and share knowledge.

BRUSSELS, 24 May 2012 – Today the Innovative Medicines Initiative (IMI) is launching a €223.7 million programme which will see leading academics and five major pharmaceutical companies join forces to tackle antimicrobial resistance and to speed up the delivery of much-needed new antibiotics to patients.

Antibiotic resistance poses a major health threat to society and despite the recognised need for new antibiotics, the reality is that only two new classes of antibiotics have been brought to market in the last 40 years. As well as significant scientific challenges and complex regulatory requirements, antibacterial drug development is no longer a financially viable option for a pharmaceutical company as the cost of development is often greater than the potential return on investment. As a result of this, too few companies remain dedicated to addressing this essential societal need. If this situation continues with no intervention, we risk leaving society in a situation where prescribers will have few, if any, therapeutic options to treat bacterial infections. To avoid a real public health challenge it is essential that action be taken now.

IMI’s programme is part of the European Commission’s Action Plan against the rising threats from Antimicrobial Resistance, which was launched in November last year. Today sees the launch of the first set of projects to be funded in this area. Announced today in IMI’s 6th Call for proposals, a joint budget of up to €223.7 million is foreseen for the projects (€109 million of IMI funding + €114.7 million through in kind contributions by participating EFPIA companies).

This major programme on antimicrobials (which is estimated to utilise up to €500 million in funding over the next 7 years) offers an antidote to the fragmentation and lack of incentives which are currently holding back antibiotics research. The initial projects will focus on building and training networks of researchers, facilitating and increasing the exchange of research data, and improving the efficiency of clinical trials on new antibiotics through better laboratory tests and better trial design.

The novel trial design will be applied in clinical trials testing experimental antibiotics to fight particularly resistant bacteria. For instance, trials will target the notorious methicillin-resistant *Staphylococcus aureus* (MRSA), which causes difficult-to-treat infections that are of particular concern in hospitalised patients. In addition, new methods will be explored to improve antibiotic uptake by a specific group of (Gram-negative) resistant bacterial pathogens. Antibiotic uptake is the key challenge in the development of drugs against these life threatening infections.

Commenting on the latest IMI call, Commissioner for Research, Innovation and Science Máire Geoghegan-Quinn said: “Antimicrobial resistance is one of the biggest health challenges we face. It puts lives at risk and severely disrupts hospital services. The research from this initiative will result in much-needed new antimicrobials and improve our arsenal in the fight against dangerous superbugs.”

Richard Bergström, Director-General of EFPIA said: “Our researchers and the scientific community have realised that we can only deal with this urgent threat by working together and pooling our knowledge. IMI is perfectly suited for such open innovation. And by co-funding clinical trials, policy makers in Europe have created a strong incentive for companies and investors to come back to this field of research.”

Michel Goldman, IMI’s Executive Director commented: “This is a historic opportunity for Europe to overcome a public health problem which threatens millions of lives worldwide. For researchers in universities, hospitals and small and medium-sized enterprises it is also a unique opportunity to speed up their research in the area of antimicrobial resistance, as the collaboration will give them access to the knowledge and expertise of the pharmaceutical industry.”
Antimicrobial resistance (AMR) is a major global public health threat and a problem in both humans and animals. Resistance can also spread from animals to humans through the food chain or direct contact. Methicillin-resistant Staphylococcus aureus (MRSA) is a major threat worldwide.

In Europe, 25,000 deaths were reported in 2007 as a result of AMR. This clinical burden is associated with soaring treatment and societal costs, with the cost of AMR being estimated at around €1.5 billion per year in Europe (ECDC/EMEA joint technical report "The bacterial challenge: time to react", 2009).

Despite the recognised need for new antimicrobials for clinical use, the reality is that only two new classes of antibiotics have been brought to market in the last 30 years and many drug developers have left the field.

Key barriers to the development and delivery of effective antibiotics are:
1) Discovery and development of new antibacterial agents is scientifically challenging;
2) Substantial regulatory challenges to the introduction of novel antibacterial agents;
3) Low return on investment relative to other medicines making it an unattractive area for drug developers therefore limiting the future antibiotic pipeline.

About IMI
IMI is the world’s largest public-private partnership in health care. IMI is improving the environment for pharmaceutical innovation in Europe by engaging and supporting networks of industrial and academic experts in collaborative research projects. The European Union contributes €1 billion to the IMI research programme, which is matched by in-kind contributions worth at least another €1 billion from the member companies of the European Federation of Pharmaceutical Industries and Associations (EFPIA).

The Innovative Medicines Initiative is currently funding 30 projects, many of which are already producing impressive results. The projects all address major bottlenecks which will lead to accelerate the development of safer and more effective treatments for patients.

More info: www.imi.europa.eu

Annex 6.1.17: European Commission Funded FP7 Projects on Antimicrobial Resistance

This table provides a list of European Commission funded projects concerning AMR. The contributions listed are not representative of the total budget for each project but rather the contribution amount from the European Commission itself.

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Years Funded / EC Contribution*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multidrug resistance and the evolutionary ecology of insect immunity (EVORESIN)</td>
<td>2010 – 2015 / €1 292 502</td>
</tr>
<tr>
<td>The Integron Cassette Dynamics and the Integrase Gene Expression (ICADIGE)</td>
<td>Unavailable / €193 594</td>
</tr>
<tr>
<td>Preserving old antibiotics for the future : assessment of clinical efficacy by a pharmacokinetic/pharmacodynamic approach to optimize effectiveness and reduce resistance for off-patent antibiotics (AIDA)</td>
<td>2011 - 2016 / €5 999 860</td>
</tr>
<tr>
<td>New antimicrobials (NAM)</td>
<td>2008 – 2012 / €1 425 693</td>
</tr>
<tr>
<td>European multicenter network to evaluate pharmacokinetics, safety and efficacy of Meropenem in neonatal sepsis and meningitis (NEOMERO)</td>
<td>2010 – 2013 / €5 900 000</td>
</tr>
<tr>
<td>Biofilm Alliance (BALI)</td>
<td>2011 – 2016 / €2 999 709</td>
</tr>
<tr>
<td>Knowing the enemy: unravelling a novel regulatory system involved in bacterial virulence (CSS AND VIRULENCE)</td>
<td>2012 – 2016 / €100 000</td>
</tr>
<tr>
<td>Impact of Specific Antibiotic Therapies on the prevalence of hUman host ResistaNt bacteria (SATURN)</td>
<td>2010 – 2014 / €5 999 436</td>
</tr>
<tr>
<td>A comprehensive dissection of pneumococcal-host interactions (PNEUMOPATH)</td>
<td>2009 – 2012 / €2 999 839</td>
</tr>
<tr>
<td>Translational research on combating antimicrobial resistance (TROCAR)</td>
<td>2009 – 2012 / €2 999 444</td>
</tr>
<tr>
<td>Detecting and eliminating bacteria using information technologies (DEBUGIT)</td>
<td>2008 – 2011 / €6 414 915</td>
</tr>
<tr>
<td>The Ecology of Antibiotic Resistance (ARISE)</td>
<td>2012 – 2017 / €1 900 000</td>
</tr>
<tr>
<td>Integrated whole blood acoustophoresis and homogeneous nucleic acid detection cartridge for rapid sepsis diagnostics (ACUSEP)</td>
<td>2010 – 2013 / €2 870 410</td>
</tr>
<tr>
<td>Nano-structured copper coatings, based on Vitolane technology, for antimicrobial applications (CUVITO)</td>
<td>2010 – 2013 / €1 000 000</td>
</tr>
<tr>
<td>Revealing Antibiotic Resistance Evolution (RARE)</td>
<td>2012 – 2016 / €100 000</td>
</tr>
<tr>
<td>An integrated tool-kit for the clinical evaluation of microbial detection and antibiotic susceptibility point-of-care testing technologies (TEMPOTEST-QC)</td>
<td>2010 – 2013 / €3 064 462</td>
</tr>
<tr>
<td>Chips for Life (C4L)</td>
<td>2012 – 2014 / €2 876 300</td>
</tr>
<tr>
<td>A stealth attack tool for preventing clinical drug resistance through a unique self-regenerating surface (BACATTACK)</td>
<td>2012 – 2015 / €2 990 698</td>
</tr>
<tr>
<td>Training and Research AImed at Novel Antibacterial Solutions in Animals and People (TRAIN-ASAP)</td>
<td>2012 – 2015 / €3 515 586</td>
</tr>
</tbody>
</table>
## Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Years Funded / EC Contribution*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification and validation of novel drug targets in Gram-negative bacteria by global search: a trans-system approach (ANTIPATHOGN)</td>
<td>2009 – 2013 / €5 943 961</td>
</tr>
<tr>
<td>Investigating sRNAs as the master on/off switch of <em>Vibrio cholerae</em> virulence (VCSRNAHV)</td>
<td>2009 – 2011 / €50 000</td>
</tr>
<tr>
<td>The effects of antibiotic administration on the emergence and persistence of antibiotic-resistant bacteria in humans and on the composition of the indigenous microorganisms at various body sites (ANTIESDEV)</td>
<td>2009 – 2013 / €5 368 088</td>
</tr>
<tr>
<td>Role of Biotransformation on the Dynamics of Antimicrobial Resistance (ROBODAR)</td>
<td>2011 – 2015 / €100 000</td>
</tr>
<tr>
<td>Novel approaches to bacterial target identification, validation and inhibition (NABATIVI)</td>
<td>2009 – 2013 / €5 506 000</td>
</tr>
<tr>
<td>New high-quality mined nanomaterials mass produced for plastic and wood-plastic nanocomposites (MINANO)</td>
<td>2010 – 2013 / €1 494 447</td>
</tr>
<tr>
<td>The population biology of drug resistance: Key principles for a more sustainable use of drugs (PBDR)</td>
<td>2011 – 2016 / €2 272 403</td>
</tr>
<tr>
<td>Development of new nanocomposites using materials from mining industry (NANOMINING)</td>
<td>2010 – 2013 / €1 800 000</td>
</tr>
<tr>
<td>Tracing antimicrobial peptides and pheromones in amphibian skin (TAPAS)</td>
<td>2008 – 2013 / €900 000</td>
</tr>
<tr>
<td>Membrane-active peptides across disciplines and continents: An integrated approach to find new strategies to fight bacteria, dengue virus and neurodegeneration (MEMPEPACROSS)</td>
<td>2010 – 2014 / €181 800</td>
</tr>
<tr>
<td>Surface functionalization of cellulose matrices using cellulose embedded nano-particles (SURFUNCELL)</td>
<td>2008 – 2012 / €5 472 795</td>
</tr>
<tr>
<td>Microbial translocation across host barriers (MICROTRANS)</td>
<td>2010 – 2015 / €1 499 710</td>
</tr>
<tr>
<td>The role of peptidoglycan in bacterial cell physiology: from bacterial shape to host-microbe interactions (PGNFROMSHAPETOVIR)</td>
<td>2008 – 2013 / €1 650 000</td>
</tr>
<tr>
<td>Preventing community and nosocomial spread and infection with MRSA ST 398 - instruments for accelerated control and integrated risk management of antimicrobial resistance (PILGRIM)</td>
<td>2009 – 2011 / €2 993 824</td>
</tr>
<tr>
<td>Rendering environmental pathogens sensitive to antibiotics prior to infection (RESTORING SENSITIVIT)</td>
<td>2010 – 2014 / €100 000</td>
</tr>
<tr>
<td>Occurrence, distribution and cost of antibiotic resistance in marine sediment bacteria (MARIBACT)</td>
<td>2010 – 2013 / €45 000</td>
</tr>
</tbody>
</table>

* EC contributions are not current PPP adjusted. EC contributions are current year as indicated by initial funding year.
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

Sources:
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance


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Annex 6.1.18: Activity Review of the WHO and Antimicrobial Resistance

This table provides a summary of the activities conducted by the WHO concerning AMR. These efforts and activities include events, publications and policy briefs.

<table>
<thead>
<tr>
<th>Events¹</th>
<th>Title of Event</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The 4th Session of the Codex ad hoc Intergovernmental Task Force on Antimicrobial Resistance</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>2nd meeting of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (WHO – AGISAR)</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>The 3rd Session of the Codex ad hoc Intergovernmental Task Force on Antimicrobial Resistance</td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td>First Meeting of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)</td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td>The 2nd session of the Codex ad hoc Intergovernmental Task Force on Antimicrobial Resistance</td>
<td>2008</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Publications</th>
<th>Title of Publication</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The evolving threat of antimicrobial resistance - Options for action²</td>
<td>2012</td>
</tr>
<tr>
<td></td>
<td>WHO Guidelines on Hand Hygiene in Health Care³</td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td>Medicines Use in Primary Care in Developing Countries: Fact Book summarizing Results from Studies Reported between 1990 and 2006⁵</td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td>Progress report on 2007 Rational Use of Medicines Resolution⁷</td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td>Joint WHO – CDC Conference on Health Laboratory Quality Systems⁸</td>
<td>2008</td>
</tr>
<tr>
<td></td>
<td>Policy and procedures of the WHO/NICO Microbiology External Quality Assessment Programme in Africa⁹</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>How to Improve the Use of Medicines by Consumers¹⁰</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>WHO Operational Package for Assessing, Monitoring and Evaluating Country Pharmaceutical Situations¹¹</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>Secretariat’s report on RUM¹²</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>Progress report: WHA A60/28 – Progress reports on technical and health matters – Improving the containment of antimicrobial resistance¹³</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>Discussion: Report on Progress of Implementation of Resolution on Antimicrobial Resistance adopted by the Assembly in 2005¹⁴</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>Resolution WHA: 10.16¹⁵</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>Developing Pharmacy Practice: A Focus on Patient Care¹⁶</td>
<td>2006</td>
</tr>
<tr>
<td></td>
<td>Resolution WHA: 58.27¹⁵</td>
<td>2005</td>
</tr>
</tbody>
</table>
Policy Briefs | Year
--- | ---
Fact sheet N°255: *Campylobacter* | 2011
Policy Package To Combat Antimicrobial Resistance | 2011
Ensure uninterrupted access to essential medicines of assured quality | 2011
Commit to a comprehensive, financed national plan with accountability and civil society engagement | 2011
Strengthen surveillance and laboratory capacity | 2011
Regulate and promote rational use of medicines, including in animal husbandry and ensure proper patient care | 2011
Reduce use of antimicrobials in food-producing animals | 2011
Enhance infection prevention and control | 2011
Foster innovations and research and development for new tools | 2011

Sources:
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance


### Annex 6.1.19: Examples of Concerted Action Addressing Antimicrobial Resistance in Europe

This table presents a brief summary of concerted efforts to address AMR. These efforts are not inclusive of the efforts that have been taken since 2004.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Location</th>
<th>Initiative Name / Founding Year (Annual Budget / Year)*</th>
<th>Purpose / Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC¹</td>
<td>Europe</td>
<td>ESAC / 2004</td>
<td>Consolidate the continuous collection of comprehensive antibiotic consumption data</td>
</tr>
<tr>
<td>European Parliament, EC²</td>
<td>Europe</td>
<td>EARS-Net / 2004</td>
<td>Perform surveillance in Europe concerning AMR and the health threats it poses to humans</td>
</tr>
<tr>
<td>EMA, CHMP³</td>
<td>Europe</td>
<td>Think-Tank Group / 2004</td>
<td>Encourage stakeholders to casually discuss their perspectives concerning antibiotic R &amp; D, Promote collaboration amongst different stakeholders</td>
</tr>
<tr>
<td>EU, EISA, Others⁴</td>
<td>Europe</td>
<td>Unavailable</td>
<td>Encourage prudent use of antibiotics in animals, Develop and implement best practices for both animal and public health</td>
</tr>
<tr>
<td>EU (27 member states), EEA (three countries)⁵</td>
<td>Europe</td>
<td>ECDC / 2005</td>
<td>Identify, assess and communicate human related health threats, Enhance Europe’s defense system against such threats</td>
</tr>
<tr>
<td>ECDC, EMA, ReAct⁶</td>
<td>Europe</td>
<td>Joint Working Group / 2008 (€46 000 / 2008)</td>
<td>Formally produce a report concerning AMR and the gaps in antibiotic R &amp; D, Propose recommendations to address AMR</td>
</tr>
<tr>
<td>EU, EFPIA⁷</td>
<td>Europe</td>
<td>IMI / 2008</td>
<td>Stimulate drug R &amp; D in Europe through private-public partnerships, Provide the necessary resources for drug R &amp; D</td>
</tr>
<tr>
<td>US Health and Human Services, EC, Others⁸</td>
<td>United States, Europe</td>
<td>TATFAR / 2009, Unknown (€2 billion / 2008 – 2017)</td>
<td>Encourage international collaboration to combat AMR, Formulate recommendations concerning AMR, Provide opportunities for stakeholder collaboration</td>
</tr>
<tr>
<td>EC, ESPID, Others⁹</td>
<td>Europe</td>
<td>ARPEC / 2009</td>
<td>AMR and antibiotic consumption surveillance targeted towards European children, Better understand AMR in the younger population</td>
</tr>
</tbody>
</table>
# Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

<table>
<thead>
<tr>
<th>Participant</th>
<th>Location</th>
<th>Initiative Name / Founding Year (Annual Budget / Year)*</th>
<th>Purpose / Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWAB</td>
<td>Europe</td>
<td>E-learning module / 2010 Unavailable</td>
<td>Develop an e-learning tool to promote continuous education about AMR and prudent antibiotic use</td>
</tr>
<tr>
<td>ECDC</td>
<td>Europe</td>
<td>IMI / 2008</td>
<td>Stimulate antimicrobial drug development</td>
</tr>
<tr>
<td>Professional societies¹⁰</td>
<td></td>
<td></td>
<td>Stimulate antimicrobial development pipeline</td>
</tr>
<tr>
<td>EU</td>
<td>Europe</td>
<td>IMI / 2008</td>
<td>Present collaborative opportunities between the public and private sector</td>
</tr>
<tr>
<td>EFPIA</td>
<td></td>
<td>(€2 billion / 2008 -2017)</td>
<td></td>
</tr>
</tbody>
</table>

*Budget costs are not current PPP adjusted. Budget costs are current year indicated within the parenthesis.

Sources:
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance


# Annex 6.1.20: Examples of Public Private Partnerships Concerning Antimicrobial Resistance

This table presents several examples of public private partnerships that have been formed to address the issue of AMR. These collaborative efforts address AMR from multiple perspectives such as the development of new antimicrobials, diagnostics, open platforms and other efforts.

<table>
<thead>
<tr>
<th>Location</th>
<th>Public Organization</th>
<th>Private Organization</th>
<th>Amount** (Year Issued)</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>Government Affiliates (Benefactor)</td>
<td>Pfizer (Recipient)</td>
<td>€7.95 million (2012)</td>
<td>Develop anti-infectives as an alternative to antibiotics for animals</td>
</tr>
<tr>
<td>Europe</td>
<td>EC* (Benefactor)</td>
<td>Unavailable</td>
<td>€223.7 million (2012)</td>
<td>IMI has issued its annual call for proposals to develop tools against antimicrobial resistance</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>National Government (Benefactor)</td>
<td>Unavailable</td>
<td>£500,000 (2012)</td>
<td>Research relating to extended spectrum β lactamases</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Institute for the Promotion of Innovation by Science and Technology in Flanders (Benefactor)</td>
<td>arGEN-X (Recipient)</td>
<td>€1.3 million (2011)</td>
<td>Research and development of human monoclonal antibodies from the SIMPLE Antibody™ platform</td>
</tr>
<tr>
<td>France</td>
<td>OSEO Innovation (Benefactor)</td>
<td>Deinove (Recipient)</td>
<td>US$ 1.8 million (2010)</td>
<td>Research and development for multidrug-resistant infections</td>
</tr>
<tr>
<td>Europe &amp; United States</td>
<td>TATFAR</td>
<td>Unavailable</td>
<td>Unavailable (2009)</td>
<td>Publicize funding opportunities to EU &amp; United States research communities</td>
</tr>
<tr>
<td>Europe</td>
<td>University Medical Center Groningen &amp; Erasmus University Medical Center</td>
<td>TI Pharma / Pepscan Therapeutics</td>
<td>€600 000 (2012)</td>
<td>Identification of immunodominant cell surface-exposed targets in multidrug-resistant bacterial pathogens</td>
</tr>
<tr>
<td>Europe</td>
<td>Erasmus Medical Center, University Medical Center Groningen &amp; University Medical Center Utrecht</td>
<td>TI Pharma / IQ Corporation, Pepscan Presto BV</td>
<td>Unavailable (2007)</td>
<td>Develop a medicine that attacks MRSA on several fronts</td>
</tr>
</tbody>
</table>
### Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

<table>
<thead>
<tr>
<th>Location</th>
<th>Public Organization</th>
<th>Private Organization</th>
<th>Amount** (Year Issued)</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States⁹</td>
<td>Biomedical Advanced Research and Development Authority (Benefactor)</td>
<td>GlaxoSmithKline (Recipient)</td>
<td>US$ 94 million (2011)</td>
<td>Develop antibiotic against Gram-negative pathogens</td>
</tr>
<tr>
<td>United States¹⁰</td>
<td>NIAID (Benefactor)</td>
<td>Sequella (Recipient)</td>
<td>US$ 3.8 million (2011)</td>
<td>Develop antibiotics for C. diff</td>
</tr>
<tr>
<td>United States¹¹</td>
<td>NIAID (Benefactor)</td>
<td>Novobiotic Pharmaceuticals, LLC (Recipient)</td>
<td>US$ 299,867 (2011)</td>
<td>Research for novel antibiotics concerning AMR</td>
</tr>
<tr>
<td>United States¹¹</td>
<td>NIAID (Benefactor)</td>
<td>Immuvens, Inc. (Recipient)</td>
<td>US$ 151,529 (2011)</td>
<td>Research and development for T cell receptors to prevent MRSA infections</td>
</tr>
<tr>
<td>United States¹¹</td>
<td>NIAID (Benefactor)</td>
<td>Cubrc, Inc. (Recipient)</td>
<td>US$ 828,940 (2011)</td>
<td>Develop broad spectrum antibiotics</td>
</tr>
<tr>
<td>United States¹²</td>
<td>Department of Defense (Benefactor)</td>
<td>Trius Therapeutics (Recipient)</td>
<td>US$ 29.5 million (2010)</td>
<td>Develop new antibiotics against potential bioterroristic microbes</td>
</tr>
<tr>
<td>United States¹³</td>
<td>Department of Health and Human Services (Benefactor)</td>
<td>Achaogen Inc. (Recipient)</td>
<td>US$ 64 million (2010)</td>
<td>Develop antibiotics for the plague and tularemia infections</td>
</tr>
<tr>
<td>India¹⁵</td>
<td>Council for Scientific and Industrial Research (Benefactor)</td>
<td>Samir Brahmachari (Recipient)</td>
<td>US$ 12 million (2008)</td>
<td>Created the Open Source Drug Discovery project to re-annotate the Mycobacterium tuberculosis genome</td>
</tr>
<tr>
<td>World¹⁶</td>
<td>More than 25 groups (Benefactor)</td>
<td>Eli Lilly and Company (Recipient)</td>
<td>US$ 70 million (2003)</td>
<td>Funds activities and issues concerning MDTR</td>
</tr>
</tbody>
</table>

*The Innovative Medicines Initiative (IMI) is composed of the European Commission and the pharmaceutical industry.

** Costs are not current PPP adjusted. Costs are current year indicated within the parenthesis.
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Sources:


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The table and figure below show the number and type of new molecular antibiotics that have been FDA approved from 2004 – 2012.

Table 1

<table>
<thead>
<tr>
<th>Drug Name (FDA Application)</th>
<th>Active Ingredients</th>
<th>Review Classification</th>
<th>Company</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketek (NDA #021144)</td>
<td>Telithromycin</td>
<td>Standard</td>
<td>Sanofi Aventis Us</td>
<td>04/01/2004</td>
</tr>
<tr>
<td>Tindamax (NDA #021618)</td>
<td>Tinidazole</td>
<td>Standard</td>
<td>Mission Pharma</td>
<td>05/17/2004</td>
</tr>
<tr>
<td>Xifaxan (NDA #021361)</td>
<td>Rifaximin</td>
<td>Standard</td>
<td>Salix Pharms</td>
<td>05/25/2004</td>
</tr>
<tr>
<td>Tygacil (NDA #021821)</td>
<td>Tigecycline</td>
<td>Priority</td>
<td>Wyeth Pharms Inc.</td>
<td>06/15/2005</td>
</tr>
<tr>
<td>Altabax (NDA #022055)</td>
<td>Retapamulin</td>
<td>Standard</td>
<td>Glaxo Grp Ltd</td>
<td>04/12/2007</td>
</tr>
<tr>
<td>Doribax (NDA #022106)</td>
<td>Doripenem</td>
<td>Standard</td>
<td>Janssen Pharms</td>
<td>10/12/2007</td>
</tr>
<tr>
<td>Besivance (NDA #022308)</td>
<td>Besifloxacin Hydrochloride</td>
<td>Standard</td>
<td>Bausch And Lomb</td>
<td>05/28/2009</td>
</tr>
<tr>
<td>Vibativ (NDA #022110)</td>
<td>Telavancin Hydrochloride</td>
<td>Standard</td>
<td>Theravance Inc.</td>
<td>09/11/2009</td>
</tr>
<tr>
<td>Teflaro (NDA #200327)</td>
<td>Ceftaroline Fosamil</td>
<td>Standard</td>
<td>Cerexa</td>
<td>10/29/2010</td>
</tr>
<tr>
<td>Dificid (NDA #201699)</td>
<td>Fidaxomicin</td>
<td>Priority</td>
<td>Optimer Pharms</td>
<td>05/27/2011</td>
</tr>
</tbody>
</table>

Figure 1

Annex 6.1.22: Incentives to Encourage Antimicrobial Research and Development

This table presents a list of incentives that may potentially stimulate the antimicrobial development pipeline. Many of these incentives are proposed. Some of these incentives have been successfully implemented.

<table>
<thead>
<tr>
<th>Name of Incentive</th>
<th>Description</th>
<th>Status (Location)</th>
</tr>
</thead>
</table>
| • Special Population Limited Medical Use Drugs\(^1\)                              | • Special approval process for drugs targeted towards the most serious infections where limited therapeutic options are available  
                                                                                     • Marketed towards only affected population  
                                                                                     • Encourage prudent antibiotic use                                                                                                         | Proposed (United States)  |
| • Institute of Medicine Review of FDA Anti-Infective Clinical Trial Design\(^1\)  | • Review FDA’s current review process and make recommendations to improve FDA’s efficiency                                                                                                                 | Proposed (United States)  |
| • Foundation for the National Institutes of Health Initiative\(^1\)              | • FDA seeks external assistance in reviewing evidence concerning the regulatory affairs of antimicrobial clinical trials                                                                                      | Implemented (United States)|
| • GAIN Act\(^1\)                                                                | • Extended patent length of antimicrobial drug                                                                                                                                                    | Implemented (United States)|
| • Push Incentive\(^1,2\)                                                        | Providing value in the early stages of R & D to the industry via:  
                                                                                     • Tax credits  
                                                                                     • Grants  
                                                                                     • Direct Funding  
                                                                                     • PPP                                                                                                                                  | Proposed (Several)       |
| • IMI\(^1\)                                                                     | • Push incentive by encouraging PPPs  
                                                                                     • Provides funding in the early stages                                                                                                         | Implemented (EU)          |
| • Pull Incentive\(^1\)                                                          | • Extending exclusivity periods                                                                                                                                                                           | Proposed (Several)        |
| • Centralized specimen biorepository\(^1,2\)                                    | • Storage for clinical specimens to spur diagnostic R & D  
                                                                                     • Housing specimens to eliminate the redundancy for several stakeholders to collect the same types of specimens s                                                                 | Proposed (Several)        |
| • Cancer Human Bio-Bank by the National Cancer Institute\(^1\)                  | • Flexible and alternative clinical trial design                                                                                                                                                    | Implemented (United States)|
| • Continuous review of legal framework\(^3\)                                    | • Discover supporting data that would standardize optimal antibiotic use                                                                                                                                | Implemented (United States)|
| • Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance\(^3\) |                                                                                                                                     |                           |
### Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

<table>
<thead>
<tr>
<th>Name of Incentive</th>
<th>Description</th>
<th>Status (Location)</th>
</tr>
</thead>
</table>
| **Open Source**  | Open source technology that provides non-proprietary methods for drug discovery  
| (India's Open Source Drug Discovery)³ | Participants are rewarded accordingly | Proposed (Several)  
| | Implemented (India) | |
| **Needs driven approach**  | Utilize the target product profile to focus on the needs in settings where resources are lacking | Proposed (Several)  
| **Neglected Diseases Initiative (DNDi)², ³** | | Implemented (Several) |
| **The Urgent Need: Regenerating Antibacterial Drug Discovery and Development⁴**  | Expanding pharmacokinetics & pharmacodynamics to expedite antimicrobial development  
| | Special / alternative review process for antimicrobials  
| | Conditional approval  
| | Extended use of surrogate markets | Proposed (United Kingdom) |
| **Strategies to Address Antimicrobial Resistance Act⁵**  | Formally create a specialized team within the Department of Health and Human Services addressing AMR | Proposed (United States) |
| **Antibiotic Innovation and Conservation Fee⁵**  | Antibiotic fees in which 75% of proceeds would go towards antibiotic R & D and 25% towards stewardship programmes | Proposed (United States) |
| **Improving lead identification and chemistry**  | Broad access to compound collections  
| **Partnership: Rare and Neglected Diseases Program and Rapid Access to Intervention Development Program²** | Access to the proprietary information behind these collections | Proposed (Several)  
| | Implemented (United States) | |
| **South-South platforms**  | Clinical trials to be conducted in Southern countries | Proposed (Several)  
| **European and Developing Countries Clinical Trials Partnership**  | | Implemented (Europe / Africa) |
| **African Network for Drugs and Diagnostics Innovation²**  | | Implemented (Several) |
| **Separate incentives from drug sales⁶**  | Provide incentives that separate the financial return from the sales of the drug  
| | Discourage monopoly protection on antibiotics | Proposed (Several) |
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Sources:


These tables present a summary of the antibiotic development pipeline as of 2011. These tables demonstrate the lack of antibiotics within the R & D pipeline. Moreover, these tables show that the development pipeline for Gram–negative pathogens is incredibly limited.

Table 1

<table>
<thead>
<tr>
<th>Compound name</th>
<th>Chemical class</th>
<th>Target</th>
<th>Dev. stage</th>
<th>Main indication</th>
<th>Route</th>
<th>Developing company</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC-3205</td>
<td>Pleuromutilin</td>
<td>Ribosome</td>
<td>Phase 1</td>
<td>–</td>
<td>Oral</td>
<td>Nabriva</td>
</tr>
<tr>
<td>BC-7013</td>
<td>Pleuromutilin</td>
<td>Ribosome</td>
<td>Phase 1</td>
<td>–</td>
<td>Topical</td>
<td>Nabriva</td>
</tr>
<tr>
<td>CG400549</td>
<td>Triclosan</td>
<td>FabI</td>
<td>Phase 1</td>
<td>–</td>
<td>iv</td>
<td>Crystal Genomics</td>
</tr>
<tr>
<td>AF-1252</td>
<td>New lead</td>
<td>FabI</td>
<td>Phase 1</td>
<td>–</td>
<td>iv</td>
<td>Affininium</td>
</tr>
<tr>
<td>FAB-001</td>
<td>Triclosan</td>
<td>FabI</td>
<td>Phase 1</td>
<td>–</td>
<td>iv</td>
<td>FAB Pharma</td>
</tr>
<tr>
<td>Delafloxacin</td>
<td>Fluoroquinolone</td>
<td>DNA gyrase</td>
<td>Phase 2</td>
<td>cSSSI/CAP</td>
<td>iv/oral</td>
<td>Rib-X</td>
</tr>
<tr>
<td>TP-434</td>
<td>Tetracycline</td>
<td>Ribosome</td>
<td>Phase 2</td>
<td>cIAI</td>
<td>iv/oral</td>
<td>Tetraphase</td>
</tr>
<tr>
<td>BC-3781</td>
<td>Pleuromutilin</td>
<td>Ribosome</td>
<td>Phase 2</td>
<td>cSSSI</td>
<td>iv/oral</td>
<td>Nabriva</td>
</tr>
<tr>
<td>Solithromycin</td>
<td>Ketolide</td>
<td>Ribosome</td>
<td>Phase 2</td>
<td>CAP</td>
<td>iv/oral</td>
<td>Gempa</td>
</tr>
<tr>
<td>ACHN-490</td>
<td>Aminoglycoside</td>
<td>Ribosome</td>
<td>Phase 2</td>
<td>UTI/AP</td>
<td>iv</td>
<td>Achaogen</td>
</tr>
<tr>
<td>CB-183,315</td>
<td>Lipopeptide</td>
<td>Membrane</td>
<td>Phase 2</td>
<td>CDAD</td>
<td>Oral</td>
<td>Cubist</td>
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<tr>
<td>Ramoplanin</td>
<td>Lipoglycodepsipeptide</td>
<td>Cell wall</td>
<td>Phase 2</td>
<td>CDAD</td>
<td>Oral</td>
<td>Nanotheartectics</td>
</tr>
<tr>
<td>GSK-1322322</td>
<td>New lead</td>
<td>PDF</td>
<td>Phase 2</td>
<td>cSSSI</td>
<td>iv</td>
<td>GSK</td>
</tr>
<tr>
<td>JNJ-Q02</td>
<td>Fluoroquinolone</td>
<td>DNA gyrase</td>
<td>Phase 2/3</td>
<td>CAP/abSSSI</td>
<td>iv/oral</td>
<td>Furiex</td>
</tr>
<tr>
<td>Nemonoxacin</td>
<td>Quinolone</td>
<td>DNA gyrase</td>
<td>Phase 2/3</td>
<td>CAP/DFI</td>
<td>Oral</td>
<td>TaiGen/Warner</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>Glycopeptides</td>
<td>Cell wall</td>
<td>Phase 3</td>
<td>abSSSI</td>
<td>iv</td>
<td>The Medicine Co</td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>Glycopeptides</td>
<td>Cell wall</td>
<td>Phase 3</td>
<td>abSSSI</td>
<td>iv</td>
<td>Durata</td>
</tr>
<tr>
<td>Torezolid</td>
<td>Oxazolidinone</td>
<td>Ribosome</td>
<td>Phase 3</td>
<td>SSI</td>
<td>iv/oral</td>
<td>Trius</td>
</tr>
<tr>
<td>Radezolid</td>
<td>Oxazolidinone</td>
<td>Ribosome</td>
<td>Phase 3</td>
<td>SSI/CAP</td>
<td>iv/oral</td>
<td>Rib-X</td>
</tr>
<tr>
<td>Amadacycline</td>
<td>Tetracycline</td>
<td>Ribosome</td>
<td>Phase 3</td>
<td>cSSSI/CAP</td>
<td>iv/oral</td>
<td>Paratek</td>
</tr>
<tr>
<td>Cethromycin</td>
<td>Ketolide</td>
<td>Ribosome</td>
<td>Phase 3</td>
<td>CAP</td>
<td>Oral</td>
<td>Advanced Life Sciences</td>
</tr>
</tbody>
</table>

*Abbreviations: abSSSI: acute bacterial skin and skin structure infection; cSSSI: complicated skin and skin structure infection; CAP: community acquired pneumonia; DFI: diabetic foot infection; cIAI: complicated intra-abdominal infection; UTI: urinary tract infection; AP: acute pyelonephritis; CDAD: Clostridium difficile associated diarrhea.*
### Table 2

Antibacterial compounds in development

<table>
<thead>
<tr>
<th>Glycopeptide</th>
<th>Dalbavancin</th>
<th>Gram-positive (excluding VRE)</th>
<th>IV; once-weekly</th>
<th>cSSTi</th>
<th>Phase III</th>
<th>Durata Therapeutics (Pfizer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycopeptide</td>
<td>Telavancin</td>
<td>Gram-positive (excluding VRE)</td>
<td>IV</td>
<td>cSSTi and HAP</td>
<td>Marketed for SSTi in USA; HAP approval stalled at FDA</td>
<td>Astellas (Theravance)</td>
</tr>
<tr>
<td>Glycopeptide</td>
<td>Ortavancin</td>
<td>Gram-positive (including VRE)</td>
<td>IV; single dose treatment</td>
<td>cSSTi</td>
<td>Phase III</td>
<td>The Medicines Company (Lilly)</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>Ceftaroline</td>
<td>Gram-positive and gram-negative excluding ESBLs etc. and non-fermenters</td>
<td>IV</td>
<td>SSTi, CAP</td>
<td>Pre-registration</td>
<td>Forest (Cerexa)</td>
</tr>
<tr>
<td>Glycopeptide-cephalosporin hybrid</td>
<td>TD-1792</td>
<td>Gram-positive</td>
<td>IV</td>
<td>SSTi, HAP</td>
<td>Phase IIa</td>
<td>Theravance</td>
</tr>
<tr>
<td>Ketolide</td>
<td>Ceftromycyn</td>
<td>Gram-positive and respiratory tract infection pathogens</td>
<td>Oral and IV</td>
<td>Community-acquired RTIs biothreat pathogens</td>
<td>Phase III</td>
<td>Advanced Life Sciences (Abbott)</td>
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<tr>
<td>Ketolide</td>
<td>EDP-420</td>
<td>Gram-positive and respiratory tract infection pathogens</td>
<td>Oral</td>
<td>Community-acquired RTIs</td>
<td>Phase II/III</td>
<td>Enanta (Shionogi)</td>
</tr>
<tr>
<td>Fluoroketolide</td>
<td>Solithromycin</td>
<td>Gram-positive and respiratory tract infection pathogens</td>
<td>IV/oral</td>
<td>Community-acquired RTIs biothreat pathogens</td>
<td>Phase I/II</td>
<td>Cempra (Optimer)</td>
</tr>
<tr>
<td>Pleuromutilin</td>
<td>BC-3781</td>
<td>Gram-positive and respiratory tract infection pathogens</td>
<td>Oral IV</td>
<td>Community-acquired RTis and SSTis</td>
<td>Phase II Preclinical</td>
<td>Nabriva</td>
</tr>
<tr>
<td>Peptide deformylase inhibitor (new class)</td>
<td>GSK1322322</td>
<td>Gram-positive and Respiratory tract pathogens</td>
<td>Oral</td>
<td>Community-acquired RTis and SSTis</td>
<td>Phase I</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Oxyzolidinone</td>
<td>Torezolid</td>
<td>Gram-positive (including linezolid- and daptomycin resistant strains)</td>
<td>IV/oral</td>
<td>cSSTi</td>
<td>Phase IIa</td>
<td>Titus (DongA)</td>
</tr>
<tr>
<td>Oxyzolidinone</td>
<td>Radezolid</td>
<td>Gram-positive (including linezolid- and daptomycin resistant strains)</td>
<td>IV/oral</td>
<td>SSTi</td>
<td>Phase IIa</td>
<td>Rib-X</td>
</tr>
<tr>
<td>Oxyzolidinone</td>
<td>PNJ-100480</td>
<td>TB</td>
<td>Oral</td>
<td>TB</td>
<td>Phase I</td>
<td>Pfizer</td>
</tr>
<tr>
<td>FabI Inhibitor (new class)</td>
<td>AFN-1252</td>
<td>Staphylococci</td>
<td>Oral</td>
<td>Staph infections</td>
<td>Phase I</td>
<td>Affinium</td>
</tr>
<tr>
<td>FabI Inhibitor (new class)</td>
<td>MUT056399</td>
<td>Staphylococci</td>
<td>IV</td>
<td>Staph infections</td>
<td>Phase I</td>
<td>FAB Pharma</td>
</tr>
<tr>
<td>Aminomethylcycline (tetacycline)</td>
<td>PTK0796</td>
<td>Gram-positive, RTI and SSTi pathogens</td>
<td>IV/oral</td>
<td>cSSTi, CAP</td>
<td>Phase III</td>
<td>Novartis (Paratek)</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>Delafloxacin</td>
<td>Broad-spectrum including fluoroquinolone-resistant MRSA</td>
<td>IV/oral</td>
<td>cSSTi,</td>
<td>Phase III</td>
<td>Rib-X</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>Finafloxacin</td>
<td>Broad-spectrum, enhanced activity at acid pH</td>
<td>IV/oral</td>
<td></td>
<td></td>
<td>Merlion</td>
</tr>
</tbody>
</table>
Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug Name</th>
<th>Pathogen</th>
<th>Route</th>
<th>Company</th>
<th>Phase</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolone</td>
<td>JNJ-Q2</td>
<td>Enhanced gram-positive activity</td>
<td>IV/oral</td>
<td>Phase I</td>
<td>Jisj</td>
<td></td>
</tr>
<tr>
<td>Fluorocycline (tetracycline)</td>
<td>TP-434</td>
<td>Broad gram-positive and anaerobic activity including <em>Acinetobacter</em> but not <em>P. aeruginosa</em>, less active versus <em>Proteus</em> and some <em>K. pneumoniae</em></td>
<td>IV/oral</td>
<td>Tetraphase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>ACHN-490</td>
<td>MDR enterobacteriae and <em>S. aureus</em>, including aminoglycoside-resistant and metallo-β-lactamase producers</td>
<td>IV</td>
<td>Phase I</td>
<td>Achaogen</td>
<td></td>
</tr>
<tr>
<td>Leucyl-tRNA synthase inhibitor (new class)</td>
<td>CSK2251052</td>
<td>MDR enterobacteriae and <em>P. aeruginosa</em></td>
<td>IV</td>
<td>Anacor/GSK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>CXA-101</td>
<td>MDR <em>P. aeruginosa</em> and susceptible enterobacteriae</td>
<td>IV</td>
<td>Phase II</td>
<td>Cubist</td>
<td></td>
</tr>
<tr>
<td>Penicillin/β-lactamase-inhibitor (new class)</td>
<td>CXA-101/tazobactam (CXA-201)</td>
<td>MDR <em>P. aeruginosa</em> and enterobacteriae, excluding metallo-β-lactamases</td>
<td>IV</td>
<td>Phase I</td>
<td>Cubist</td>
<td></td>
</tr>
<tr>
<td>Non-β-lactam β-lactamase-inhibitor (new class)</td>
<td>NXL104</td>
<td>Class A, C and some class D β-lactamases, including OXA-48</td>
<td>IV</td>
<td>AstraZeneca (Novexel)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalosporin/β-lactamase-inhibitor</td>
<td>Cefirololine/ NXL104</td>
<td>MDR enterobacteriae, excluding metallo-β-lactamases</td>
<td>IV</td>
<td>Phase II ready</td>
<td>AstraZeneca/Forest</td>
<td></td>
</tr>
<tr>
<td>Cephalosporin/β-lactamase-inhibitor</td>
<td>Ceftazidime/ NXL104</td>
<td>MDR <em>P. aeruginosa</em> and enterobacteriae, excluding metallo-β-lactamases</td>
<td>IV</td>
<td>Phase III ready</td>
<td>AstraZeneca/Forest</td>
<td></td>
</tr>
<tr>
<td>Non-β-lactam β-lactamase-inhibitor (new class)</td>
<td>MK-7655</td>
<td>Class A and C β-lactamases</td>
<td>IV</td>
<td>Merck &amp; Co</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenem/β-lactamase-inhibitor</td>
<td>Imipenem/ MK-7655</td>
<td>MDR <em>P. aeruginosa</em> and enterobacteriae, excluding metallo-β-lactamases; <em>Acinetobacter</em></td>
<td>IV</td>
<td>Phase II ready</td>
<td>Merck &amp; Co</td>
<td></td>
</tr>
<tr>
<td>Sulfactam (siderophore monobactam)</td>
<td>BAL30072</td>
<td>MDR <em>P. aeruginosa</em> <em>Acinetobacter</em> including metallo-β-lactamases and enterobacteriae</td>
<td>IV</td>
<td>Preclinical</td>
<td>Basilea</td>
<td></td>
</tr>
<tr>
<td>Monobactam/ carbapenem</td>
<td>BAL30072/ meropenem</td>
<td>Most MDR gram-negatives including resistant Enterobacteriaceae and anaerobes</td>
<td>IV</td>
<td>Preclinical</td>
<td>Basilea</td>
<td></td>
</tr>
<tr>
<td>Monocarban (siderophore monobactam)</td>
<td>MC-1</td>
<td>MDR <em>P. aeruginosa</em> including metallo-β-lactamases <em>S. maltophilia</em> and enterobacteriae</td>
<td>IV</td>
<td>Preclinical</td>
<td>Pfizer</td>
<td></td>
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</tbody>
</table>
Sources:


This chart provides a summary of the FDA approved vaccines for distribution within the US from 2005 – 2012. As shown, many of these vaccines do not address AMR pathogens, especially Gram–negative pathogens.

<table>
<thead>
<tr>
<th>Year Licensed*</th>
<th>Trade Name</th>
<th>Indication</th>
<th>Bacteria of Interest</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>Adacel</td>
<td>Booster immunization against tetanus, diphtheria and pertussis as a single dose in individuals 11 through 64 years of age.</td>
<td>C. diphtheriae, C. tetani, &amp; B. pertussis</td>
<td>Sanofi Pasteur, Ltd</td>
</tr>
<tr>
<td>2005</td>
<td>Boostrix</td>
<td>Booster immunization against tetanus, diphtheria and pertussis as a single dose in individuals 10 years of age and older.</td>
<td>C. diphtheriae, C. tetani, &amp; B. pertussis</td>
<td>GlaxoSmithKline Biologicals</td>
</tr>
<tr>
<td>2007</td>
<td>Menactra</td>
<td>Active immunization of individuals 9 months through 55 years of age for the prevention of invasive meningococcal disease caused by N. meningitidis serogroups A, C, Y and W-135.</td>
<td>N. meningitidis serogroups A, C, Y &amp; W-135</td>
<td>Sanofi Pasteur, Inc</td>
</tr>
<tr>
<td>2008</td>
<td>KINRIX</td>
<td>Active immunization against diphtheria, tetanus, pertussis and poliomyelitis as the fifth dose in the diphtheria, tetanus and acellular pertussis (DTaP) vaccine series and the fourth dose in the inactivated poliovirus vaccine (IPV) series in children 4 through 6 years of age whose previous DTaP vaccine doses have been with INFANRIX® and/or PEDIARIX® for the first three doses and INFANRIX® for the fourth dose.</td>
<td>C. diphtheriae, C. tetani, &amp; B. pertussis</td>
<td>GlaxoSmithKline Biologicals</td>
</tr>
<tr>
<td>2008</td>
<td>Pentacel</td>
<td>For active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease caused by H. influenzae type b when administered to children 6 weeks through 4 years old.</td>
<td>C. diphtheriae, C. tetani, B. pertussis &amp; H. influenzae type b</td>
<td>Sanofi Pasteur Limited</td>
</tr>
<tr>
<td>2008</td>
<td>TENIVAC</td>
<td>Use in adults 60 years of age and older for active immunization for the prevention of tetanus and diphtheria.</td>
<td>C. diphtheriae &amp; C. tetani</td>
<td>Sanofi Pasteur, Ltd</td>
</tr>
<tr>
<td>2008</td>
<td>Hiberix</td>
<td>For active immunization for the prevention of invasive disease caused by H. influenzae type b when administered as a booster dose in children 15 months through 4 years old.</td>
<td>H. influenzae type b</td>
<td>GlaxoSmithKline Biologicals, S.A.</td>
</tr>
</tbody>
</table>
## Update on 2004 Background Paper, BP 6.1 Antimicrobial resistance

<table>
<thead>
<tr>
<th>Year Licensed*</th>
<th>Trade Name</th>
<th>Indication</th>
<th>Bacteria of Interest</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Menveo</td>
<td>For active immunization to prevent invasive meningococcal disease caused by <em>N. meningitidis</em> serogroups A, C, Y and W-135 when administered to individuals 2 through 55 years of age.</td>
<td><em>N. meningitidis</em> serogroups A, C, Y &amp; W-135</td>
<td>Novartis Vaccines and Diagnostics, Inc</td>
</tr>
<tr>
<td>2012</td>
<td>MenHibrix</td>
<td>Indicated for active immunization to prevent invasive disease caused by <em>N. meningitidis</em> serogroups C and Y and <em>H. influenzae</em> type b for children 6 weeks of age through 18 months of age.</td>
<td><em>N. meningitidis</em> serogroups C and Y &amp; <em>H. influenzae</em> type b</td>
<td>GlaxoSmithKline Biologicals</td>
</tr>
</tbody>
</table>

*The year licensed is according to the most recent modification(s) of the:
  - Components of the vaccine
  - Indication

*This search was completed on 28 June 2012 via [http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm)
  (Updated 20 June 2012)
Update on 2004 Background Paper

Background Paper 6.2
Pandemic Influenza

By Vicki L. Wong, MPH
Boston University School of Public Health

21 April 2013
Update on 2004 Background Paper, BP 6.2 Pandemic Influenza

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Update on 2004 Background Paper, BP 6.2 Pandemic Influenza

Executive Summary

The threat of an influenza pandemic and its potential impact on health, social and economic conditions has long been recognized by the WHO and EU. The 2004 pandemic influenza background paper from the Priority Medicines Report highlighted several priority research areas including: low vaccine uptake and production capacity; expensive antiviral agents; and the need for increased EU funding towards influenza virus, vaccine and antiviral agents research. These research areas were identified as critical in the ability of Europe to respond to the next influenza pandemic.

In April 2009, a new influenza A (H1N1) virus emerged in Mexico and the United States. The virus quickly spread worldwide and was officially declared a global epidemic, the first one of the 21st century. Box 6.2.1 outlines a generally accepted understanding of the 2009 influenza pandemic.

Box 6.2.1: General summary of the 2009 H1N1 influenza pandemic

- The pandemic virus was less virulent than was anticipated in many pandemic preparedness plans.
- Highest disease incidence was in 0-4 year old age group although cumulative incidence of infection was in school-aged children.
- Deaths associated with virologically confirmed influenza were lower than the number of excess deaths typically associated with interpandemic influenza.
- Majority of deaths occurred at a younger age than typically seen with seasonal influenza.
- Although older adults had lower morbidity rates, this population had the highest case fatality ratio.
- Pregnant and post-partum women and indigenous populations, recognized risk groups during interpandemic influenza seasons, were also at increased risk for a severe outcome.
- Intensive care units were burdened by the increase in the number of young adults with severe disease due to the pandemic virus, though this was not experienced in all countries.
- Although the 2009 pandemic influenza A (H1N1) seems to have replaced all seasonal influenza A (H1N1) subtypes, it has not replaced influenza A (H3N2) subtypes which have continued to co-circulate as a small proportion of all types influenza A viruses. This is in contrast to previous pandemics where the pandemic virus replaced all influenza A viruses.
- Unlike the pattern for interpandemic influenza A (H1N1) viruses, no significant neuraminidase resistance of the 2009 pandemic influenza A (H1N1) has been reported to date, although variants with reduced oseltamivir sensitivity may be emerging in the Asia-Pacific region.
Although the 2009 H1N1 influenza virus was only moderately severe, it revealed the many areas surrounding the prevention and mitigation of influenza that require continued focus and research. The pathogenic and transmissibility mechanisms of the influenza virus are not yet fully understood. Improvements in the current methodologies of assessing the health and economic burdens are needed. Global and country surveillance systems need modification to more accurately estimate morbidity and mortality. Moreover, barriers to immunization should be identified and addressed. Despite increased global vaccine production capacity between 2006 and 2009, the number of available pandemic vaccine was insufficient during the 2009 influenza pandemic. However, increasing vaccine production capacity is not enough as universal access to these vaccines must also be assured during a pandemic. Vaccine effectiveness studies should be conducted in order to determine recommendations for vaccine use by specific age and risk groups. Strengthening global and country vaccine coverage monitoring systems will provide further insight into vaccine provision and the impact of immunization policies.

Current influenza control strategies include vaccination and the use of antiviral agents. The development of safe and effective vaccines with cross-strain and long-lasting protection against influenza will be imperative to reducing influenza-related morbidity and mortality. Antiviral therapy remains unchanged since 2004. Given the likelihood that influenza virus strains will confer resistance to monotherapy, novel antiviral agents will need to have broad spectrum activity and improved pharmacological profiles. During the 2009 H1N1 pandemic, rapid influenza diagnostic tests (RIDTs) had not been developed to specifically detect influenza A (H1N1). Numerous RIDTs have since been developed however comprehensive studies should be conducted on their diagnostic accuracy and cost-effectiveness.

Over the past 10 years, the EU has established a wide range of influenza-related surveillance networks, consortiums and research projects. These efforts are critical as pandemic preparedness is a monumental task that requires diligence, commitment and cooperation at the national and international levels in order to ensure adequate capacity in responding to the next influenza pandemic.
1. The Influenza Virus

1.1 Biological properties

The influenza viruses belong to the family Orthomyxoviridae and are classified into three types (A, B and C) according to antigenic differences among their nucleoprotein (NP) and matrix (M) proteins. Influenza A viruses circulate naturally in a global avian reservoir; however, some viral strains have crossed the species barrier establishing in pigs, horses and most notably, infecting humans. Influenza B viruses almost exclusively infect humans although they present a less pathogenic profile than influenza A viruses. Influenza C viruses are rare and have been known to infect humans, dogs and swine.

Influenza A viruses are enveloped negative-stranded RNA viruses comprised of eight gene segments that encode 10 proteins: hemagglutinin (HA), neuraminidase (NA), matrix proteins (M1 and M2), nonstructural proteins (NS1 and NS2), the nucleocapsid (NP), and the three polymerases (PB1, PB2 and PA). Influenza A viruses are further classified based on the rod-shaped HA trimer and mushroom-shaped NA tetramer antigens, two glycoproteins that serve as prominent features of the virus envelope. These two proteins are critical for the infection of susceptible cells of a host as the HA proteins facilitate viral attachment and the NA proteins are responsible for viral release. Together the HA and NA antigens elicit immune responses that prevent infection or reduce viral replication, respectively. Until recently, a total of 16 HA subtypes (H1-H16) and 9 NA subtypes (N1-N9) had been identified in avian hosts. Of the 144 total possible combinations, only three combinations of the HA/NA subtypes have been established as human influenza (H1N1, H2N2, and H3N2). More recently, H7 and H9 subtypes have been known to cause infection in humans.

RNA polymerases lack the proofreading ability of DNA polymerases resulting in high mutation rates, specifically point mutations of the HA or NA antigens. These mutations from its predecessors, known as “antigenic drift”, can lead to new, distinct antigenic variants and is well characterized in human and poultry influenza viruses. Further research on the magnitude of antigenic difference among variants and specific amino acids directly related to antigenic difference may provide insight on how best to develop and utilize vaccinations as a control strategy. Additionally, the eight individual gene segments of the influenza virus allows for genetic reassortment when two influenza viruses infect the same cell. The host animal consequently serves as a “mixing vessel” and the result is an “antigenic shift” with generations of novel influenza viruses acquiring characteristics of both parent viruses. These two mechanisms permit a genetic diversity among influenza viruses that describe the recurring seasonal influenza epidemics of varying pattern and severity as well as the continuing risk of the emergence of a novel pandemic strain.

1.2 Pathogenicity and transmissibility

Avian influenza viruses are divided into highly pathogenic avian influenza (HP) or low pathogenic avian influenza (LP). The distinction between LP and HP avian influenza is their local versus system replication, respectively. Although multiple studies have demonstrated that the virulence of influenza viruses is polygenic, the complete pathogenic mechanism is not yet fully understood.
In 1997, avian H5N1 influenza appeared in the poultry markets of Hong Kong, infecting 18 humans, six of whom died.\(^2\) However, avian influenza viruses do not efficiently infect and replicate in humans therefore host range restriction was disabled by that particular virus strain.\(^2\) The viral and host factors that determine host range restriction are poorly understood; determining the genetic mechanism that confers interspecies transmissibility could provide an important marker for identifying virus strains capable of human transmission.

### 1.3 Risk for a pandemic

The 1997 H5N1 influenza outbreak in Hong Kong was the first known incidence of a purely avian virus causing severe human disease and death.\(^2\) By 2006, the H5N1 virus had spread across 54 countries spanning three continents.\(^2\) Interestingly, as of 2013, despite large outbreaks and considerable human exposure to the H5N1 virus since 2003, only 615 confirmed cases have been reported.\(^5\) The inefficient human-to-human transmission is the only factor inhibiting H5N1 from transforming a zoonotic disease to be a pandemic virus. In the presence of the correct combination of genetic modifications, there is a substantial possibility for the enormous replicative capacity of a highly mutable virus, such as H5N1, to emerge as a pandemic virus. The potentially devastating health and economic impacts of a pandemic gives cause for further research into the ecology, virology, and pathogenesis of the avian influenza viruses.

### 2. Interpandemic Influenza Disease Burden

Every year, influenza accounts for large numbers of cases and deaths worldwide.\(^6\) The number of cases in any given year depends largely on the infection rate, morbidity and mortality rates associated with that particular influenza infection as well as the size of the population affected.\(^7\) Weather conditions, especially humidity and temperature are also factors that influence virus survival and transmission.\(^8\) The populations typically most affected are the elderly and those with high-risk medical conditions.\(^6\) The World Health Organization (WHO) estimates that annual influenza epidemics result in approximately three to five million cases of severe illness and 250 000-500 000 deaths globally.\(^8,9\)

#### 2.1 Excess influenza-associated morbidity and mortality

Estimating the health and economic burdens of influenza is essential to framing influenza preventions and control policies; however, accurately documenting the burden of influenza is often compromised by several factors. Ambulatory and hospitalized adults tend to exhibit different clinical presentations and virological courses. Patients are also admitted to the hospital with a wide range of diagnoses, including non-respiratory diagnoses. Symptoms typical of influenza such as fever, myalgia, sore throat, and cough may be subdued or absent at the time of admission, resulting in some influenza cases going undiagnosed. Even when influenza symptoms are recognized as such, only a small percentage of cases are virologically confirmed. Still, these diagnostic tests are never 100% sensitive or specific. Finally, morbidity resulting from influenza infection can be complicated by additional medical conditions, such as acute myocardial infections, secondary bacterial infections, pulmonary disease, cardiovascular disease, diabetes, and compromised immunity.\(^6,10,11\)
As stated in the original background paper, few studies had been conducted on estimates of excess influenza-associated mortality in European countries. Studies have since underlined varying methods divided into two broad categories that have been used to estimate the burden of influenza. One such method is to calculate excess outcomes including general practice consultations, hospitalization and deaths that occur during epidemic influenza periods above a “baseline” incidence. Baseline measurements can be defined as incidence of influenza during the summer, incidence during the winter of non-epidemic years or also when there are no influenza virus strains circulating. A study conducted in Portugal measured excess mortality associated with influenza activity during the 2008 influenza season. Influenza activity data consisted of weekly estimates of influenza-like illnesses (ILI) incidence rates obtained by the Portuguese general practitioners sentinel network. Weekly aggregated mortality data was generated by the Daily Mortality Monitoring (VDM) System. Results from the study include an overall impact of 1,961 excess deaths or an excess death rate of 18 per 100,000 inhabitants. Impact was higher in women than men and 82% of total deaths occurred in persons 75 years and older. Another study conducted in the Netherlands estimated influenza-associated mortality and hospitalization, looking also at low-risk individuals under 65 years of age. Influenza-associated hospitalization was highest in 0-1 year olds and the elderly as compared to low-risk (under 65 years of age) adults. Within the low-risk population of persons under the age of 65, hospitalization was highest for 0-4 year olds and was also significant for 5-64 year olds. Excess influenza-associated mortality was also demonstrated among 50-64 year olds and the elderly, though not in the younger age categories.

The alternative method used to estimate the burden of influenza is the development of statistical techniques utilizing underlying temporal patterns in the occurrence of individual organisms to attribute non-specific incidence data to various causative agents. This method may be able to provide more robust estimates of disease burden. A study conducted in England and Wales aimed to estimate the burden of influenza in terms of general practice consultations, hospital admissions and deaths using this statistical method. Results showed that in primary care, those younger than 45 year of age comprised the majority of the burden while the elderly are more likely to be hospitalized and to die.

Data from these studies highlight several aspects of the methods used to estimate the burden of disease that should be addressed in future studies. Improved official influenza surveillance data is needed to ensure accurate estimation of morbidity and mortality during a pandemic. There is a degree of uncertainty in the accuracy of the excess outcomes approach as these estimates depend on the definition of a particular year’s influenza season, which can lead to an overestimated influenza burden especially if other causes of morbidity or mortality are prevalent at the same time as influenza. Likewise, if these causes are absent during the influenza season, the influenza burden may be underestimated. These methods also use different definitions of viral seasons and end-points, variations of the study period and differences in healthcare systems, all of which result in lack of comparability across studies. Additionally, these statistical models are not easily applied to tropical and subtropical regions where influenza seasons are variable and spread over many months during the year.
2.2 Economic burden

As recognized in the 2004 background paper, influenza also imparts an economic burden on affected communities and countries. New studies have since been published on this economic impact, which includes direct health care costs and indirect costs (e.g. work absenteeism and loss of productivity).\(^\text{15}\) The majority of health care costs lie within physician visits and hospitalization. A study in the United States estimates that approximately 50% of the 50-60 million people affected with influenza visit their doctor while between 114 000 and 142 000 people are hospitalized each year.\(^\text{15}\) This amounts to annual direct medical costs between US$ 3 and 5 billion per year.\(^\text{15}\) However, the most significant costs are the indirect costs of work absenteeism and the associated costs of loss of productivity, accounting for more than 80% of the total societal cost of seasonal influenza epidemics.\(^\text{16}\) Site studies conducted in North America, Western Europe, Asia and Australia revealed that the mean number of workings days lost ranged between 1.5 and 4.9 days per influenza episode for those with laboratory-confirmed influenza.\(^\text{16}\) Studies in France and Germany estimate a US$ 10-15 billion cost due to loss of productivity alone.\(^\text{16}\) Aside from the acute infection phase, full recovery can take up to one to two weeks.\(^\text{16}\) Moreover, 80% of adults state that they find their work performance impaired upon returning to work.\(^\text{16}\) As the healthy adult working population is the largest group affected by influenza, exploring the vaccination of working population is warranted.

2.3 Vulnerable populations

2.3.1 Children

Although several studies conducted in Europe have described the impact of influenza and common infective complications such as otitis media in children; few studies have been conducted on more severe influenza-associated complications including febrile seizures (FS) and acute encephalopathy. Febrile seizures account for approximately 20% of all hospitalized infants and young children with influenza.\(^\text{17}\) Numerous studies have shown a higher incidence of febrile seizure in children hospitalized with influenza than with other respiratory infections.\(^\text{18}\) Results from 2011 and 2012 studies conducted in Greece and Denmark indicated that 25.4% and between 30-47% of all FS cases could be attributed to influenza.\(^\text{19,20}\)

Acute encephalopathy is a less common yet more serious complication associated with influenza. The epidemiology of influenza-associated acute encephalopathy has been extensively studied in Japan, where there is a high prevalence of this complication, although cases have also been reported in North America, Europe and Taiwan.\(^\text{17}\) The Japanese Ministry of Health conducted a study where of the 217 identified cases of clinically diagnosed influenza-associated encephalopathy, 82.5% were in children less than five years of age.\(^\text{17}\)

Recent studies have also demonstrated that the highest hospitalization rates attributed to influenza occur among children younger than two years of age.\(^\text{19}\) This confirms that the burden of influenza impacts children and their families, resulting in significant school absenteeism, antibiotic use, medical care visits and parental work loss, as noted in 2004. Several countries, including Argentina, Canada, Finland, Mexico, Singapore, and the United States have recently extended vaccination recommendations to include the younger age population.\(^\text{21}\) In response to the increasing concern of influenza burden on children, in 2007,
the European Centre for Disease Prevention and Control (ECDC) published a technical report on routine influenza vaccination in children, emphasizing the initial importance of determining specific national profiles of the disease burden. The report concluded that European data on paediatric disease burden was inadequate and would subsequently hinder government policy decisions regarding influenza vaccinations for children. As a result, the European Paediatric Influenza Analysis (EPIA) project was created in 2008 to collect and analyse data on the paediatric influenza burden in Europe. Although all European countries were invited to participate in the EPIA project, currently only seven countries are active participants: Denmark, England, Finland, Italy, The Netherlands, Scotland, and Spain. Initial findings from the EPIA project indicate considerable variability between countries regarding the burden of influenza-like illnesses. These findings underline the fundamental issue of the absence of a standardized protocol for national surveillance systems in Europe.

Box 6.2.2: Background of the EPIA Project

- In the 1980s, efforts were initiated to create a European surveillance project.
- In 1996, the project had evolved to the European Influenza Surveillance Scheme (EISS). EISS was later succeeded by the European Influenza Surveillance Network (EISN).
- The main objectives of the EISS were to aggregate and interpret epidemiological and virological surveillance data, to monitor influenza prevention and control policies in Europe and to contribute to European planning and response to pandemic influenza through surveillance, investigation and provision of information.
- EISS began with seven participating countries: Belgium, France, Germany, the Netherlands, Portugal, Spain and the United Kingdom.
- Initial funding came through the national governments with subsequent funding by the European Commission (DG SANCO) then grant funding through the European Centre for Disease Prevention and Control (ECDC).
- Since 2008, the responsibility for the former activities of the EISS has been transferred to the ECDC.
- The EPIA was formed around the EISS with its first modeling work focused on the influenza-like illness data and virological data collected by EISS from 1996–2008.
Box 6.2.3 Guiding Principles of the EPIA Project

- EPIA is a private-public collaborative project with funding from AstraZeneca, PLC.
- Managing organizations include the Netherlands Institute for Health Services Research (NIVEL) and SDI, a United States market insight and analytics firm.
- Data ownership/sharing is decided by members or according to rules of data sources.
- EPIA is open to all countries in Europe.
- EPIA is a publication-driven project.
- EPIA is a research project, not a surveillance project.
- The sponsor does not have access to the EPIA data.
- The project is guided by an independent Steering Committee comprised of five persons from various European Union Member States representing the following fields: influenza researchers, paediatricians, epidemiologists and virologists.

2.3.2 Pregnant women and perinatal outcomes

The World Health Organization considers pregnant women at higher risk for morbidity and mortality from influenza infection and therefore recommends that all pregnant women be immunized during the influenza season. However, individual countries have varying policies on the routine vaccination of pregnant women. As noted in the 2004 background paper, data on the burden of seasonal influenza in healthy pregnant women is limited and remains unchanged. Results from a few notable studies support the recommendation that all pregnant women will benefit from receiving an influenza vaccination. Furthermore, 2007 data confirms that pregnant women with comorbidities should also be vaccinated during the influenza seasons regardless of their stage in pregnancy. As pregnant women are a high-risk group for influenza infection, additional research is clearly needed to obtain concrete estimates of the influenza burden as well as the cost-effectiveness of implementing targeted influenza immunization programmes.

2.4 Tropical and developing countries

Few studies had been reported on the influenza burden in tropical and developing countries and this remains unchanged. Tropical and subtropical regions have mild winters that are subject to seasonal fluctuations in influenza incidence although the seasonal pattern is less evident than in temperate areas. In addition, there may be more than one period of viral activity making it difficult to elucidate the seasonality of influenza and measure its impacts. Several studies have observed higher disease burden in tropical and subtropical regions as compared to the United States. A recent 2012 study conducted in the subtropical region of Guangdong province in China concluded that a greater proportion of children less than five years of age had influenza infections compared to children in other age groups. Direct economic costs within the study period totaled approximately US$ 1 million. The importance of influenza surveillance and understanding the seasonality of influenza in individual regions cannot be underestimated. Lack of disease burden data can hinder a country’s ability to formulate a national vaccination policy, as is the case in Viet Nam. The ability to design effective control strategies and mitigate disease burden is ever more essential in the event of a pandemic.
3. 2009 Influenza A (H1N1) Pandemic Disease Burden

3.1 Emergence of a novel virus

In early April 2009, a new influenza A (H1N1) virus emerged in Mexico and the United States. Confirmation that the viruses in Mexico and the United States were identical provided evidence that the new virus met the WHO criteria for a pandemic strain. However, by the time of its discovery, the virus had advanced beyond the possibility of successful containment. The virus quickly spread worldwide through human-to-human transmission and on 11 June 2009, the WHO elevated the influenza pandemic alert level to Phase 6, officially declaring a global pandemic, the first of the 21st century.

This 2009 H1N1 virus was found to be antigenically distinct from human seasonal influenza viruses although genetically related to viruses known to circulate in pigs, thus the virus is now referred to as ‘swine-origin influenza virus’ (S-OIV) A/H1N1. Molecular studies of the virus have since determined that it had been derived from several viruses including the North American H3N2 triple-assortment, the classical swine H1N1 lineage and the Eurasian ‘avian-like’ swine H1N1 virus. The pulmonary replication level of the 2009 H1N1 virus has been higher than that of seasonal influenza A (H1N1) viruses in experimentally infected animals; however the 2009 pandemic strain lacks the mutations that are associated with increased pathogenicity in other influenza viruses.

3.2 Epidemiology

The 2009 influenza A (H1N1) virus surfaced in a small village in Veracruz, Mexico; however it was overlooked as no illness resulted in hospitalization. The first two cases in the United States appeared in Southern California, in a ten-year-old boy and in a nine-year-old girl with febrile respiratory illnesses that required hospitalization. The virus propagated rapidly and by 18 April 2010, more than 214 laboratory-confirmed cases had been reported. Countries in the southern hemisphere reported more pandemic H1N1 cases in 2009 than any of the seasonal subtypes. Pandemic dissemination was more gradual in the northern hemisphere, occurring initially in the United States, Spain, Great Britain, Japan, and Germany before progressing to other countries. Infections rates also increased rapidly in Central and South America and Asia, and particularly in Thailand. However, very little epidemiological data is available regarding transmission of the virus in Africa. As of 2010, the number of influenza A (H1N1) cases worldwide remained unknown as a result of most cases being diagnosed clinically and not being laboratory-confirmed.

3.3 Mode of transmission

Initial transmission to humans is believed to have occurred at least several months prior to preliminary recognition of the first outbreak. The mode of transmission appeared to be similar to seasonal influenza viruses and involve close unprotected contact with respiratory droplets. Most outbreaks occurred in schools, day-care facilities, camps, and hospitals. Contrary to initial findings at the beginning of the pandemic, subsequent transmission studies in animal models demonstrated that the 2009 H1N1 pandemic virus transmits as efficiently as interpandemic influenza. Interestingly as of 2010, there had been no evidence that pigs played any role in the epidemiology or circulation of the virus in humans.
incubation period varied between approximately two to seven days which is comparable to interpandemic influenza.\textsuperscript{30}

3.4 Clinical presentation

Infection with the novel 2009 H1N1 pandemic virus caused mostly a mild, self-limiting upper respiratory illness characterized by fever, cough, sore throat, myalgia, chills, rhinorrhea, conjunctivitis, headache and shortness of breath.\textsuperscript{28} As of 2010, more than 50\% of patients presented with gastrointestinal symptoms including nausea, vomiting, and diarrhea.\textsuperscript{28} Young children also seemed to have marked irritability, severe lethargy, poor oral intake, dehydration resulting in shock, and seizure.\textsuperscript{30} Additional complications included invasive bacterial coinfections, encephalopathy, and diabetic ketoacidosis.\textsuperscript{30} Overall, the spectrum of clinical presentation varied from asymptomatic cases to primary viral pneumonia resulting in respiratory failure, acute respiratory distress, multi-organ failure, and death.\textsuperscript{28}

3.5 Influenza-associated morbidity and mortality

As stated in Section 3.1, quantifying the health burden of influenza is difficult as the illness can present a wide range of symptoms resulting in under-diagnosis, patients are not laboratory-confirmed as having influenza, diagnostics tests are not 100\% sensitive or specific and finally, influenza can also be masked by other comorbidities. Despite a substantial increase in laboratory testing during the pandemic, these recorded hospitalizations and deaths are a crude underestimation of the true pandemic burden.\textsuperscript{31} Nevertheless, a global estimate of the mortality associated with the 2009 H1N1 pandemic is necessary to document the effect of the pandemic in order assist in guiding allocation and delivery of prevention and treatment measures for future pandemics.\textsuperscript{32} However, by 2011 more than two years after the onset of the H1N1 pandemic, there still remained great controversy in regards to the morbidity and mortality burden of this pandemic relative to past influenza seasons.\textsuperscript{31}

A distinguishing feature of the 2009 H1N1 pandemic is that the virus disproportionately affected children and young adults as compared to the older age groups.\textsuperscript{28} In 2011, a national study, the first of its kind, was conducted in Mexico investigating the excess mortality and years of life lost (YLL) associated with the pandemic as compared to interpandemic influenza.\textsuperscript{31} Findings showed that Mexico experienced a higher excess mortality burden relative to that in the United States, Europe, or Australia including 11.1 excess all-cause deaths per 100 000 population and 445 000 YLL as a result of a series of three pandemic waves that occurred in the spring, summer and autumn of 2009.\textsuperscript{33,34} The two groups most severely affected by the pandemic were individuals aged 5-19 and 20-59 years.\textsuperscript{31} A separate study also conducted in Mexico corroborated the results of the national study with 14.9\%, 28\% and 22.9\% of hospitalizations in individuals aged 5-14, 15-29 and 30-44, respectively, compared to only 6.1\% in those over 60 years of age.\textsuperscript{35} Proportion of deaths demonstrated a similar trend with 21\%, 31.9\% and 27.1\% in individuals 15-29, 30-44, and 45-59, respectively, compared to only 8.9\% of deaths in those over 60 years of age.\textsuperscript{35}

Immediately following the outbreak, on 20 April 2009, the California Department of Public Health and 61 local health departments conducted a study to describe the epidemiological characteristics of the first 1 088 hospitalized and fatal cases reported due to the 2009 H1N1 pandemic virus.\textsuperscript{36} The median age, 27, for hospitalized individuals was discovered to be
younger than is typical for interpandemic influenza.\textsuperscript{36} Infants had the highest rate of hospitalization while the highest mortality rates were in those 50 years and older.\textsuperscript{36} A different study in the United States evaluating hospitalized patients with laboratory-confirmed influenza also determined that 45\% of the patients were children under 18 years of age and only 5\% were older than 65.\textsuperscript{37} Studies conducted in other countries further confirmed the initial morbidity and mortality patterns. Separate studies in England and Denmark reported a high incidence of infection in children with a disproportionately large impact on the age group 5-24 years.\textsuperscript{38,39} Studies in Australia and Argentina also reported the highest rates of hospitalization in children.\textsuperscript{28}

All studies mentioned have additionally demonstrated comparatively low morbidity in individuals older than 60 years of age. This deviation from the normal distribution of morbidity from interpandemic influenza suggests that the older population had acquired partial immunity to the 2009 H1N1 pandemic virus, presumably as a consequence of a prior exposure to an antigenically related influenza viruses resulting in the development of cross-protective antibodies.\textsuperscript{30,38} However, despite this partial immunity the highest case fatality rates were reported in the 50-60 year old population.\textsuperscript{28}

A modeling study published in 2012 developed a new approach to estimate global mortality and the number of YLL associated with the first year of circulation of the 2009 H1N1 pandemic virus in each country.\textsuperscript{32} The overall global distribution of deaths associated with the H1N1 pandemic in each country during the first year virus circulation is shown in Figure 6.2.1. Results from the study estimated that between 105,700 to 395,600 people died of associated respiratory illness and an additional 46,000 to 179,900 people died of associated cardiovascular complications.\textsuperscript{32} The overall global estimate from this study was more than 15 times higher than the number of laboratory-confirmed deaths reported to the WHO in the first 16 months of the pandemic.\textsuperscript{32} Furthermore, a disproportionate number of total cardiovascular and respiratory deaths, 51\%, occurred in the Africa and South-East Asian regions, as seen in Figure 6.2.2.\textsuperscript{32} Findings from this study illustrate the existing gap in the production and delivery of influenza vaccines to the Africa and South-East Asia regions. In order to improve global response to future influenza pandemic, concerted efforts must be made in addressing these disparities.
3.6 Economic burden

In addition to the health burden, attention should also be directed to the economic burden sustained during a pandemic. Assessing economic impact includes direct health care costs as well as the indirect costs of work absenteeism and loss of productivity; however, quantifying this impact can be difficult. A study conducted in 2010 stated that the global economic impact of the H1N1 pandemic remained unknown. A preliminary study from 2009...
estimated the economic impact of the pandemic in Mexico to more than $3.2 billion, which is approximately 3% of the gross national product. Subsequently, efforts were initiated to estimate the economic impact of the pandemic on the United Kingdom using a computable general equilibrium modeling experiment. The main outcome measures of this 2009 study included various scenarios with different pandemic severity, vaccination, school closure, and prophylactic absenteeism specified in terms of gross domestic product and output from different economic sectors. The findings of this study projected that depending on disease severity, of low to high fatality scenarios, the cost of a pandemic could result in between 0.5–4.3% reduction of gross domestic product (GDP). In the event of a mild pandemic, school closures and its related absenteeism would increase the economic impact; however for a more serious pandemic, the economic impact of school closures decreases while the advantages in mitigating the pandemic would increase. Furthermore, widespread behavioral change such as large scale prophylactic absence from work would also substantially increase costs with few health benefits. A pandemic influenza itself will not produce unprecedented economic impacts as even a high fatality rate with elevated levels of infection would only reduce GDP by less than 4.5%. However, balancing appropriate school closure policies and behavior change such as prophylactic absence from work with effective vaccination programs will be critical in determining the economic impact of an influenza pandemic.

3.7 Vulnerable populations

Complications from interpandemic influenza are often associated with underlying conditions, which were also cause for concern during the 2009 H1N1 pandemic. These risk factors include children under the age of five, pregnant women, individuals with chronic lung, renal and hepatic disorders, chronic cardiovascular conditions, metabolic disorders, neurologic conditions, hemoglobinopathy, long history of smoking, individuals over the age of 65, the morbidly obese and immunosuppressed patients. A study conducted in the United States in 2009 determined that out of 272 hospitalized patients with laboratory-confirmed H1N1 infection, 73% presented with at least one underlying medical condition including asthma, diabetes, heart, lung and neurologic diseases and pregnancy.

During pregnancy, numerous changes occur in the immune system to allow tolerance to paternally derived fetal antigens. These alterations on maternal immunity leave the mother susceptible to increased severe manifestations of certain infections, including influenza. Pregnant women, especially those in their second and third trimester or who were less than two weeks post-partum, appeared to be at higher risk for severe disease during the 2009 H1N1 pandemic. Following initial reports of infection in pregnant women, the U.S. Centers for Disease Control and Prevention (CDC) elevated surveillance of pregnant women. During the first months of the outbreak, between 15 April to 18 May, 2009, the CDC received reports of 34 confirmed or probably cases of pandemic H1N1 infection in pregnant women, of which 11 were admitted to the hospital. During the first month alone, the estimated rate of hospital admission in pregnant women was higher than that of the general population. Six deaths were also reported between 15 April and 16 June in which all the women had developed pneumonia and subsequent acute respiratory distress.

Severe obesity was also reported at higher rates, by a factor of five to 15, compared to the general population among patients with severe or fatal cases of 2009 H1N1 infection. Other disadvantaged groups including the indigenous populations of North America and the
Australasia-Pacific region reported increased rates of severe H1N1 infection by factors of five to seven.\textsuperscript{30} The WHO classified the 2009 H1N1 pandemic as moderately severe due to the residual immunity retained by the older population while the majority of cases presented with a mild and self-limiting illness.\textsuperscript{43} Although this new virus appeared less virulent than the 1918 H1N1 virus, the inability to predict which specific subtype will transmit to humans demonstrates the need of addressing the gaps in knowledge to effectively manage the next pandemic.\textsuperscript{28} Future efforts should focus on increased virological surveillance of transmission and pathogenesis of disease and improved understanding of disease burden in low-resource settings and among disadvantaged populations.

4. EU Funded Pandemic and Avian Influenza Research Projects

European research on vaccine development for pandemic influenza has been financed since 2001 by the European Union. Early projects worked to develop an egg-free vaccine, which is faster and safer to produce, along with innovative application techniques. Research is now underway with the objectives of fighting the disease at the source (infected birds) and protecting human populations through pandemic influenza vaccines. Future EU research will improve vaccine efficiency by adding adjuvants, substances that enhance the body’s immune response to vaccine antigens. Additionally, research teams are currently focused on developing a universal flu vaccine that could provide a lifetime of protection from influenza.

The Framework Programme is the European Union’s primary funding mechanism for supporting collaborative, transnational research and development. Under the Fifth Framework Programme for Research (1998 to 2002, FP5) €6 million were spent on avian and pandemic influenza in 22 institutions and national reference laboratories across eight European countries.\textsuperscript{44} For the Sixth Framework Programme (2002 to 2006, FP6), activities were extended and reinforced with a set of new projects launched in both the animal and human health sectors and with more than a three-fold increase in the EU contribution (€16 million plus a share in two large Networks of Excellence and an Integrated Project).\textsuperscript{44} To date, a total of over 120 laboratories across 21 European countries have been funded for research on influenza within these Framework Programmes.\textsuperscript{44} The European Commission has published a comprehensive report of all FP5 (1999 to 2002) and FP6 (2002 to 2006) funded projects that are either exclusively dedicated to research on any aspect of influenza (the majority of projects) or address a broader range of diseases, but with a significant part devoted to influenza which can be accessed in Appendix 6.2.1.

In 2007, the European Commission allocated an additional €20 million for research into avian and pandemic influenza. Relating to animal health, issues such as developing vaccines for avian species; improved diagnosis and early warning systems; the ecology and pathogenesis of avian influenza infections; migratory birds; avian influenza virus survival; reinforcement of community and national reference laboratories; and technology transfer to developing countries will be addressed. Relating to human health, issues such as clinical research on pandemic influenza vaccines, better understanding of the influenza virus and strengthening support to surveillance will be addressed. Several EU-funded projects including investigations of pandemic influenza vaccines, antiviral drugs, universal vaccines, and influenza in animals are also in progress. Examples include:
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- NOVAFLU - developing more effective strategies for the human vaccination against epidemic and pandemic influenza.
- AVIFLU - studying the pathogenesis of avian influenza, as well as improving diagnosis and control of avian infections.
- FLUAID - developing diagnostic tools and vaccines to be used in outbreak management and in the application of control measures based on vaccinations to combat avian influenza infection. Leading European institutes will cooperate with Asian laboratories as part of this research project.
- UNIVERSAL VACCINE - developing a powerful, new, safe, and easily-administered nasal vaccine for humans that provides lifelong protection against influenza. Website: http://www.universalvaccine.org
- VIZIER - identifying potential new drug targets against RNA viruses by providing a comprehensive structural characterization of the replicative machinery of a carefully selected and diverse set of viruses. Website: www.vizier-europe.org
- VIRGIL - the first European surveillance network capable of addressing current and emerging antiviral drugs resistance developments in the field of viral hepatitis and influenza. Website: www.virgil-net.org

The current Seventh Framework Programme (FP7) (2007 to 2013) will operate with an EU budget of €55 billion organized under four programmes corresponding to the four basic components of European research: cooperation, ideas, people, and capacities. Health research is one of ten high-level themes identified by FP7 which lies within the Cooperation Work Programme. The Cooperation Work Programme will operate with a budget of approximately €32.2 billion with €6 billion allocated to health research.

For the first time, research will be dedicated to emerging infectious diseases, including influenza. Primarily, the influenza projects of the health sector are related to pre-clinical and clinical development of new, innovative, safe and effective vaccines. Proposals will focus on universal influenza vaccines, providing longer-lasting and broader protection against multiple strains of influenza virus, with the ultimate aim of efficiently protecting the general population from seasonal and pandemic influenza. Various complementary scientific aspects such as basic virology, diagnostics, epidemiology, pathogenesis, surveillance, immune responses, animal viruses, novel drugs, clinical management of patients, behavioural aspects and optimized communication strategies are also covered by FP7 research. The first call for proposals is related to:

- Broadly protective vaccines, mechanisms of protection
- Standardization of immunological assays/surrogate markers for vaccine trials
- Point-of-care diagnostic tests: real-time polymerase chain reaction (PCR)
- Pandemic containment and mitigation strategies
- Surveys and novel mathematical models to evaluate effectiveness of containment measures
- International collaboration projects: pandemic preparedness/health system analysis in Viet Nam, Thailand, Indonesia, and Taiwan

A detailed description of proposed health research areas within the Cooperation Work Programme can be viewed in Appendix 6.2.2. A new framework programme, Horizon 2020, will be launched in 2014 with a €80 billion budget and will continue to support vaccine research and development for infectious diseases, including influenza. This section emphasizes the European Commission’s continued support for influenza research. In light of
the 2009 pandemic, the comprehensive report of influenza research projects initiated between 2001 to 2007 underscores the importance of periodic reviews of current research to identify the strengths and weaknesses of Europe’s funding and research portfolios.
5. Influenza Prevention and Control Strategies

5.1 Vaccination

Vaccination is considered the most effective mechanism to prevent the spread of influenza and also to mitigate the severity of illness and impact of disease. The sudden appearance and rapid global transmission of the 2009 influenza A (H1N1) pandemic resulted in a global prioritization to develop a vaccine. A primary concern was for the potential of the virus to gain additional virulence properties.

The 2009 interpandemic influenza vaccine was ineffective against the pandemic strain due to a lack of cross-protective immunity between the interpandemic and pandemic influenza strains and further emphasized the urgency for prompt vaccine development.

Due to the high mutation rate of influenza viruses, in order to achieve a complementary match between the circulating and vaccine viruses, the composition of interpandemic influenza vaccines must be reformulated every season based on recommendations by the WHO. Estimating influenza vaccine effectiveness (IVE) early in the influenza season assists in measuring the degree of match between the selected vaccine strains and the circulating strains. However, vaccine composition reformulation dictates that IVE estimates cannot be used to approximate IVE in subsequent years therefore IVE should be measured and monitored every year. For a pandemic situation, strain specific vaccines do not become available until four to six months after the beginning of vaccine development. Consequently, the pandemic virus is already in circulation as pandemic vaccines are being administered necessitating that IVE results be computed and delivered rapidly. In the context of a pandemic, vaccine effectiveness data should be provided by age group, by number of doses received, and by vaccine brand. The availability of annual IVE estimates at the beginning of each interpandemic season or pandemic is essential in order to:

- decide on recommendations for the use of the vaccine by specific age and risk groups,
- target complementary or alternative public health measures (e.g. antiviral agents) for population subgroups in which the vaccine is less effective,
- estimate more precisely the impact of current vaccination strategies on the burden of disease,
- provide quantification to the current virological system of comparing antigenic matches of vaccine and circulating viruses,
- encourage further investigations on the immunogenicity of various vaccine composition platforms,
- better manage and respond to reports of vaccine failures (especially during a pandemic),
- provide a basis for adequate risk management and cost-effectiveness analyses.

In 2007, the ECDC established the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) network with the aim of monitoring interpandemic and pandemic influenza vaccine effectiveness in the Member States of the European Union and European Economic Area (EU/EEA). The first step in the design of this network was to identify key methodological and practical issues in developing protocols for pilot studies. This was accomplished through a survey distributed among Member States, a literature review on IVE methods and consultations with influenza experts. Results from the survey and literature review
highlighted the variety of data sources used to estimate IVE and the difficulty with interpreting IVE data, which varies with age, risk group, outcome specificity, and virus-vaccine mismatch. Consultation with influenza experts yielded the following recommendations: measure IVE in the same population in various seasons; control for positive and negative confounding; and include laboratory-confirmation as an outcome measure in study designs.\textsuperscript{50}

During the 2008 to 2009 influenza season pilot case-control studies were conducted in five countries, including Denmark, Hungary, Portugal, Romania, and Spain.\textsuperscript{48} In order to develop a sustainable system, the framework of existing general practitioner-based (GP) influenza sentinel surveillance systems was utilized and all participating countries are members of the EISN.\textsuperscript{48} The study population was restricted to community-dwelling elderly and IVE (influenza vaccine effectiveness) was measured against laboratory-confirmed influenza.\textsuperscript{48} To control for health seeking behavior, recent studies suggested comparing individuals consulting for ILI and are influenza positive to individuals consulting for ILI who test negative for influenza (negative controls).\textsuperscript{48} The feasibility of conducting a pooled analysis was additionally explored in order to increase the precision of estimates and to provide a summary IVE for the five studies. Country-specific and pooled IVE estimates indicated a protective effect of the 2008 to 2009 interpandemic vaccine in the elderly population in a year with a good match between the vaccine virus and the influenza A (H3) strain predominantly circulating in Europe.\textsuperscript{48} These results also suggested the feasibility in Europe of using test-negative controls to estimate interpandemic IVE against laboratory-confirmed influenza.\textsuperscript{48} Pooling of country-specific data was found to be necessary to have early interpandemic or pandemic IVE estimates and would also increase the precision of these estimates for subgroup analysis. A final observation indicated that future studies based on sentinel GPs to measure pandemic IVE will depend on the vaccination and control strategies of respective countries.\textsuperscript{48}

During the 2009 to 2010 influenza season the I-MOVE network conducted case-control studies in seven countries (including France, Hungary, Ireland, Italy, Romania, Portugal, and Spain) based on sentinel GP surveillance networks.\textsuperscript{51} The objective of these studies was to estimate the effectiveness of 2009-2010 pandemic influenza vaccines against laboratory-confirmed pandemic influenza A (H1N1) (pH1N1).\textsuperscript{51} Data from all seven studies were also pooled to provide an overall adjusted estimate of IVE. Results demonstrated that one dose of a pandemic vaccine conferred adequate protection against laboratory-confirmed pH1N1.\textsuperscript{51} IVE was higher in individuals aged 65 years and older and also in those without any chronic disease conditions.\textsuperscript{51} Furthermore, point estimates suggested good IVE as early as eight days post-vaccination.\textsuperscript{51} Future studies should increase the sample size per country in order to allow for more precise stratified and pooled analyses.

A separate study conducted in Germany assessed the IVE of a monovalent AS03-adjuvanted vaccine, Pandemrix\textsuperscript{®}, which was used almost exclusively during the 2009 pandemic in this country.\textsuperscript{52} One dose vaccination was recommended for all age groups. However as stated earlier, immunogenicity data was the only basis for the licensure of these pandemic vaccines therefore it is essential to estimate IVE in order to confirm that a one dose vaccination regimen induces sufficient protection across all age and risk groups.\textsuperscript{52} Preliminary results showed excellent IVE in individuals aged 14-59 years and moderately high IVE in those 60 years and older.\textsuperscript{52} The vaccine was also found to be effective in chronically ill persons.\textsuperscript{52}
Future studies should further analyze IVE in the elderly and individuals with chronic conditions.

It is worth noting that following the H5N1 influenza outbreak, the amount of global attention, research and ultimately, funding directed towards influenza increased substantially. Many pharmaceutical companies have since invested in developing new vaccines; therefore, it is only practical and financially responsible that the effectiveness of these vaccines be monitored, both from the pharmaceutical industry and public health perspectives. This network was in the beginning stages of development when the 2009 H1N1 pandemic occurred. The basis for licensure of the pandemic vaccines that were produced relied on immunogenicity data available at the time; however, it is unknown how well they correlate with protection. As strong immunogenicity does not always result in robust vaccine effectiveness, the importance of estimating effectiveness of vaccines at the population level was further reiterated by the 2009 H1N1 influenza pandemic.

On 3-4 December 2012, the WHO and CDC convened the International Meeting on Influenza Vaccine Effectiveness with the aim to review the current landscape of IVE evaluation, to identify data pooling opportunities and to develop a consensus for best practices for IVE studies. The meeting identified key issues surrounding IVE evaluation including limited data available particularly in low- and middle-income countries (LMIC) and the need for standardization of methodology in measuring IVE to improve comparability between studies. International data pooling was also emphasized as an important strategy for generating regional and global IVE estimates. Final discussions focused on the critical need to communicate IVE findings appropriately and effectively as well as to develop a guidance document for best practices in IVE studies. With the potential to drive evidence-based public health decisions, IVE studies are essential for future influenza vaccine policy development.

5.1.1 Vaccine policies and coverage

A novel vaccine provision study

In 2003, the World Health Assembly (WHA) adopted a resolution on the “Prevention and control of influenza pandemics and annual epidemics.” In this resolution, the WHA recognized the substantial public health burden of influenza. Consequently, the WHO acknowledged the role of immunization in preventing and reducing this health burden by providing recommendations for the vaccination of high-risk population groups. This position is similarly reflected by many government public health policies, as more than 40% of countries worldwide include interpandemic influenza vaccination in their national immunization schedules. The 2003 WHA resolution also set a goal for countries with influenza vaccination policies, requesting for an increase in vaccine rates for all high-risk individuals. Despite this collective concern on the need to increase vaccination coverage, systematic worldwide data has not been available to assist public health authorities in assessing vaccine provision, uptake or the impact of immunization policies. Although the original background paper did provide data of vaccine provision in 56 countries from 1997 to 2003 conducted by the Macroepidemiology of Influenza Vaccination study group, no formal mechanism has been established to provide continuing information on a regional or global basis.
To address the lack of a formal monitoring system, the International Federation of Pharmaceutical Manufacturers and Associations Influenza Vaccine Supply task force (IFPMA IVS) developed a survey in 2008 to assess global influenza vaccine provision and reported the results of 141 countries from 2004 to 2007.\(^4\) In 2010, this database was updated and extended to include information from 157 countries from 2004 to 2009.\(^4\) A secondary objective included using a subgroup of 26 countries to collect data on immunization recommendations, reimbursement and communication policies to evaluate correlation with national vaccine provision data.\(^4\) A third and final study objective utilized United Nations (UN) data and a novel vaccine provision “hurdle” rate (set at 15.9% of the population, based on WHO immunization recommendations for the elderly) to compare vaccine provision with country development status.\(^4\)

Results from this study indicated a total worldwide distribution increase of 72% from 262 million doses in 2004 to 449 million doses in 2009 as depicted in Figure 6.2.3.\(^4\) On a WHO regional basis, distribution increased in all regions although growth was not uniform.\(^4\) The Americas and Europe consistently accounted for 75% to 80% of total vaccine provision each year.\(^4\)

**Figure 6.2.3 Global interpandemic influenza vaccine dose distribution from 2004 to 2009 divided by WHO region\(^4\)**

Over the six-year survey period, vaccine provision increased in more than 70% of the 157 study countries with notable rises in Europe (France, Germany, Italy, the Netherlands, Spain, and the United Kingdom), the Americas (Brazil, Colombia, Mexico, and the USA) and in China, Japan, and Thailand.\(^4\) However, growth was not consistent, as the United States’
distribution peaked in 2007 and subsequently decreased 23% in the following two years.\textsuperscript{54} A number of countries also experienced a decline of dose distribution, with a marked decrease in the Republic of Korea where provision deceased 27% over the study period.\textsuperscript{54} Overall, despite encouraging growth at the national, regional and global levels, no country distributed sufficient vaccines for half of its total population and only 20\% of study countries achieved the study “hurdle” rate of 159 doses per 1,000 population, shown in Figure 6.2.4.\textsuperscript{54} Furthermore, in excess of two-thirds of countries did not provide adequate doses to encompass 10\% of their populations while remarkably, one-third of countries did not distribute enough to protect even 1\% of their populations.\textsuperscript{54} Figure 6.2.4, shown below, does demonstrate an improvement in most EU countries as compared to a similar figure on page 17 of the 2004 background paper.

On a per capita basis, vaccine supply did not correlate directly with national income.\textsuperscript{54} By UN designation, the study included 46 more developed and 108 less developed countries.\textsuperscript{54} Of the 31 countries with vaccine provision greater than 159 doses per 1,000 population, 29\% (nine countries) were less developed.\textsuperscript{54} In the subgroup analysis of 26 countries, the presence of official vaccination recommendations did not demonstrate good correlation with higher vaccine provision.\textsuperscript{54} However, reimbursement and the use of extensive communication activities correlated 3.5-4.1 times more strongly with vaccine supply than the presence of an immunization policy alone.\textsuperscript{54}

The findings from this study reveal that despite the widely recognized benefits of influenza vaccination, national recommendations are not being fully implemented and immunization rates remain low.\textsuperscript{54} For example, in 2009 the United States distributed sufficient vaccine for 36\% of its population although its Advisory Committee on Immunization Practices (ACIP) recommends that approximately 85\% of the population be vaccinated.\textsuperscript{54} The strong correlation of reimbursement and communication activities with vaccine coverage reiterate previous research in Europe concluding that increasing vaccine rates require public education campaigns and funding for vaccinations in addition to healthcare workers proactively recommending immunization to at-risk individuals.\textsuperscript{54} The importance of continued efforts to increase vaccine coverage cannot be undermined as the use of interpandemic influenza vaccines not only protect against annual epidemics but also provides the foundation for pandemic preparedness. Annual interpandemic vaccine utilization sustains production capacity, which ultimately facilitates the global capability to respond during a pandemic.
Figure 6.2.4 Global interpandemic influenza vaccine dose distribution per 1,000 population (2009)

Based on epidemiology of the population groups most affected during the initial phase of the pandemic, international organizations including the WHO Strategic Advisory Group of Experts (SAGE), the EU Health Security Committee (HSC), and the U.S. CDC issued evidence-based vaccination recommendations for target groups in order to assist in standardizing national policies. Although recommendations varied slightly across the organizations, health care workers (HCWs), pregnant women, and individuals with underlying chronic conditions were uniformly included as priority groups. The WHO SAGE recommended that all countries prioritize immunizing HCWs first as a mitigation strategy to protect the essential health infrastructure and to vaccinate all other priority groups in the following order, as shown in Table 6.2.1. In addition, the WHO SAGE stated that initially as there will be an insufficient amount of pandemic vaccines available, a stepwise approach to vaccinating priority groups will need to be considered.

In August 2010, the ECDC requested the Vaccine European New Integrated Collaboration Effort (VENICE) consortium to conduct a survey collecting information on influenza A (H1N1) pdm09 vaccination policies and vaccination coverage in the EU, Norway, and Iceland. Prior to the 2009 H1N1 pandemic, most EU/EEA countries had already included pandemic vaccines as a component of their national mitigation plans. All 29 EU/EEA countries participating in the VENICE project responded to the survey with 26 countries implementing pandemic vaccination programmes and one country providing vaccination recommendations but did not have a specific programme. Twenty-five countries also published official documentation in the form of a policy or guidelines on vaccination recommendations. Almost all countries with pandemic vaccination programmes had the same policy across the country with the exception of Sweden, who reported having different regional strategies.

Despite international recommendations set forth, results from the VENICE study indicate differing recommendations for target groups between countries. Vaccination of healthcare workers and pregnant women was recommended by all 27 countries with established vaccine recommendations. Variation in age group recommendations also existed with 12 countries recommending vaccination for all ages while six countries had recommendations for specific age groups in children and three countries had recommendations for specific adult age groups. All pandemic vaccine recommendations countries recommended vaccination for individuals with chronic respiratory, cardiovascular or renal disease; however, only 16 countries recommended vaccination for individuals with morbid obesity. Interestingly, although most countries identified similar target groups for vaccination, results demonstrate substantial variability in vaccination coverage. Reported vaccination coverage for the entire population ranged from 0.4% to 59% in 22 countries with the highest coverage reached in the Netherlands and the Nordic countries (30% to 59%). Vaccination coverage for HCWs ranged from 3% to 68% (13 countries); 0.0% to 58% for pregnant women (12 countries) and 0.2% to 74% for children (12 countries).

The notable variability in vaccination coverage between study countries even with similar vaccination recommendations is an important indicator of the improvement needed in effectively translating vaccine recommendations, whether at the national or international levels, into higher vaccination coverage. Individual countries should focus on strengthening or implementing vaccination coverage monitoring systems. Accordingly, international
organizations must create or utilize a standardized methodology in conducting annual population based surveys in order to strengthen vaccine coverage comparisons between countries.

Table 6.2.1: International organization recommendations for 2009 pandemic A (H1N1) vaccination

<table>
<thead>
<tr>
<th>Key Recommendations</th>
<th>WHO Strategic Group of Experts</th>
<th>EU Health Security Committee</th>
<th>U.S. Centers for Disease Control and Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General considerations &amp; criteria for selecting priority and target groups</strong></td>
<td>‘Countries should determine their order of priority based on country-specific conditions.’</td>
<td>‘It is within the mandate and responsibility of Member States to develop a vaccination strategy for influenza A (H1N1) 2009.’ No priority order between categories below.</td>
<td>‘Vaccination efforts should focus initially on persons in five target groups, listed below.’ No priority order between categories below.</td>
</tr>
<tr>
<td><strong>Priority and Target Groups</strong></td>
<td><strong>Healthcare workers</strong> • All countries should immunize HCWs as a first priority to protect health infrastructure</td>
<td><strong>Healthcare workers</strong></td>
<td><strong>Healthcare workers and emergency medical services personnel</strong> • Persons who have direct contact with patients or infectious material</td>
</tr>
<tr>
<td><strong>Pregnant women</strong></td>
<td>• Increased risk for severe disease</td>
<td><strong>Pregnant women</strong></td>
<td><strong>Pregnant women</strong></td>
</tr>
<tr>
<td><strong>Persons from age six months and up with chronic medical conditions</strong></td>
<td>• To reduce morbidity and mortality</td>
<td><strong>All persons from age six months and up with underlying chronic medical conditions</strong> • Increased risk for severe disease</td>
<td><strong>Children and adolescents aged 5-18 years with medical conditions</strong> • Increased risk for influenza-related complications</td>
</tr>
<tr>
<td><strong>Healthy young adults (aged 16-48 years)</strong></td>
<td>• To reduce morbidity and mortality</td>
<td><strong>Persons who live with or provide care for infants ages less than months</strong></td>
<td><strong>Children aged six month to four years</strong></td>
</tr>
<tr>
<td><strong>Healthy children</strong></td>
<td>• To reduce transmission</td>
<td><strong>Healthy adults (aged between 49 and 65 years) &amp; (aged above 65 years)</strong></td>
<td><strong>Children aged six month to four years</strong></td>
</tr>
<tr>
<td><strong>Healthy adults (aged between 49 and 65 years) &amp; (aged above 65 years)</strong></td>
<td>• To reduce morbidity and mortality</td>
<td><strong>Children aged six month to four years</strong></td>
<td><strong>Healthy adults (aged between 49 and 65 years) &amp; (aged above 65 years)</strong></td>
</tr>
</tbody>
</table>


### 5.1.2 Cost-effectiveness

The health burden of influenza is globally acknowledged as a threat to public health. The WHO estimates the global disease burden from influenza of up to one billion infections, three to five million cases of severe disease and between 300 000 and 500 000 deaths annually. Early estimates from the United States in February 2010 indicated 59 million illnesses, 265 000 hospitalizations, and 12 000 deaths from the 2009 H1N1 virus. Studies
have shown that the working population, known as healthy adults aged 15-64 years, constitutes the largest group affected by influenza. Although most people recover within one to two weeks, it does not attenuate the health and economic impact of the disease.

A 2009 study evaluated the effectiveness of influenza vaccination among working adults aged 50-64 years in reducing the rate of ILI and productivity losses. Findings from the study revealed that ILI occurred frequently with related morbidity among the study participants of working adults aged 50-64 years. Influenza-like illness was associated with 45% of days of illness due to all causes and 39% of work days lost due to all causes in the unvaccinated participants. Among the vaccinated participants, there was a substantial 45% reduction in the risk of ILI and more than 60% reduction in the number of days of illness and days of work lost. A previous systematic review of influenza vaccine for healthy adults aged 65 years and under demonstrated that vaccination correlated with a mean reduction in the number of days of illness of 0.48 days per person vaccinated and also with a mean reduction in the number of lost working days of 0.21 days per person vaccinated. Similar results from the 2009 study and prior analyses provide evidence that vaccinating working adults aged 50-64 years can offer benefits consistent with those previously seen in healthy working adult (<65 years) populations. Furthermore, recent health economic studies have suggested the cost-effectiveness of vaccinating individuals aged 50-64 years in the United States, the United Kingdom, and other countries.

The outbreak of the 2009 H1N1 pandemic presented an opportunity to examine the cost-effectiveness of maternal influenza immunization against laboratory-confirmed influenza, which had not been previously studied. Initial data from the pandemic suggested that the 2009 H1N1 virus strain was generating higher morbidity and mortality among pregnant women, consistent with previous pandemics. Although the CDC ACIP committee recommends yearly influenza vaccination for all pregnant women, data shows a low 13% rate of maternal vaccination in the United States. This 2009 study used an analytic computer simulation model to simulate the decision of maternal immunization for an influenza epidemic and/or pandemic. Incremental cost-effectiveness ratios determined that when influenza prevalence reached ≥7.5% and influenza-attributable mortality is ≥1.05%, it is cost-effective to vaccinate pregnant women with either a single or two-dose regimen. With higher influenza prevalence, ≥30%, the single-dose strategy demonstrated cost-savings while the two-dose strategy remains highly cost-effective. These results provide evidence of the cost-effectiveness of maternal influenza vaccination at disease prevalence rates resembling both interpandemic seasons and pandemic outbreaks. Furthermore, the study showed that cost-effectiveness becomes increasingly established as prevalence and severity of influenza increases within the population. However, a different study published in the same year by the same author reported reticence among pregnant women in accepting vaccination using a pandemic avian influenza vaccine that had been rapidly developed. Even so, the demonstrated safety of interpandemic vaccines during pregnancy, the ethical obligations that exist for protecting vulnerable populations and favorable cost-effectiveness justify strong and continued support for maternal influenza vaccinations.

Historically, the target groups for national vaccination recommendations have included nursing home residents, the elderly, and individuals with underlying medical conditions. Recent evidence, however, indicates substantial health and economic consequences associated with influenza among children as well. Studies describe children as having the highest rates of illness from influenza infections resulting in increased healthcare
utilization. Hospitalization rates have also been reported to be similar to those observed among the elderly. Additional concerns include indirect costs such as productivity losses for parents and the transmission of influenza within households and communities. Yet despite the availability of effective vaccines to prevent influenza in children and the increasing documentation of the health and economic costs of influenza in children, broad variation exists within international vaccination recommendations for children. In 2011, a systematic review was conducted yielding 20 different studies that had assessed the cost-effectiveness of influenza vaccination in children. Most studies showed that vaccination of healthy children would be cost-saving or cost-effective. Two studies indicated that vaccination of the highest risk children resulted in the greatest cost-savings. A major limitation of most of these studies was that few incorporated the potential benefits of vaccinating school children in regards to reducing transmission within households or communities. This omission may have resulted in the underestimation of the benefits of vaccinating school children. The decision by policy-makers, clinicians, and patients to include children in vaccination programmes is an important task with tangible consequences. Future research dictates an opportunity that requires the consideration and understanding of the health and economic consequences of illness and also the cost-effectiveness of vaccination.

5.1.3 Global production capacity

Although vaccination is one of the most effective methods to mitigating the impact of an influenza pandemic, a successful vaccination response hinges upon a timely and adequate vaccine supply. Recognizing the threat of pandemic influenza and the need to substantially strength global preparedness and response activities, the 2005 World Health Assembly (WHA) requested that the WHO collaborate with its international and national partners in order to reduce the global shortage of influenza vaccines. In May 2006, the WHO convened a consultation to develop a plan for identifying and implementing the best methods to reduce the anticipated gap between influenza vaccine demand and supply during a pandemic. It was realized at that time that if a pandemic were to occur, there would be a shortage of the sufficient amount of vaccine needed, in the range of several billion doses, in order to protect the world’s population. An additional observation was the marked variation between countries in their respective priorities, resources and capacities for establishing national influenza vaccination policies and programmes. A third and equally important observation from this meeting was that all major influenza vaccine manufacturers were located almost exclusively in Australia, North America, Europe, and to a limited extent, Asia. This realization provided concrete evidence that many resource-constrained countries did not have the means to access interpandemic influenza vaccines and therefore would be the most severely affected during a pandemic.

To address these prominent gaps in vaccine supply, three mutually reinforcing strategies were identified:

1) increase the use of interpandemic influenza vaccine;
2) increase influenza vaccine production capacity; and
3) promote influenza vaccine research and development.

These strategies consequently became the foundation for a global pandemic influenza action plan to increase vaccine supply, which was thereafter known as the Global Action Plan for Influenza Vaccines (GAP).
The second activity for increasing influenza vaccine production capacity encompassed both short-term and medium- to long-term objectives. The short-term objective was to facilitate sufficient vaccine production to immunize two billion people within six months following the availability of a pandemic virus vaccine candidate. The medium- to long-term objective was to produce enough vaccine to immunize the world’s population of 6.7 billion people.

A principal achievement of the GAP plan is its prominent role as the catalyst for the significant expansion in global influenza vaccine manufacturing capacity. Interpandemic vaccine production increased from 350 million doses in 2006 to approximately 900 million doses by June 2009. In 2010, the WHO conducted a survey of vaccine manufacturers in order to quantify the increase in global influenza vaccine production capacity since the inception of GAP and actual production in response to the 2009 H1N1 pandemic. The survey was distributed to 33 current or potential influenza vaccine manufacturers, listed in Table 6.2.2, with projected production capacity by the second quarter of 2010. The questionnaire requested data on actual production (in millions of doses) of monovalent influenza A (H1N1) pandemic vaccine by formulation as of 1 December 2009 and forecasted production of any formulation by 1 March 2010 and 1 June 2010.

<table>
<thead>
<tr>
<th>ADImmune Corporation</th>
<th>Denka Seiken</th>
<th>Novartis Vaccines &amp; Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter</td>
<td>GlaxoSmithKline Biologicals</td>
<td>Omnivest</td>
</tr>
<tr>
<td>Berna-Crucell</td>
<td>GPO Thailand</td>
<td>Panacea Biotec</td>
</tr>
<tr>
<td>Bharat Biotech</td>
<td>Green Cross Corporation</td>
<td>Sanofi Pasteur</td>
</tr>
<tr>
<td>Biken</td>
<td>Henan Hualan Biological Engineer Inc.</td>
<td>Serum Institute of India</td>
</tr>
<tr>
<td>Changchun Changsheng Life Sciences Limited</td>
<td>Institute of Virology</td>
<td>Shenzhen Neptunus Bioengineering Co.</td>
</tr>
<tr>
<td>Chemo-Sero-Therapeutic Research Institute</td>
<td>Vaccines and Sera Torlak</td>
<td>Sinopharm</td>
</tr>
<tr>
<td>Bio Farma</td>
<td>IVAC</td>
<td>Sinovac Biotech</td>
</tr>
<tr>
<td>Cantacuzino Institute</td>
<td>MedImmune</td>
<td>Vabiotech</td>
</tr>
<tr>
<td>CSL Biotherapies</td>
<td>Microgen</td>
<td>Zhejiang Tianyuan Bio-Pharmaceuticals Co., Ltd</td>
</tr>
<tr>
<td>Dalian Aleph Biomedical Co., Ltd</td>
<td></td>
<td>Zydus Cadila</td>
</tr>
</tbody>
</table>


Results from the survey revealed that the number of monovalent pandemic H1N1 vaccines produced by 1 December 2009 was 534 million doses. Forecasted production by 1 March 2010 and 1 June 2010 was 1 303 million doses and 1 367 million doses, respectively. Of the 1 367 million doses to be produced by June 2010, 46% (636 million doses) were projected to originate from the WHO Europe (EUR) geographic Region, 30% (410 million doses) from the Americas (AMR) Region, and 21% (293 million doses) from the Western Pacific (WPR) Region. This distribution of vaccine production aligns with the distribution of the number of global vaccine production facilities. At the time of survey administration, there were 41 current and potential influenza vaccine production facilities spread across 25 countries. Nine of these countries also had recently acquired the capability to manufacture influenza
vaccines (Figure 6.2.5). Sixteen (39%) of the 41 facilities are located in the WPR and 12 facilities (26%) are located in the EUR. Seven manufacturers in the Americas Region (AMR, n=2), the Eastern Mediterranean Region (EMR, n=2), the South-East Asia Region (SEAR, n=2), and the WPR (n=1) are expected to begin vaccine production over the next five years. A notable observation from the survey was the lack of current and potential manufacturers in the sub-Saharan Africa (AFR) Region. Even with the emergence of new vaccine manufacturers globally, more than 80% of interpandemic influenza vaccine doses produced in the 2009-2010 season will have come from the seven large manufacturers located in the United States, Canada, Australia, western Europe, Russia, China, and Japan.

**Figure 6.2.5 Countries with influenza vaccine production capacity in 2006 and 2010**

Finally, the survey demonstrated that regardless of extensive efforts by all stakeholders during the 2009 pandemic, the number of available pandemic vaccine doses for use was well below the WHO’s GAP targets. A WHO survey previously conducted in May 2009 estimated an annual global production of 4.9 billion doses; however, forecasted pandemic vaccine production 12 months after the availability of vaccine virus was only 28%, 1.37 billion doses, of the initial estimate. Furthermore, as the short term goal of GAP was to be able to provide enough vaccine to immunize two billion people, the actual production by December 2009 was only 534 million doses of monovalent pandemic vaccine.

Expanding the global production capacity is not sufficient enough, however, to ensure universal access to influenza vaccine during a pandemic. Moreover, it is not realistic or possible to establish vaccine production in every country. For these reasons, the WHO funded grants to manufacturers are contingent upon an agreement to sell 10% of their vaccine production at an affordable price to United Nations agencies for distribution to countries without production capacity. The ability to expand to almost 900 million doses...
was achieved mainly by the considerable investment by multinational manufacturers in new and enlarged production plants.\textsuperscript{62} Despite substantial growth in global production capacity, the 2009 H1N1 pandemic underlined remaining gaps in the availability of vaccine, especially in developing countries. A sizeable portion of the projected pandemic vaccine production was already reserved prior to the onset of the pandemic through advanced-purchase agreements by high-income country governments. This resulted in the substantial delay of pandemic H1N1 vaccine to most developing countries until January 2010, more than eight months following the declaration of a pandemic by the WHO.\textsuperscript{62} The historic adoption of the Pandemic Influenza Preparedness (PIP) Framework at the 64\textsuperscript{th} WHA in May 2011 was the culmination of five years of protracted negotiations.\textsuperscript{61} The PIP Framework provides comprehensive political and technical guidance on ensuring an efficient, effective, equitable, fair, and transparent mechanism for sharing influenza viruses and access to vaccines and other benefits.\textsuperscript{61} The complete document can be accessed in Appendix 6.2.3.\textsuperscript{63}

In 2011, the WHO convened the second WHO GAP consultation in order to review progress made from the first five years and lessons learned from the 2009 H1N1 pandemic.\textsuperscript{61} This second meeting assembled representatives from United Nations agencies, national governments, funders, regulatory authorities, manufacturers, nongovernmental organizations, and the research community. Proposed actions for increasing influenza vaccine production capacity include \textsuperscript{61}:

- Continued evaluation of new methods and approaches for production optimization;
- Investigating the feasibility of multipurpose facilities;
- Reduction of the vaccine production timeline;
- Strengthening national regulatory agencies in order to efficiently assess and approve influenza vaccines;
- Ensuring stringent post-marketing surveillance and
- Facilitating increased safety and risk communication between governments.

Annual interpandemic vaccine utilization sustains production capacity (See Section 5.1.1); however production capacity alone also does not automatically advance equitable access to vaccines. Therefore, pandemic preparedness is a monumental task that requires diligence and the commitment and cooperation at the national, bilateral and international levels including public and private sector partnerships, in order to build adequate capacity to respond to the next influenza pandemic.

5.1.4 WHO technology transfer initiative

In accordance with GAP’s vaccine production capacity objective, the WHO influenza vaccine technology transfer initiative was introduced in 2007, seeking to create regionally based, independent and sustainable influenza vaccine production capacity in developing countries.\textsuperscript{64} Financial support has been provided by the Public Health Agency of Canada, the Ministry of Foreign Affairs of Japan, the United Kingdom Department for International Development, the United States Department of Health and Human Services, and the Asian Development Bank.\textsuperscript{61} To date, approximately US$ 28 million of seed funding has been granted to 11 developing country manufacturers (Brazil, Egypt, India, Indonesia, the Islamic Republic of Iran, Mexico, the Republic of Korea, Romania, Serbia, Thailand, and Viet Nam).\textsuperscript{61} Funding has also enabled the establishment of a centre for excellence for training and transfer of influenza vaccine production technologies to new manufacturers.\textsuperscript{64}
To facilitate the technology transfer process, the WHO also created an influenza vaccine technology ‘hub’ – a novel concept to pooling resources for vaccine manufacturing capacity-building. The Netherlands Vaccine Institute (NVI), which over the past decade has implemented numerous technology transfer projects to developing country manufacturers for various vaccines, was selected to conduct all training and technology transfer. The technology ‘hub’ model encompasses a complete manufacturing process that is void of intellectual property restrictions and other barriers resulting in simultaneous accessibility by multiple recipients. By establishing partnerships with technology proprietors, WHO has been able to negotiate a non-exclusive royalty-free license to develop, manufacture and sell to the public sector both interpandemic and pandemic egg-derived live-attenuated influenza vaccines (LAIV). WHO will then provide sub-licenses to manufacturers in developing countries. In the first two years of operation, a transferable pilot process for egg-based inactivated whole virus influenza A vaccine production was established as well as a course curriculum on production and quality control. Future expansion of the curriculum include cell-culture based technology for viral vaccine production, split virion influenza production, and generic adjuvant formulation. Technology transfer facilitated by the ‘hub’ model has thus far succeeded in building production capacity in developing countries.

To measure interim results of the technology transfer initiative, a survey was administered in 2010 to all 11 developing country manufacturers receiving grants from the WHO. Three manufacturers (27%) responded as having already produced and distributed interpandemic influenza vaccine in their countries. The other eight countries indicated projected commencement of commercial-scale vaccine production between 2010 and 2012. Additionally, five countries (India, Indonesia, the Republic of Korea, Romania and Thailand) produced licensed pandemic influenza vaccines between 2009 and 2011. Finally, although two countries do not plan to introduce interpandemic influenza vaccination in their national programmes by this date, the remaining nine manufacturers (82%) will be able to meet the demand for interpandemic influenza vaccine in their country by 2015.

Technology transfer is a complicated process that requires the creation of a solid partnership the technology provider and the country recipient. The technology provider must be committed and also willing to transfer a complete production process. The recipient must also have established experience in vaccine production and the ability to conduct research into new technologies. The Instituto Butantan-Sanofi Pasteur partnership can be viewed as a model for successful technology transfer which has led to the technological independence of the institute in serving as a strategic public health tool. The avian influenza outbreak in 2003 was a powerful indicator for Brazil to increase its influenza pandemic preparedness. At the time, the country did not have the influenza production capacity therefore Brazil pursued a technology transfer partnership to construct a dedicated influenza vaccine production facility. In the interim, the plan was to formulate and finish monovalent bulk vaccines supplied by an international vaccine manufacturer, who would become the technology provider. Brazil selected Sanofi Pasteur as its technology transfer partner due to the company’s extensive experience in large-scale influenza vaccine production and also the established relationship of the company with Brazil. The technology transfer would be for an egg-based inactivated split interpandemic influenza vaccine as well as a whole virion adjuvanted H5N1 vaccine. With funding from the Ministry of Health and the State of Sao Paolo Office of Health and final validation from Sanofi Pasteur, the construction of a new influenza production plant was completed and ready for production by September 2010. Beginning in 2011, the new facility plans to produce 20-25 million doses of trivalent southern
hemisphere interpandemic vaccine every year. Following receipt of a financial grant from the WHO technology transfer initiative, a pilot plant was constructed to allow the development of basic technology to produce small vaccine lots for evaluation in animal models and under good manufacturing practices (GMP) rules, for a Phase I clinical trial to evaluate safety and immunogenicity. From 2007 to 2009, the pilot plant produced six lots of H3N2, 10 lots of H5N1 (split), 17 lots of H5N1 (whole virion), and 1 lot of H1N1 (split).

Given limited to no production capacity in many countries, technology transfer and utilization of the ‘hub’ model is cost-effective. However this novel technology transfer platform is a considerable endeavor that will necessitate financial and technical support and commitment from governments and the private sector. Consideration for local and regional demands along with selection of vaccine production technologies appropriate to the local setting must be also ensured during this process. It is only through continued collaborative efforts that a sustainable production capacity will be achieved.

5.1.5 WHO international H5N1 vaccine stockpile

One of GAP’s priorities is to promote equitable, timely, and sufficient access to influenza vaccines during a pandemic, with a specific focus on countries with no influenza vaccine production capacity. In order to achieve this objective, the WHO was called upon to seek international support for a H5N1 influenza vaccine stockpile that would benefit developing countries. A previous WHO meeting held in early October 2007 had discussed policy options for the use of H5 vaccines, including potential use during the interpandemic period and also the potential use of a stockpile in the event of a pandemic. Scientific evidence presented at this meeting demonstrated no significant safety concerns with the H5 vaccines reviewed. The primary outcome of this meeting included two proposed policy options for use of a WHO H5N1 vaccine stockpile: i) for rapid containment in response to a pandemic signal and ii) to provide assistance to countries with no vaccine production capacity by vaccinating essential groups of the country population considered to be critical to maintain functionality of the country.

In late October 2007, the WHO convened an informal consultation on the technical specifications for an WHO international H5N1 influenza vaccine stockpile. The objective of the meeting was to generate recommendations for the establishment, operation and sustainability of the proposed vaccine stockpile. Technical specifications discussed included quality, safety, efficacy, regulatory pathways, logistic parameters and guiding principles for access to the stockpile. The perspectives of key stakeholders, including industry, developing country recipients, regulatory agencies, and donors were also taken into consideration.

Key lessons from the management of other WHO vaccine stockpiles (e.g. yellow fever and meningitis) were presented prior to further discussion of technical specifications of the proposed stockpile. Vaccine stockpiles can assume different characteristics depending on the disease, the use of the vaccine, and principles such as equitable access. The creation of an international vaccine stockpile is also a complex process which in addition to the stockpile itself; includes ancillary equipment, shipping, vaccination campaigns, waste management, and surveillance elements. Funding and maintenance of production capacity were also noted as important factors to ensure vaccine supply continuity. Finally, a distinguishing factor of the H5N1 vaccine stockpile from current vaccine stockpiles is that the proposed use of the H5N1 stockpile is intended for outbreak control rather than a mass vaccination
therefore only a small proportion of the vaccine is expected to be released to a given population.68

Results from the previous meeting on policy options for the use of H5 vaccines were utilized in accordance with this meeting in order to generate recommendations for the WHO Department of Immunization, Vaccines, and Biologicals (IVB) SAGE group for decision-making. Box 6.2.4 outlines a summary of recommendations on the technical specifications for a WHO international H5N1 vaccine stockpile. The comprehensive meeting report can be accessed in Appendix 6.2.4.68

Box 6.2.4: Summary recommendations for a WHO international H5N1 vaccine stockpile

- In the event of human-to-human transmission of H5N1 virus, stockpiled vaccines would be used for rapid containment of a pandemic and equitable distribution to low- and middle-income countries (LMIC) to immunize essential populations as defined by the Member State.
- Although clinical and non-clinical requirements differ for pandemic versus interpandemic vaccines, the WHO guidelines on clinical and non-clinical evaluation of vaccines are considered applicable for an H5N1 vaccine stockpile.
- Strain selection and the continued appropriateness of the H5N1 stain to induce immunity against drift variants should be based on WHO recommendations.
- Vaccines should be licensed by a functional national regulatory authority (NRA) and submitted for WHO prequalification.
- Clear selection criteria for acceptance of vaccines should be developed. Based on current evidence, only inactivated influenza vaccines (IIV) should be considered.
- Data requirements for regulatory approval of an H5N1 stockpile vaccine are additional to those for interpandemic vaccines.
- Written criteria should define what needs to be done, by whom and when.
- The WHO should update the draft target specifications to assess continued potency of stockpiled vaccine.
- The WHO should facilitate data exchange among laboratories studying the stability of stockpiled vaccine.
- Country pandemic preparedness plans should include acceptance of vaccines from the stockpile.


During the 2009 H1N1 pandemic, the WHO EURO was active in facilitating various vaccine procurement activities.43 These activities included vaccine development and procurement, negotiating with vaccine manufacturers, prequalification of pandemic H1N1 vaccines, and stockpiling to ensure provision of vaccines at a reduced price to lower income countries of the WHO European Region.43 In September 2009, the EC also provided technical assistance with developing public tender notices to EU Member States that had not yet procured pandemic H1N1 vaccines.43
5.2 Antiviral agents

Although vaccination plays a prominent role in the prevention and control of influenza, its utility, if not adequately available, is insufficient during a pandemic. This is due to the time required to approve, register, and manufacture a new vaccine. Therefore in the interim, antiviral therapy is an effective and critical tool to mitigating the effects of an influenza pandemic. Current antiviral agents can be classified as either neuraminidase inhibitors (NAIs) or M2 inhibitors. Commercially-available NAIs include oseltamivir and zanamivir; M2 inhibitors include amantadine and rimantadine. NAIs are the preferred treatment option due to the continued high prevalence of influenza A (H1N1) and influenza A (H3N2) resistance to the M2 inhibitors. The high resistance to one of the two classes of antiviral agents underscores the need for the development and approval of new NAIs other than oseltamivir and zanamivir. In 2010, two new NAIs; laninamivir and peramivir, were approved for clinical use for the treatment of influenza A infection in Japan. A 2012 study was conducted to evaluate the clinical effectiveness of all four NAIs, oseltamivir, zanamivir, laninamivir, and peramivir on influenza A (H1N1) and (H3N2) infected patients during the 2010-2011 season. Duration of fever was used as the indicator of clinical effectiveness. For influenza A (H3N2) infected patients, the peramivir treatment group had the fastest time of fever alleviation compared to the other NAIs. No significant difference in the time to alleviation was observed for the other antivirals. Only oseltamivir and zanamivir were compared in the influenza (H1N1) infected patients and no significant difference was observed in the time to fever alleviation. Currently available NAIs are effective but the potential for drug resistance justifies further analysis of the effectiveness of the newly licensed NAIs to treat influenza infection.

5.2.1 Cost-effectiveness

During the 2009 influenza A (H1N1) pandemic, oseltamivir and zanamivir were used to treat infection; however, the virus was most susceptible to these drugs during the first 48 hours of infection. Early antiviral treatment with NAIs was recommended for H1N1 infected patients with severe symptoms or underlying conditions associated with a high risk of developing interpandemic influenza complications in all high-income countries except for the United Kingdom. These recommendations were based on existing knowledge and understanding of antiviral treatment for interpandemic influenza. However, initial data following the onset of the H1N1 pandemic indicated that unlike interpandemic influenza, a high proportion of severe and fatal influenza complications were occurring in previously healthy young individuals. Given these data and the decreased efficacy of NAIs more than 48 hours after the onset of symptoms, a re-evaluation of antiviral treatment recommendations for whether to treat all patients with antiviral therapy or only those at high risk for complications was needed. In late 2009, a decision model study was conducted using available data in order to estimate the clinical and economic outcomes associated with early initiation of NAIs in all symptomatic patients versus only those at high risk for influenza complications. Study results confirmed that systematic treatment of ILI during an influenza A (H1N1) epidemic wave was both effective and cost-effective. Regardless of risk status, antiviral treatment with NAIs should have been initiated for all patients who present to care with ILI during the influenza A (H1N1) pandemic wave. However, during the interpandemic influenza season when probability of influenza is low, the administration of NAIs for treatment of influenza infection is less effective and less cost-effective.
5.2.2 Stockpiling

Stockpiling antiviral agents is a functional strategy to mitigating the impact of future influenza pandemics; however, limited data exists in regards to the optimal long-term size of a stockpile under the different capabilities of countries around the world. A 2011 study used an epidemic economic model to evaluate the costs of antiviral stockpile sizes and their effects on total mortality. Study countries included Brazil, China, Guatemala, India, Indonesia, New Zealand, Singapore, the United Kingdom, the United States, and Zimbabwe. This study demonstrated that stockpiling antivirals considerably reduced mortality. Stockpiling in more developed countries showed greater potential to avoid expected costs therefore for perfect allocation, covering 15% of the country population is needed. For misallocation, 25% to 30% coverage is necessary to minimize deaths and reduce economic costs. Stockpiling in less developed countries stockpiling could also assist in avoiding substantial fatalities. For all countries, antivirals should not be the preferred treatment of susceptible individuals but rather be reserved for treatment of influenza infected individuals, where its use would be more successful. Furthermore, under current antiviral pricing, results also indicated that stockpiling is not cost-effective for more than two-thirds of the world’s population. Interestingly, oseltamivir and zanamivir are expected to go off-patent in the next five years (2016 and 2013, respectively). The use of generic antivirals would enable stockpiling to be more cost-effective for China, Indonesia, and India. However, for resource-limited countries, generic antivirals would still not be cost-effective underlining the need for international collaboration to ensure equitable access to antiviral treatment.

Assuring an international commitment to antiviral stockpiling the PIP Framework, discussed in Section 5.1.3, includes antiviral stockpiling as part of the pandemic influenza preparedness benefit sharing system.

Antiviral therapy has been proven effective to treat influenza infection; however escalating antiviral resistance to current drugs provides the research opportunity to develop novel therapeutics with reduced drug resistance potential. Additional analysis is also needed to verify the global use of antivirals in order to determine its cost-effectiveness during the 2009 H1N1 pandemic. This information will be critical in the global preparation for future pandemics.

5.3 Rapid influenza diagnostic tests

Rapid and accurate laboratory diagnosis of viral infection is paramount to reducing the morbidity and mortality burden of influenza and its associated social and economic consequences. Studies have demonstrated improved viral clearance in infected persons who began treatment within the first four days of illness, emphasizing the need for rapid and accurate laboratory diagnosis in both inpatient and outpatient settings.

Rapid influenza diagnostic tests (RIDTs) are rapid, simple-to-use, point-of-care antigen tests that can generate results in 10-30 minutes. Previous studies on interpandemic influenza have demonstrated high specificities of RIDTS but varying sensitivity levels. Comparisons of rapid tests evaluated in different studies are difficult to make due to variability across study designs regarding sample sizes, patient age, specimen type, and comparators. Different populations have also been reported to yield different sensitivities, with higher sensitivities in young children as compared to adults. This may be due to
higher levels and longer duration of viral shedding in children.\textsuperscript{75} In addition, most current RIDTs do not distinguish different influenza A virus subtypes. While influenza can be ruled in using RIDTs, influenza cannot be ruled out with negative results, thus nucleic acid testing or viral culture must be employed for further confirmation.\textsuperscript{74}

During the 2009 H1N1 outbreak, commercially-available RIDTs had not been developed specifically to detect influenza A (H1N1) therefore their performance in detecting this new virus was unknown.\textsuperscript{77} Multiple studies have since investigated the diagnostic accuracy of current RIDTs to detect H1N1 infection. Results are inconclusive as some studies reported lower sensitivity while other reported similar sensitivity as compared to interpandemic influenza.\textsuperscript{77,78,79} As an influenza virus testing method, RIDTs fill the void as a first-line test. More importantly it has utility in patient and outbreak management, enabling clinicians to initiate prompt infection-control measures as well as begin antiviral treatment in high-risk populations earlier. However, it is equally imperative that clinicians understand its limitations, that a negative test should be confirmed using RT-PCR or cell culture.

### 5.3.1 Cost-effectiveness

As stated above, early treatment within 48 hours of onset has been associated with lower risks for disease progression therefore a rapid clinical decision to treat hospitalized patients is imperative. Recent studies have reported inconclusive results on the diagnostic accuracy of ‘point-of-care’ antigen tests and although PCR tests are highly sensitive, they are expensive and have longer turnaround times (TAT). A 2012 study evaluated the potential costs and outcomes of diagnostic test-guided and empirical antiviral treatment approaches in hospitalized patients with severe respiratory infection in Hong Kong.\textsuperscript{80} A decision tree was designed to simulate the outcomes of four management strategies, including: immunofluorescence assay (IFA)-guided treatment, PCR-guided treatment, empirical treatment with PCR and empirical treatment alone.\textsuperscript{80} Total direct medical cost, survival rate from influenza infection, and quality-adjusted life years (QALYs) were used as key performance indicators.\textsuperscript{80} Results from this study suggest that when interpandemic virus strains were predominant during an influenza season, empirical antiviral treatment alone is a cost-effective option when influenza prevalence levels exceed 2.5\%\textsuperscript{,80} When prevalence is less than 2.5\% PCR-guided treatment is the most cost-effective approach.\textsuperscript{80} In contrast, when the 2009 H1N1 virus strain was predominant, empirical treatment alone would be the more cost-effective option for a wider range of prevalence levels, from 0.4\% to over 25\%.\textsuperscript{80}

Many RIDTs have been developed since the 2009 H1N1 epidemic; however, comprehensive studies on their diagnostic accuracy and cost-effectiveness are absent. A future research priority should be to focus on the potential role of RIDTs for the next influenza pandemic.

### 6. Vaccination Strategies

Influenza A infection induces an initial innate immune response followed by an adaptive immune response with T cell infiltrates in the lungs.\textsuperscript{81} This robust response is also usually characterized by a significant amount of immunopathology.\textsuperscript{81} The combined immune response and accompanying pathology leaves the host susceptible to secondary bacterial pneumonia, known to be a major cause of death during influenza pandemics.\textsuperscript{81}
Vaccination remains the most effective measure in the prevention and control of influenza and the WHO has urged countries to broaden influenza vaccination programs in order to achieve high vaccination coverage. However, limitations of current vaccination strategies have resulted in the development of novel technologies in vaccine platforms, production methodology, and delivery mechanisms.

6.1 Inactivated versus live attenuated vaccines

Inactivated and live attenuated vaccines are both effective in the prevention of influenza; however, the protection conferred by each varies widely depending on the antigenic match between the viruses in the vaccine and the viruses that are circulating at the time. Because of the antigenic variation between virus strains, the WHO convenes twice annually to recommend the viruses for inclusion in influenza vaccines for the Northern and Southern Hemispheres.

Inactivated influenza vaccines have been used for nearly 70 years with reported 75-90% protection rates. The basis of protective immunity is the induction of strain-specific neutralizing antibodies, which means that the vaccine only provides protection against viruses that are closely antigenically aligned with those in the vaccine. Consequently, inactivated vaccines confer less protection against antigenic drift variants within a subtype of the influenza virus and also do not provide protection against viruses from different subtypes. Influenza vaccines are a sterile, aqueous suspension of a strain or strains of influenza virus. There are four types of available inactivated influenza vaccines:

1) A suspension of whole virus particle inactivated by a suitable method (whole virion vaccine);
2) A suspension treated so that the virus particles have been partially or completely disrupted by biochemical means (split vaccine);
3) A suspension treated so that the preparation consists predominantly of hemagglutinin and neuraminidase antigens (subunit vaccine);
4) A suspension of inactivated influenza virus particles, split or subunit components formulated with an adjuvant.

Since 1967, the WHO Expert Committee on Biological Standardization has provided recommendations for the production and quality control of inactivated influenza vaccines. The most recent revision in 2005 takes into consideration new development methods on influenza vaccine production including: mammalian cell culture production, the use of adjuvants, the development of reverse genetics for the generation of vaccine viruses, and increased levels of pandemic planning (see Appendix 6.2.5). The 1997 (H5N1 virus), 1999 (H9N2 virus) and the 2003 (H5N1 and H7N7 viruses) outbreaks of avian influenza prompted serious concern of a possible pandemic outbreak. These events illustrated that different strategies for the production and use of vaccines are necessary in response to a pandemic. Reducing the time between the emergence of a human influenza pandemic virus and the availability of safe and effective pandemic influenza vaccines has been recognized as a high priority in global health security. To promote coordination between national regulatory authorities, the 58th report of the WHO Expert Committee on Biological Standardization released guidelines on regulatory preparedness for pandemic influenza vaccines, which can be viewed in Appendix 6.2.6.
Live attenuated influenza vaccines (LAIV) are composed of attenuated viruses that contain the same HA and NA antigens as in inactivated vaccines, as required by the World Health Organization and national regulatory authorities. LAIV vaccines have been shown to induce neutralizing serum antibodies, mucosal antibodies, and cellular immunity. Cross-reactive T-cell responses elicited by LAIV can provide heterosubtypic immunity, which can limit viral infection and replication, and reduce disease severity. Given that the influenza virus replicates in nasopharyngeal epithelial cells, LAIV is administered by intranasal drops or spray, an easy route of administration. One of the potential disadvantages to the use of live, attenuated vaccines is that the possibility exists that the attenuated microbe in the vaccine could revert to a virulent form and become pathogenic. However, LAIV has been shown in clinical studies to be genetically stable with no loss of attenuation. Additionally, LAIV cannot be administered to individuals with compromised immune systems. Despite these obstacles, the WHO states that LAIV may be more appropriate for the production of pandemic vaccines because it requires less complex downstream processing than what is needed for inactivated vaccines.

In 1979, the WHO drafted recommendations for the production and quality control of live attenuated influenza vaccines, to take into account the increased interest in immunization using live attenuated viruses. These recommendations, which apply to seasonal and pandemic vaccines, were subsequently revised in 2009 to provide national regulatory authorities and vaccine manufacturers with guidance in developing processes to assure the quality, safety, and efficacy of human live attenuated influenza vaccines for intranasal administration. As the technical report has not been published yet, a preliminary draft of these recommendations can be viewed in Appendix 6.2.7.

6.2 Vaccine production methodology

Vaccines have typically been produced from viruses propagated in hen eggs. However, the supply of eggs is limited and would be even more so in the event of a zoonotic outbreak of avian influenza or other diseases affecting chicken flocks. Egg-based production necessitates advanced planning, which is ultimately not feasible in the case of sudden increased demand such as a pandemic and is susceptible to microbial contamination. A new virus strain may also grow poorly in eggs or yield low levels of HA protein, resulting in the need for egg-adaptation through serial passage. Interestingly, although the inactivated vaccines produced lower-than-expected yields of HA protein, the live attenuated 2009 H1N1 viruses reached very high titres in eggs, allowing this vaccine to be distributed first and in a single dose.

In light of these constraints, the WHO has recommended using established mammalian cell lines as an alternative culture system. The use of a cell culture production system has several advantages: assured availability of substrate for virus growth that would allow for increased flexibility to meet fluctuations in demand, avoids the generation of egg-adaptive mutations in the HA protein, provides better manufacturing control through a closed-system fermentation process and is safer for individuals who are sensitive to egg proteins. Three cell lines, Madin Darby canine kidney (MDCK), Vero and PER.C6., have demonstrated effectiveness in vaccine production. A clinical trial conducted in healthy adults in the USA, Finland and Poland during the 2007-08 influenza season, evaluated the clinical efficacy of a cell culture-derived influenza vaccine compared to an egg-derived trivalent inactivated subunit influenza vaccine. Results concluded that the cell culture-derived and the egg-
derived vaccines were effective in preventing influenza, were well-tolerated and presented good safety profiles. Of the three available cell lines, the only cell line that has universal regulatory acceptance is Vero cells. Moreover, pandemic influenza vaccines derived from this cell line have been well-tolerated and immunogenic.

However, cell culture production is not without its limits. For inactivated vaccines, the process would require the production of high-yield re-assortments with sufficient HA protein. Multiple passage through tissue culture may introduce cell-line-specific mutations that can lead to the selection of variants with antigenic and structural changes in the HA protein, resulting in decreased efficacy of vaccines. Regulatory issues surrounding cell culture include the presence of potential extraneous agents in mammalian cells and the unknown side effects that may occur as a result of residual host cell and media proteins in combination with new adjuvants.

6.3 Adjuvants

The use of adjuvants to modulate vaccine immunogenicity has been in practice for more than 80 years. Adjuvants are compounds that enhance the ability of a vaccine to elicit strong and robust immune responses. In this conventional role, adjuvants are presently used to: 1) increase the response to a vaccine in the general population; 2) increase seroconversion rates in populations with reduced responsiveness due to age or disease; 3) facilitate the use of smaller doses of antigen and 4) also allow for vaccination with fewer injections. Adjuvants behave by prolonging the antigen exposure time to the immune system, enhancing the delivery of antigen to antigen-presenting cells or by providing immunostimulatory signals that potentiate the immune response. An ideal adjuvant is able to increase a vaccine’s immunogenicity without adversely affecting the safety of the immunogen. While some adjuvants have substantially improved immune responses, they have also been associated with intolerable toxicities. Known adverse events following immunization of these adjuvanted influenza vaccines include the formation of sterile abscesses and cysts at the injection site, systemic febrile reactions and the excess occurrence of Bell’s Palsy. When the avian influenza vaccines were in development, the WHO encouraged the use of adjuvants in the case of a pandemic given the limitations in vaccine supply worldwide and the susceptibility of influenza viruses to mutate.

The function and safety of adjuvants have mostly been derived empirically without a strong understanding of their cellular and molecular mechanisms of action. Innate and adaptive immunity, both involved in the protection against invasive pathogens, were previously understood as functioning independently of each other. However, recent data suggests the emergence of a second role for adjuvants: engaging components of the innate immune system to produce the most effective forms of immunity by modulating the adaptive immune response. The use of adjuvants to influence the balance of induced-antibody and cell-mediated immunity have been investigated in preclinical and clinical studies to: 1) provide functionally appropriate types of immune response; 2) increase the generation of memory cells; 3) increase the speed of initial response, which is critical in a pandemic outbreak; and 4) alter the breadth, specificity or affinity of the immune response.
6.3.1 Aluminum salts

Historically, aluminum compounds have been the most widely used adjuvants for more than 80 years. There are numerous aluminum compositions; however, aluminum hydroxide (AlOH), aluminum phosphate and alum remain the most commonly utilized adjuvants in vaccines for humans. The immuno-modulating and immuno-stimulating effects of aluminum salts occur through several potential mechanisms of action. Aluminum compounds can function as an antigen depot by slowly releasing the antigen over time, can induce local inflammation by attracting antigen presenting cells (APCs) to the injection site and also improve uptake by APCs, as the antigen adsorbed to aluminum salts appears to the immune system as a particulate antigen as opposed to a soluble antigen. Although aluminum compounds have demonstrated safety, reported adverse events include sterile abscesses, eosinophilia, myofasciitis and granuloma formation.

While some initial studies failed to demonstrate improved immune responses in primed individuals who had received an aluminum-adjuvanted vaccine, other studies demonstrated a modest improvement in antibody response, especially in unprimed individuals. When candidate H5N1 vaccines were able to achieve antibody responses only through high dosage levels, studies were initiated to investigate whether aluminum salts could further enhance the immunogenicity of subvirion H5N1 vaccines. Results from a 2008 Phase I-II clinical trial reported that a meaningful beneficial effect of AlOH adjuvant was not observed after evaluating varying doses of HA with or without 600 µg of AlOH in healthy adults. These findings confirm conclusions from previous studies using subvirion H5N1 vaccines. Studies have also been conducted using aluminum-adjuvanted whole-virus vaccines; however, results remain inconclusive due to the exclusion of a comparable non-adjuvanted control group in some studies and demonstrated poor immune responses with the adjuvanted vaccine in other studies.

Despite a lack of evidence supporting a biologically meaningful effect, currently aluminum salts are the only licensed adjuvants in the USA. During the 2009 H1N1 pandemic, out of the eight vaccines utilized in Europe, only one included an aluminum adjuvant (Fluval P, Omnivest).

6.3.2 Oil-in-water emulsions

Oil-in-water emulsions are another group of compounds commonly used for vaccine adjuvants. MF59 and AS03 have emerged as potential adjuvants for influenza vaccines. MF59 is licensed in Europe for use with a seasonal vaccine for the elderly and with more than 27 million doses distributed, post-marketing surveillance studies have yet to identify any safety concerns related to this vaccine. Early studies evaluating MF59 with the potential pandemic vaccine strains, H5N3 and H9N2, in healthy young adults showed significantly improved antibody responses in the adjuvanted vaccine groups compared to the non-adjuvanted vaccine group. Subsequently a 2008 study evaluated the MF59 and alum adjuvants with a candidate H5N1 vaccine in healthy adults and also found significantly higher antibody responses in the MF59 vaccine group as compared to the alum and non-adjuvanted vaccine groups. In 2011, a study demonstrated additional efficacy of MF59 with a trivalent inactivated vaccine in infants and young children. Another study conducted in 2011 further elucidated the effects of MF59 on the quantity, diversity, specificity and affinity maturation of antibody responses to an H1N1 pandemic vaccine in different age groups.
determined that MF59 increased the diversity and volume of neutralizing antibody responses to the vaccine while also increasing the strength with which the antibodies were binding to the influenza virus.\textsuperscript{96} During the 2009 H1N1 pandemic, out of the eight vaccines utilized in Europe, two included a MF59 adjuvant.\textsuperscript{94} AS03 is another emulsion currently being investigated as an adjuvant for influenza vaccines. A 2007 study evaluating an AS03-adjuvanted H5N1 vaccine in healthy adults demonstrated significantly improved antibody responses in the adjuvanted vaccine group compared to the non-adjuvanted vaccine group.\textsuperscript{92} A recent study conducted in 2011 further demonstrated the immunogenicity of a single dose AS03-adjuvanted H1N1 2009 vaccine in individuals 18-64 years of age and also in individuals older than 64 years of age.\textsuperscript{97} This single dose vaccination was also able to induce long-term persistence of the immune response until at least six months after the initial dose.\textsuperscript{97} Out of the eight pandemic vaccines used during the 2009 H1N1 pandemic, only one, Pandemrix\textsuperscript{TM} (GSK) included the AS03 adjuvant.\textsuperscript{94}

Although both MF59 and AS03 have been shown to induce more local or systemic reactions within three days of vaccination compared to non-adjuvanted vaccines, there have been no serious adverse events reported.\textsuperscript{49} Following the 2009 H1N1 pandemic, a 2011 study concluded that the MF59-adjuvanted H1N1 vaccine, Focetria\textsuperscript{TM}, was generally well tolerated with transient adverse events and mild to moderate in intensity.\textsuperscript{98} Overall, MF59 and AS03 stimulate stronger antibody responses that also have the potential to be cross-protective against other virus strains.\textsuperscript{92} As a result, these oil-in-water adjuvants allow for antigen dose sparing and fewer doses.\textsuperscript{91}

In 2009, the WHO held a virtual consultation on the safety of adjuvanted influenza vaccines.\textsuperscript{99} The purpose of the consultation served to review known and theoretical safety concerns associated with adjuvants in influenza vaccines and to discuss methods to prospectively evaluate vaccine safety.\textsuperscript{99} A summary of the report can be accessed in Appendix 6.2.8.\textsuperscript{99} Although adjuvants have demonstrated their potential to substantially improve immune responses to influenza vaccines, a research priority in future studies should be to evaluate the safety and immunogenicity of adjuvants in vulnerable populations such as the young, the elderly, pregnant women, and in immunocompromised individuals.\textsuperscript{92} Adjuvants may not have been necessary to augment the immune response to the 2009 H1N1 pandemic vaccines; however, their significance cannot be undermined in the ability to respond to future influenza pandemics.

6.4 Alternative vaccine platforms

6.4.1 Reverse genetics

The development of antigenically relevant vaccine viruses is an important component to vaccine production. The viruses must be safe for inclusion into a vaccine and also carry efficient manufacturing properties. Absence of a suitable virus can severely impede vaccine production, a circumstance not favorable in the event of a pandemic. As described on page 25 of the 2004 background paper, the disadvantages of the genetic re-assortment technique for creating vaccine reference strains has led to the use of reverse genetics technology. The conventional genetic re-assortment technique is not able to be used with highly pathogenic avian viruses because the resulting re-assortments are highly pathogenic for embryonated eggs and may be capable of human infection. However, using reverse genetics technology, a safe H5N1 candidate vaccine virus was created.\textsuperscript{100} Results from ferret studies demonstrated
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that this candidate vaccine virus, NIBRG-14, was safe and appropriate for pandemic influenza vaccine manufacture. Some European countries have also used this virus to gain regulatory approval of an H5N1 vaccine as part of the core dossier regulatory approach developed by the EMA as a ‘fast track’ procedure for pandemic vaccine approval. Following the pandemic threat of H5N1, more than 17 candidate vaccine viruses have been developed using reverse genetics technology. Utilizing lessons learned from the H5N1 vaccine development, vaccine viruses were quickly developed for the 2009 H1N1 pandemic. As of October 2009, 16 H1N1 2009 vaccine viruses have been established. The WHO has provided guidelines on the development of influenza vaccine reference viruses using reverse genetics, which can be viewed in Appendix 6.2.9.

6.4.2 Recombinant DNA technologies

The constraints of conventional production strategies have led to the development of recombinant DNA techniques as new production platforms. Upon selection of the influenza vaccine virus strains, the genetic sequence of the HA proteins can be used to generate HA and NA antigens in cell culture. The purified antigens will then serve as the active ingredients for the candidate vaccine. This novel approach would eliminate the need to handle pathogenic viruses and also to adapt the viruses to grow in eggs or cells. The use of recombinant proteins, virus-like particles, viral vectors, and DNA plasmids are technologies currently being investigated and although most are in the early stages of development, they have the potential to substantially reduce production timelines.

6.4.3 Universal vaccines

The ideal influenza vaccine is one that is safe, provides long-term and cross-strain protection and can also be manufactured rapidly. Investigative targets in the search for a universal vaccine have been the highly conserved external domain of the influenza matrix 2 (M2) protein and the conserved epitopes from the influenza NP, matrix 1 (M1), and HA proteins. Results from preclinical studies have demonstrated that candidate vaccines targeting the aforementioned conserved components of the influenza virus has stimulated broad cross-reactive antibody response either when administered alone or in combination with adjuvants. A 2012 Phase IIa clinical trial conducted in healthy adult volunteers evaluated a novel influenza vaccine in a vaccination and influenza challenge study. The vaccine demonstrated safety and immunogenicity. This study was able to provide preliminary evidence of clinical efficacy of a T-cell based influenza vaccine, with a 60% reduction of laboratory-confirmed influenza in vaccinated individuals. This study provides evidence that this novel approach could be successful; however, additional studies are needed to characterize safety and efficacy in larger populations and to assess vaccine immunogenicity in the elderly and in younger age groups. Future studies in larger populations and in vulnerable populations remain a research priority.

The following table summarizes the distribution of current and new approaches that address the challenging areas of influenza vaccine production, including egg versus cell-based production and novel platforms.
6.5 Vaccine delivery mechanisms

Despite the safety and effectiveness of vaccines, many individuals go unvaccinated each influenza season. Issues of concern include vaccine acceptance and cost. Novel vaccine delivery mechanisms that elicit stronger immune responses as well as increase influenza vaccination rates are currently being investigated.

6.5.1 Traditional needle-based vaccination

Influenza vaccines have typically been administered by intramuscular injection. This method stimulates the production of serum antibodies which protect the lower respiratory tract against influenza infection.\(^8\) While the lower respiratory tract is protected, it leaves the upper respiratory tract susceptible to initial infection because of an absence of antibody induction in the nasal mucosa.\(^8\) Additional disadvantages include safety issues surrounding the use of needles, low acceptance among patients due to needle-phobia and logistical challenges in mass vaccination programmes.\(^8\)

6.5.2 Needle-free vaccination

The disadvantages encountered with the traditional needle-based intramuscular vaccines can be circumvented through the use of needle-free vaccination systems. Current methods in development are evaluating both mucosal tissue and skin immunization systems. Mucosal immunization includes the nasal, pulmonary, oral cavity, or gastrointestinal tissues while skin immunization includes intradermal or transcutaneous delivery.\(^8\)

Needle-free vaccinations do not require trained health-care personnel to administer the vaccination to patients, thus reducing costs. As the vaccination is pain-free, individuals with needle-phobia are more likely to accept needle-free vaccination than injection-based
vaccination. A study conducted in Switzerland found that 97% of study participants would choose an intranasal vaccine spray compared to an injection, when offered the choice. Vaccine delivery through the respiratory tract, alimentary tract, or skin may also elicit mucosal immune responses at the site of virus entry and improve cellular immunity. Enhancing vaccine effectiveness may also improve vaccine acceptance among the public population. In an event where a mass vaccination campaign may be necessary, such as during a pandemic, the logistical barriers associated with the supply and disposal of syringes and needles would be substantially reduced. Furthermore, the potential use of dry vaccine formulations would eliminate the need for a cold chain for storage and distribution. Collectively, these advantages would ultimately increase the speed of vaccinations, critical in a pandemic environment.

However, one of the major weaknesses of needle-free vaccines is their limited effectiveness. Mucosal vaccinations, unless formulated as a live attenuated vaccine, requires large amounts of antigen and usually in several doses in order to elicit a strong immune response. In a pandemic situation, mucosal vaccination with inactivated vaccines is consequently impractical due to the financial and logistical measures involved. In contrast, dermal vaccination with doses similar to parenteral vaccination may be feasible with the use of proper delivery methods or appropriate adjuvants. Additionally, studies have demonstrated the adjuvants alum, MF59 and influenza virosomes ineffective for intranasal vaccinations. Although there has previously been little evaluation of possible adjuvants for transcutaneous vaccination as compared to intranasal vaccination, currently there are numerous pre-clinical assessments underway evaluating both vaccination systems.

Mucosal immunization

Mucosal tissues are large in size and exhibit immunological competence, making them attractive target sites for vaccination. Moreover, mucosal vaccinations are easy to administer and can induce both strong systemic and local immune responses, which can protect at the point of virus entry. Intranasal administration is the most widely-studied form of mucosal immunization and is the only approach that has been approved for commercial use. For increased effectiveness, presently all intranasal influenza vaccines commercially available are LAIV vaccines. Safety concerns of the higher risk for wheezing and hospitalization of young children who receive LAIV have prompted studies evaluating the use of inactivated vaccines. However, inactivated vaccines have produced adverse events as well, namely the occurrence of facial palsy following administration of a heat-labile enterotoxin (LT)-adjuvanted vaccine. The toxic properties of the LT adjuvant has stimulated the evaluation of a detoxified LT adjuvant, though these studies have only been in animals thus far. These adverse events stemming from both activated and inactivated intranasal vaccines have occurred at either the late-stages of pre-licensure development or after licensure, with a relatively low incidence. Powder formulations developed for nasal delivery have also demonstrated promising results, remaining in the nasal cavity longer than the liquid formulation. This may suggest higher bioavailability and immune responses; however, these assessments have only been conducted in animal studies.

Dermal immunization

The skin is also an appealing target site for vaccination as it is easily accessible and a highly immunocompetent organ. The skin is divided into the stratum corneum, the epidermis, and
the dermis, with the latter two rich in antigen-presenting cells (APC). Although the intact stratum corneum prevents the penetration of foreign molecules; once it has been penetrated, antigens are capable of reaching the abundance of APCs in the epidermis and dermis. It is this pathway that intradermal vaccination has the theoretical potential to allow dose sparing delivery, essential in the event of a pandemic. Intradermal delivery using traditional microneedles has been studied in various clinical trials. These trials concluded that a low-dose 0.1 mL intradermal vaccine (typically one-fifth of the standard volume of adult intramuscular influenza vaccines) induced antibody titers comparable to or higher than the conventional full dose intramuscular vaccine. However, local inflammatory reactions such as erythema occurred significantly more frequently following intradermal as compared to intramuscular vaccination. Furthermore, the procedure for intradermal delivery using traditional needles is technically challenging and therefore not suitable for routine vaccinations. However, intradermal vaccination can also be administered with specially designed needles that allow for controlled depth of skin penetration. The BD Soluvia (BD Medical Pharmaceutical Systems) device has shown favorable results in Phase II and Phase III clinical trials and the EMA has approved an intradermal influenza vaccine utilizing this device.

An additional approach to intradermal vaccine delivery is the use of arrays of pointed microneedles, which can also penetrate the stratum corneum. The advantage to this delivery is that the microneedles are designed to target cells in the epidermis without touching the nerves in the underlying tissue therefore eliciting little sensation and no pain. This mechanism is also an easy technique to administer the vaccine, requiring no specially trained medical personnel. A 2009 clinical trial demonstrated that individuals who received doses of 3 µg or 6 µg hemagglutinin per influenza strain via the MicronJet device (NanoPass Technologies, Ltd.) produced similar immune response compared to those who received 15 µg by intramuscular injection.

Jet injectors are also an alternative option to delivering vaccine to the epidermal, subcutaneous or intramuscular tissues. Suitable for mass vaccination campaigns, this needle-free mechanism offers improved safety and avoids the risk of cross-contamination by using a disposable syringe. A 2011 study investigated the safety, tolerability, and immunogenicity of an inactivated trivalent seasonal influenza vaccine administered with the needle-free disposable-syringe jet injector, LectraJet M3 RA. There were no related serious adverse events (SAEs) and adverse events that did occur (erythema and induration) were transient and well tolerated. Overall, the jet injector proved to be well-tolerated and immunogenic as compared to the traditional needle-syringe method.

Vaccines can also be delivered through the skin by the transcutaneous approach of using patches. The vaccine can be formulated on a patch with a Escherichia coli LT adjuvant or alternatively, the patch can contain only LT and is applied on the skin at the site of vaccine injection. A 2005 study conducted in the elderly concluded that subjects who had received both the vaccine and the patch had greater antibody responses compared to those who received the vaccine alone.

Although these novel vaccine delivery mechanisms seem promising, a future research priority is clinical research evaluating their immunogenicity, especially among different populations, and in conjunction with adjuvants.
7. Current Product Pipeline

7.1 Vaccines

The EU has instituted procedures, managed by the EMA, in order to expedite the authorization and availability of vaccines in the event of an influenza pandemic. As stated in the 2004 background paper, in 2004 the EMA published guidelines on the development and registration of pandemic influenza vaccines based on a 'mock-up vaccine' strategy. This 'mock-up' strategy allows a vaccine to be developed and authorized in advance of a pandemic, based on information generated with a virus strain that could potentially cause a pandemic. The official document provides guidance on the dossier structure and content for pandemic influenza vaccine marketing authorization and addresses the quality requirements, non-clinical safety requirements, and clinical requirements for the mock-up vaccine. A pandemic will not allow time for clinical trials to be conducted therefore it is recommended that immunogenic and safety data be obtained for 'mock-up vaccines' which are developed and tested during the interpandemic period. During a pandemic, once the virus strain causing the pandemic is identified, the manufacturer can include this strain in the mock-up vaccine and apply for it to be used as the actual pandemic vaccine. Under the assumption that the actual pandemic vaccine is similar to and is produced in the same manner as the 'mock-up vaccines', clinical data from the core pandemic dossier can be extrapolated to the actual pandemic vaccine resulting in rapid approval and registration for immediate use. This critical document ultimately provides the basis for a fast track authorization procedure for pandemic influenza vaccines. In 2008, the EMA published a revised edition of these guidelines, which can be accessed in Appendix 6.2.10.

The emergence of the swine-origin (S-OIV) A/H1N1 influenza virus in 2009 elicited a rapid global response in the development and production of pandemic influenza vaccines. Interpandemic influenza immunization presents unique challenges including the requirement of annual immunizations, multiple co-circulating virus strains, antigenic change of the influenza virus, and a broad age spectrum of disease. The development of pandemic influenza vaccines include the additional obstacles of the need to induce a broad spectrum and long-lasting immune response, a much more rapid manufacturing time, and a large enough production capacity to reach everyone in the world who is at risk. These challenges continue to stimulate the development of new technologies in the production of pandemic influenza vaccines.

Vaccine development has evolved to a number of diverse platforms including inactivated whole virus vaccines, split vaccines, subunit vaccines, live attenuated vaccines, adjuvanted vaccines, egg-produced vaccines, cell-cultured produced vaccines, vaccines utilizing different delivery mechanisms as well as combinations of the various vaccines mentioned above. For the 2009 influenza A (H1N1) pandemic, different vaccine types were utilized in the United States and Australia as compared to Europe. The United States and Australia, and on a limited scale in Europe, used non-adjuvanted monovalent vaccines. The United States did not have a fast-track system established for adjuvanted influenza vaccines to be registered and approved therefore no adjuvanted influenza vaccine has ever been licensed.

In contrast, within the EU, adjuvanted pandemic vaccines were more widely used. The Celvapan® (Baxter), Focetria® (Novartis) and Pandemrix® (GSK) vaccines were authorized...
through the central procedure under the EMA although the use of Pandemrix® was more common.\textsuperscript{94} The EMA reported that as of August 2010, 30.5 million people had been vaccinated with Pandemrix® compared to 6.5 million with Focetria®.\textsuperscript{94} In addition to Pandemrix® and Focetria®, by December 2009, six other influenza A (H1N1) pdm09 vaccines were available in the European Union (EU)/European Economic Area (EEA).\textsuperscript{94} Table 6.2.4 provides an overview of the composition of all centrally licensed vaccines available in the EU during the 2009 H1N1 pandemic.\textsuperscript{55}

Currently authorized pandemic vaccines in the United States and Europe are shown in Annex 6.2.1.

**Table 6.2.4: Overview of available influenza A (H1N1) pandemic vaccines in the European Union in December 2009**

<table>
<thead>
<tr>
<th>Name, producer</th>
<th>Product description</th>
<th>Culture medium</th>
<th>Haemagglutinin content</th>
<th>Adjuvant emulsion</th>
<th>Number of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celvapan, Baxter</td>
<td>Whole virion, wild-type A/California/7/2009 (H1N1), inactivated</td>
<td>Vero cell-derived</td>
<td>7.5 µg</td>
<td>None</td>
<td>All +6 months: 2 x 0.5 mL</td>
</tr>
<tr>
<td>Pandemrix, GSK</td>
<td>Split-virion, reassortant A/California/7/2009 (H1N1)-like strain, inactivated, adjuvanted</td>
<td>Egg-derived</td>
<td>3.75 RE (per full dose)</td>
<td>AS03</td>
<td>Adults, adolescents and children ≥ 10 years: 1 x 0.5 mL; Children 6 months – 9 years: 2 x 0.25 mL</td>
</tr>
<tr>
<td>Focetria, Novartis</td>
<td>Surface-antigens (haemagglutinin and neuraminidase), reassortant, A/California/7/2009 (H1N1)-like strain, inactivated, adjuvanted</td>
<td>Egg-derived</td>
<td>2.5 µg (per half dose)</td>
<td>MF59C.1</td>
<td>Adults, adolescents and children ≥ 9 years: 1 x 0.5 mL; Children 6 months – 8 years: 2 x 0.5 mL</td>
</tr>
<tr>
<td>Fluvax P. Omnivest</td>
<td>Whole virion, reassortant A/California/7/2009 (H1N1)-like strain, inactivated</td>
<td>Egg-derived</td>
<td>6 µg (per full dose)</td>
<td>Aluminium phosphate</td>
<td>Adults and adolescents ≥ 12 years: 1 x 0.5 mL; Children 12 months – 12 years: 1 x 0.25 mL</td>
</tr>
<tr>
<td>Pannensa, Sanofi Pasteur</td>
<td>Split-virion, reassortant A/California/7/2009 (H1N1)-like strain, inactivated</td>
<td>Egg-derived</td>
<td>15 µg (per full dose)</td>
<td>None</td>
<td>Adults, adolescents and children ≥ 8 years: 1 x 0.5 mL; Elderly ≥ 60 years and children 3 – 8 years: 2 x 0.5 mL; Children 6 – 35 months: 2 x 0.25 mL</td>
</tr>
<tr>
<td>Celsyn, Novartis</td>
<td>Surface-antigens (haemagglutinin and neuraminidase), reassortant, A/California/7/2009 (H1N1)-like strain, inactivated, adjuvanted</td>
<td>MOCK cell-derived</td>
<td>3.75 RE (per half dose)</td>
<td>MF59C.1</td>
<td>Adults 18 – 40 years, children 3 – 17 years: 1 x 0.25 mL; Adults &gt; 40 years: 2 x 0.25 mL</td>
</tr>
<tr>
<td>PanvaxHsin, CSL</td>
<td>Split-virion, reassortant A/California/7/2009 (H1N1)-like strain, inactivated</td>
<td>Egg-derived</td>
<td>15 µg</td>
<td>None</td>
<td>Adults, adolescents and children ≥ 9 years: 1 x 0.5 mL</td>
</tr>
<tr>
<td>CANTGRIP, Cantacuzino</td>
<td>Split-virion, reassortant A/California/7/2009 (H1N1)-like strain, inactivated</td>
<td>Egg-derived</td>
<td>15 µg</td>
<td>None</td>
<td>Adults ≥ 18 years: 1 x 0.5 mL</td>
</tr>
</tbody>
</table>

Source: Mereckiene, J. et al. Influenza A (H1N1) pdm09 vaccination policies and coverage in Europe. Euro Surveill 17, (2012).\textsuperscript{55}

### 7.1.1 Pandemic vaccine safety

Available data in 2010 demonstrated that pandemic influenza vaccines were well tolerated and performed similarly to the corresponding interpandemic vaccines in relation to vaccine safety and lack of serious adverse events.\textsuperscript{28} These data support the validity of a ‘mock-up’
strategy for rapid development of a safe vaccine during an influenza pandemic.\textsuperscript{49} Clinical trials evaluating pandemic H1N1 vaccines produced by European manufacturers also indicated good tolerability with only minor side effects in health children, adults and the elderly.\textsuperscript{49} During the 2009 pandemic, monitoring of adverse events following immunization (AEFI) depended on existing national pharmacovigilance systems, such as notification by health professionals and the public to national drug agencies and, when existing, surveillance networks for rare disorders.\textsuperscript{43} Concurrently, vaccine authorization obligations required manufacturers to undergo the same rigorous manufacturing oversight, product quality testing and lot release procedures as interpandemic vaccines.\textsuperscript{49} Manufacturers were also obligated to conduct systematic post-marketing surveillance and send monthly periodic safety update reports (PSURs) to the EMA.\textsuperscript{49} To be vigilant in investigating vaccine safety, national authorities conducted additional pharmacovigilance activities including clinical trials, additional registries, active specific vigilance, follow up of vaccinated cohorts and multi-centre studies in children and pregnant women.\textsuperscript{43} Preliminary safety data as of March 2010 reported that out of 867 556 vaccines registered in Italy, 1 246 (0.14\%) spontaneous reports of AEFI had been received.\textsuperscript{43} In The Netherlands, a prospective cohort study following 3 780 individuals vaccinated with Focetria\textsuperscript{®} found that 28\% of the 94\% respondents reported a mild AEFI.\textsuperscript{43} Individuals vaccinated with Pandemrix\textsuperscript{®} stated pyrexia as the most frequently reported AEFI.\textsuperscript{43}

The detection of rare safety signals require examining large population numbers, which is most feasibly facilitated by combining data across countries, and careful post-marketing surveillance. Following the onset of the 2009 H1N1 pandemic, the WHO and the ECDC initiated the Paniflow and Vaccine Adverse Events Surveillance and Communication (VAESCO) projects, respectively, to monitor vaccine safety.\textsuperscript{43} Paniflow is a web-based reporting tool whereas VAESCO links large computerized clinical databases and immunization registries.\textsuperscript{43} Additional details on these projects are outlined in the table below.
Table 6.2.5: International vaccine safety monitoring projects

<table>
<thead>
<tr>
<th>Coordinated by</th>
<th>VAESCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed and coordinated by Uppsala Monitoring Centre (UMC) in collaboration with the WHO and the Swiss medicines agency</td>
<td>A consortium of experts from eight EU countries</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Financial support</th>
<th>Participating European countries (as of 22 March 2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>Croatia, Lithuania, Serbia. Roll out to countries receiving stockpiled vaccine</td>
</tr>
<tr>
<td>ECDC</td>
<td>Denmark, Finland, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Objectives</th>
<th>To monitor adverse events following administration of drugs and vaccines during a pandemic with a focus on countries that do not have well-established vaccine safety information in Europe through standardizing methodologies, facilitating data comparability, and building collaborative networks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concept</td>
<td>Complement routine monitoring of adverse events through National Regulatory Agencies reporting to EMA EudraVigilance database</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concept</th>
<th>Web-based system and software</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concept</td>
<td>Cumulative data are immediately available at all levels</td>
</tr>
<tr>
<td>Concept</td>
<td>Experts from UMC analyse international patterns of events &amp; communicate to individual countries</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concept</th>
<th>Linkage of large computerized clinical databases and immunization registries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concept</td>
<td>Derive background incidence data on rare and more common conditions in larger European populations that could possibly be related to vaccine administration</td>
</tr>
</tbody>
</table>


Guillain-Barré Syndrome

As reported on page 30 of the 2004 background paper, a swine-origin influenza A (H1N1) subtype A/NJ/76 vaccine had been developed and distributed in 1976 in anticipation of an influenza pandemic. However, the vaccine was found to be associated with a seven fold increased risk of Guillain-Barré syndrome (GBS) and vaccination was immediately discontinued. Subsequent prospective surveillance studies on seasonal vaccines used in the 1978, 1979, 1980, 1992, 1992 seasons have demonstrated no or modest increases in the risk of Guillain-Barré syndrome although the exact causal mechanism of this phenomenon has never been elucidated. Despite corroborating data from multiple studies of little to no risk, the ECDC requested VAESCO to investigate a possible association between the pandemic vaccines used in Europe during the 2009/2010 winter season and GBS. Similar studies were conducted around the world including, the United States, Canada, Australia, Japan, Taiwan, and Singapore. A multi-country case-control study conducted by VAESCO in 2011 concluded that there was no increased risk of GBS following the administration of adjuvanted vaccines, Pandemrix® and Focetria®, and that this data was consistent across all countries in the study. Interestingly, while there has been no evidence of association...
between GBS and influenza vaccines, there has been a documented association of GBS with influenza infection itself.49

Narcolepsy

Narcolepsy is a rare chronic neurological sleep disorder caused by the brain’s inability to regulate sleep-wake cycles normally.94,108 Although its etiology is unknown, narcolepsy is considered to be an auto-immune disease that includes a strong genetic predisposition with the HLA DQB1*0602 allele having been associated with most cases.109 Narcolepsy is a disorder of excessive daytime sleepiness that may occur both at rest and during periods of activity, such as talking and eating.94 The most severe cases also experience cataplexy, which is a sudden loss of muscle tone causing collapse in response to an emotional stimulus.94 Onset of disease before the age of 10 is rare; the peak age of narcolepsy is late adolescence into early adulthood.109 Though symptoms generally begin in adolescence the condition is not often suspected by clinicians, leaving some cases undiagnosed until adulthood. Patients have also been misdiagnosed with depression or having attention deficit disorder (ADD).94

On 12 October 2009, Finland began a national vaccination campaign using the AS03-adjuvanted vaccine Pandemrix®.108 The first case of narcolepsy in a child that had been vaccinated with Pandemrix® was reported in February of 2010.109 By August, there were 14 cases of confirmed narcolepsy in Pandemrix®-vaccinated children prompting concern of an association between the vaccine and narcolepsy in children.109 Similarly in Sweden, the first cases of narcolepsy in children were reported to the Medical Products Agency (MPA) in the spring of 2010 with increasing number of cases by late summer.110 Following these reports, the Finnish health authorities decided to terminate the use of Pandemrix®. A recent 2012 study in Finland conducted a systematic analysis of the incidence of narcolepsy in children 17 years and younger between 2002-2010.109 Findings show a 17-fold increase in the incidence of childhood narcolepsy in 2010 as compared to 2002-2009.109 Of the 54 diagnosed childhood narcoleptic patients, 50 children had received the Pandemrix® vaccine within eight months before onset of symptoms.109 Additionally, there was a moderate (three-fold) increase of narcolepsy in adolescents with no increase seen in adults over the age of 20.109 A retrospective cohort study also conducted in Finland in 2012 evaluated the possible association between Pandemrix® and incidence of narcolepsy in children and adolescents. Findings from this study show a 12.7-fold risk of narcolepsy in 4-19 year olds within eight months after receiving a Pandemrix® vaccination as compared to those unvaccinated in the same age group.108 A similar study of children and adolescents conducted by the MPA in Sweden also found a seven-fold higher incidence of narcolepsy in those vaccinated with Pandemrix® compared to those who were not vaccinated.110 Preliminary passive reporting data from France, Norway and Ireland also described an increase in the number of narcolepsy cases in Pandemrix®-vaccinated children and adolescents.108

Following these initial studies, the ECDC and VAESCO conducted two multi-country epidemiological studies in order to investigate a possible association between the increase of narcolepsy cases following the administration of influenza A(H1N1)pdm09 vaccines.94 These studies occurred in eight countries including: Finland and Sweden, known as the signaling countries as they originally reported the safety signal; and Denmark, Italy, France, the Netherlands, Norway and the United Kingdom, known as the non-signaling countries in these studies. The case-control study was able to confirm the association between vaccination with Pandemrix® and increased risk of narcolepsy in children and adolescents (aged 5-19
years) in the signaling countries of Finland and Sweden. No association was found in adults, corroborating the results from initial Finnish and Swedish studies. Primary analysis, which is designed to avoid biases such as media attention and diagnostic awareness, resulted with no significant risk to children and adolescents in the non-signaling countries. In contrast, sensitivity analyses, which assess the robustness of results from the primary analysis, demonstrated the importance of time-related factors that can affect the strength of association between exposure and outcome. When analysis identified disease onset as the date when excessive daytime sleepiness began and only considered cases with an onset prior to media attention, results produced an increased risk for narcolepsy for children and adolescents following of influenza A(H1N1)pdm09 vaccination in both signaling and non-signaling countries. Interestingly, a similar sensitivity analysis also showed an association in adults in the non-signaling countries prior to the onset of media attention.

The 2009 influenza A (H1N1) pandemic was the first event to reveal a possible association between vaccination and narcolepsy. As stated previously, Pandemrix® was the most frequently utilized vaccine during the pandemic. Four countries, Denmark, Finland, Norway, and Sweden, offered only Pandemrix®. Other countries offered a variety of combinations of available pandemic vaccines. Variability in vaccine recommendation guidelines also existed across countries. Some countries recommended vaccinations to their entire population while other countries recommended it only to selected risk groups. Of the countries that did offer Pandemrix®, Canada and the United Kingdom did not report the safety signal even though both countries have the same genetic susceptibility to narcolepsy as the Nordic countries. Interestingly, the HLA DQB1*0602 allele is almost twice as common in northern than in southern Europe. Although the initial Finnish and Swedish studies were able to demonstrate a strong safety signal between Pandemrix® and narcolepsy in children, it must also be noted that they also achieved 75% vaccine coverage in children and adolescents and 67% vaccine coverage in children, respectively, due to the administration of vaccines through the school health systems. This is in contrast to France and Italy where they achieved 10% and 0.3% vaccine coverage rates, respectively. A recent Chinese study demonstrated a three-fold increased incidence of narcolepsy following the onset of the 2009 H1N1 pandemic season; however these results were independent of vaccination. Following review of the ECDC and VAESCO studies, in 2011, the EMA recommended restricting use of Pandemrix® to individuals under 20 years of age and only in the absence of an available interpandemic trivalent influenza vaccine and if immunization against H1N1 is still required.

The collective observations and results from the described studies suggest a multifactorial nature to this new phenomenon. A technical report summarizing the studies conducted by the ECDC and VAESCO recommends the following recommendations for future studies:

- Increase the number of cases collected from the period prior to increased public awareness of narcolepsy association.
- Collect national data from countries that were not included in the initial report, especially those with high national vaccine coverage rates in other population groups also not studied in this initial report.
- Expand the investigation to countries outside of Europe, such as Canada and Brazil, that used the AS03-adjuvanted vaccine yet did not have as much media attention regarding the possible narcolepsy association.
Update on 2004 Background Paper, BP 6.2 Pandemic Influenza

- Conduct additional epidemiological studies to determine the role of different environmental factors and the use of adjuvants in the possible association to narcolepsy.

In 2012, the EMA conducted a review of the results from the Finnish National Institute of Health and Welfare (THL) investigating differences in immunological response triggered by various pandemic influenza vaccines as a potential risk factor for the development of narcolepsy. The EMA concluded that the results were insufficient to draw any conclusions and did not lead to new concerns regarding Pandemrix® or other influenza vaccines. Based on current evidence, the role between the Pandemrix® vaccine specifically its antigen and adjuvant; and narcolepsy remains unknown. Although Pandemrix® is authorized for use in the EU, it is currently unavailable. The EMA will continue to review further analysis of the association between Pandemrix® and narcolepsy as it becomes available.

7.2 Antiviral agents

Compared to 2004, current antiviral therapy remains unchanged with four commercially licensed products including: neuraminidase inhibitors (NAIs) oseltamivir and zanamivir, and the adamantanes, amantadine and rimanatadine, which are M2 ion-channel inhibitors. Only one of these products, oseltamivir, was included in the WHO Model List of Essential Medicines for selected high-risk patients. In the initial stages of the 2009 H1N1 pandemic, NAIs were invaluable in controlling the spread of influenza. However, increased use of these antiviral agents led to the emergence of drug-resistant variants of the virus ultimately resulting in reduced drug efficacy. Additional limitations to these anti-influenza drugs lie in several critical areas: high prevalence of M2 inhibitor resistance among H3N2; H5N1 and H1N1 isolates during therapeutic use; limited antiviral efficacy among certain populations and in severe cases of influenza; and a lack of parenteral agents for seriously-ill patients. These are the principal factors that continue to drive the need for the development of new antiviral agents, particularly in regards to broad reactivity against all virus strains and subtypes, drug resistance, pandemic preparedness, and the consideration of combination therapy.

Although the existing NAIs and M2-ion channel inhibitors differ substantially in their mechanisms of action and tolerability profiles, they both utilize a pathogen-targeted approach to controlling influenza infection. In addition to this approach, candidates presently in development are investigating the use of host-targeted approaches, immunomodulators and combination therapy in inhibiting influenza viral replication and infection. There has also been increasing interest in development strategies focusing on modulating influenza-induced influenza inflammation. The cyclo-oxygenase (COX) pathway and peroxisome proliferator-activated receptor agonists (PPARs) are known key regulators of inflammation and have been identified as potential therapeutic targets.

Current and investigational antiviral agents have proven to be effective when administered as a single drug regimen; however, combination therapy is also being evaluated for the potential to elicit additive or synergistic effects in inhibiting influenza viral replication. A 2011 study demonstrated that the combination oral oseltamivir and intravenous (IV) zanamivir administered in healthy Thai adults was well tolerated and elicited no significant pharmacokinetic interactions between the two drugs. A 2012 study evaluated the RNA polymerase inhibitor favipiravir in combination with peramivir, a NAI, against pandemic
influenza A 2009 H1N1 virus infections in mice. Results also demonstrated that the combination therapy performed better than suboptimal doses of each individual compound. Another study conducted in 2012 investigated a triple combination antiviral drug (TCAD) regimen consisting of amantadine, oseltamivir, and ribavirin against amantadine-resistant 2009 influenza A H1N1 virus infections in mice. Findings demonstrated in vivo efficacy of TCAD therapy against resistant influenza strains.

It is likely that influenza virus strains will confer resistance to monotherapy; therefore future antiviral agents for the treatment management of influenza will need to have broad spectrum activity and improved pharmacological profiles. This includes greater potency that restricts viral replication, fewer dose regimens, reduced risk of antiviral resistance, and the further exploration of combination therapy to target different viral proteins or factors of viral pathogenicity. A comprehensive overview of antiviral agents in the preclinical or clinical stages is shown in Table 6.2.6.

<table>
<thead>
<tr>
<th>Table 6.2.6: Antiviral agents in development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiviral agent</strong></td>
</tr>
<tr>
<td>Pathogen-targeted approaches</td>
</tr>
<tr>
<td>Laminamivir (CS-8958)</td>
</tr>
<tr>
<td>Peramivir</td>
</tr>
<tr>
<td>Zanamivir</td>
</tr>
<tr>
<td>Favipiravir (T-705)</td>
</tr>
<tr>
<td>Host-targeted approaches</td>
</tr>
<tr>
<td>DAS-181 (Fludase)</td>
</tr>
</tbody>
</table>

Source: manufacturers’ websites

7.3 Rapid diagnostic tests

Viral culture has been the long-standing gold standard for influenza diagnosis; however, the lengthy turnaround time (TAT) for results has reduced its functionality for optimal patient management. Results from direct antibody staining (DFA) may be available in hours but this method requires specialized equipment and training to interpret results. More recently, RT-PCR has superseded this method as the gold standard due to its high detection rate and result output in hours instead of days. However, this test is the most expensive and not widely available because of the specialized equipment and expertise require. The limitations of these traditional methods have been evident in the recent development of more highly
accurate and rapid molecular assays. The 2009 influenza A H1N1 virus pandemic underlined the importance of precise assays with brief TAT and the ability to differentiate influenza strains in order to accurately monitor the spread of an outbreak and ensure effective clinical management of patients. Traditional and more recent methods of influenza virus detection are highlighted in the following table. Annexes 6.2.2 and 6.2.3 show commercially-available rapid influenza diagnostic tests and molecular diagnostic tests with longer time until results are produced.

### Table 6.2.7 Influenza virus testing methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Virus strains detected</th>
<th>Test time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral cell culture</td>
<td>A &amp; B</td>
<td>3-10 days</td>
</tr>
<tr>
<td>Direct (DFA) or Indirect (IFA) antibody staining</td>
<td>A &amp; B</td>
<td>1-4 hours</td>
</tr>
<tr>
<td>Reverse transcriptase polymerase chain reaction</td>
<td>A &amp; B</td>
<td>1-6 hours</td>
</tr>
<tr>
<td>Rapid influenza diagnostic test (RIDT)</td>
<td>A &amp; B</td>
<td>&lt; 30 minutes</td>
</tr>
</tbody>
</table>

Source: adapted from [http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm](http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm)

Future research priorities should focus on developing specific and sensitive RDTs to ensure accurate case management and epidemiological surveillance.

### 8. Future research opportunities

Following the initial outbreak of avian influenza in 1997, the threat of a potential influenza pandemic was recognized by key stakeholders. A substantial amount of financial support and research has since been allocated to increasing pandemic influenza preparedness at the international level. The subsequent unexpected emergence of the 2009 H1N1 influenza pandemic challenged these efforts in every aspect of pandemic preparedness. Fortunately, the new virus appeared less virulent than anticipated.

The EU has recognized the public health impact of influenza through the establishment of extensive influenza-related surveillance networks, consortiums, and research projects. The necessary information collected will inform future policy development and decisions. However, the prevention and control of influenza requires immense efforts and strong partnerships during both the interpandemic and pandemic periods. Cooperation and collaboration between all key stakeholders will facilitate a rapid and effective response in the event of a future pandemic.

**Future influenza research should be prioritized in the following areas:**

- The virology and pathogenicity of influenza viruses in order to predict and prepare for the next pandemic.
- Improved quantification methods to more accurately assess the economic burden of influenza.
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- Improved global and country surveillance systems in order to accurately estimate morbidity and mortality, particularly in developing countries.
- Understanding barriers to immunization uptake combined with evaluation of interventions.
- Expansion of global vaccine production capacity particularly in low and middle income countries.
- Global and country-level vaccine coverage information and monitoring systems.
- Rapid scale up of vaccine production in case the next pandemic is caused by a subtype that is less antigenic and requires two doses of vaccine.
- Standardization of methodology in measuring vaccine effectiveness.
- Vaccine platforms that produce safe and effective vaccines with cross-strain and long-lasting protection against influenza.
- Additional studies on the cost-effectiveness of vaccination.
- Development of new antiviral agents with broad reactivity against all virus strains and subtypes.
- Development of RIDTs to accurately detect and distinguish between different influenza virus subtypes.

References

11 Ison, M. G. Influenza in Hospitalized Adults: Gaining Insight into a Significant Problem. The Journal of Infectious Diseases 200, 485–488 (2009).
Update on 2004 Background Paper, BP 6.2 Pandemic Influenza


20 Harder, K. M., Mølbak, K., Glismann, S. & Christiansen, A. H. Influenza-associated illness is an important contributor to febrile convulsions in Danish children. Journal of Infection 64, 520–524 (2012).


29 European Centre for Disease Prevention and Control. The 2009 A(H1N1) pandemic in Europe : a review of the experience. (European Centre for Disease Prevention and Control, 2010).


Update on 2004 Background Paper, BP 6.2 Pandemic Influenza


Lapinsky, S. E. H1N1 novel influenza A in pregnant and immunocompromised patients. Critical Care Medicine 38, e52–e57 (2010).


Valenciano, M., Ciancio, B. & Moren, A. First steps in the design of a system to monitor vaccine effectiveness during seasonal and pandemic influenza in EU/EEA Member States. Euro surveillance:


63 World Health Organization. Pandemic Influenza Preparedness (PIP) Framework for the sharing of influenza viruses and access to vaccines and other benefits. 68 (World Health Organization, 2011).

64 Friede, M. et al. WHO initiative to increase global and equitable access to influenza vaccine in the event of a pandemic: Supporting developing country production capacity through technology transfer. Vaccine 29, Supplement 1, A2–A7 (2011).


Update on 2004 Background Paper, BP 6.2 Pandemic Influenza


Update on 2004 Background Paper, BP 6.2 Pandemic Influenza

105 European Medicines Agency. EMA Authorisation Procedures. at
   <http://www.emea.europa.eu/ema/index.jsp?curl=pages/special_topics/q_and_a/q_and_a_detail_000080.jsp>

106 Dieleman, J. et al. Guillain-Barre syndrome and adjuvanted pandemic influenza A (H1N1) 2009

107 European Centre for Disease Prevention and Control. Enhanced monitoring of vaccine safety for
   2009 pandemic vaccines. (2012). at

108 Nohynek, H. et al. AS03 Adjuvanted AH1N1 Vaccine Associated with an Abrupt Increase in the

109 Partinen, M. et al. Increased Incidence and Clinical Picture of Childhood Narcolepsy following the

110 Medical Products Agency. Report from an epidemiological study in Sweden on vaccination with
   Pandemrix and narcolepsy. (Medical Products Agency, 2011). at

111 European Medicines Agency. European Medicines Agency recommends restricting use of
   Pandemrix. (2011). at

112 European Medicines Agency. European Medicines Agency reviews hypothesis on Pandemrix and
   development of narcolepsy. (2012). at

113 Boltz, D. A., Aldridge Jr., J. R., Webster, R. G. & Govorkova, E. A. Drugs in Development for

114 Pukrittayakamee, S. et al. An Open-Label Crossover Study To Evaluate Potential Pharmacokinetic
   Interactions between Oral Oseltamivir and Intravenous Zanamivir in Healthy Thai Adults.

115 Tarbet, E. B. et al. Combinations of favipiravir and peramivir for the treatment of pandemic

116 Nguyen, J. T. et al. Efficacy of Combined Therapy with Amantadine, Oseltamivir, and Ribavirin In
Annexes

Annex 6.2.1: Current FDA and EMA approved pandemic vaccines

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Manufacturer</th>
<th>Administration route</th>
<th>Indications and dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA Approved</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza A (H1N1) 2009 Monovalent Vaccine</td>
<td>CSL Limited</td>
<td>Intramuscular injection</td>
<td>6 months – 35 months 2 x 0.25 mL approximately four weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>36 months - 9 years 2 x 0.5 mL approximately four weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 years and older Single 0.5 mL dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 years and older Single 0.5 mL dose</td>
</tr>
<tr>
<td>Influenza A (H1N1) 2009 Monovalent Vaccine</td>
<td>ID Biomedical Corporation of Quebec (IDB)</td>
<td>Intramuscular injection</td>
<td>18 years and older Single 0.5 mL dose</td>
</tr>
<tr>
<td>Influenza A (H1N1) 2009 Monovalent Vaccine</td>
<td>Novartis Vaccines and Diagnostics Ltd.</td>
<td>Intramuscular injection</td>
<td>4 - 9 years of age 2 x 0.5 mL approximately four weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 – 17 years of age Single 0.5 mL dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 years and older Single 0.5 mL dose</td>
</tr>
<tr>
<td>Influenza A (H1N1) 2009 Monovalent Vaccine</td>
<td>Sanofi Pasteur, Inc.</td>
<td>Intramuscular injection</td>
<td>6 months – 35 months 2 x 0.25 mL approximately four weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>36 months - 9 years 2 x 0.5 mL approximately four weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 years and older Single 0.5 mL dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 years and older Single 0.5 mL dose</td>
</tr>
<tr>
<td>Influenza A (H1N1) 2009 Monovalent Vaccine</td>
<td>MedImmune, LLC.</td>
<td>Intranasal spray</td>
<td>2 -9 years of age 2 x 0.2 mL approximately four weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 – 49 years of age Single 0.2 mL dose</td>
</tr>
<tr>
<td><strong>EMA Approved</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daronrix</td>
<td>GlaxoSmithKline Biologicals S.A.</td>
<td>Intramuscular injection</td>
<td>18 – 60 years of age 2 doses, three weeks apart</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Manufacturer</th>
<th>Administration</th>
<th>Age Group</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Foclivia</strong></td>
<td>Novartis Vaccines and Diagnostics S.r.l.</td>
<td>Intramuscular injection</td>
<td>18 – 60 years of age</td>
<td>2 x 0.5 mL at least three weeks apart</td>
</tr>
<tr>
<td><strong>Pandemic influenza (H5N1) (split-virion, inactivated, adjuvanted)</strong></td>
<td>GlaxoSmithKline Biologicals S.A.</td>
<td>Intramuscular injection</td>
<td>18 years and older</td>
<td>2 x 0.5 mL at least three weeks apart</td>
</tr>
<tr>
<td>GlaxoSmithKline Biologicals S.A.</td>
<td>Intramuscular injection</td>
<td>18 years and older</td>
<td>2 x 0.5 mL at least three weeks apart</td>
<td></td>
</tr>
<tr>
<td><strong>Pandemic Influenza Vaccine H5N1</strong></td>
<td>Baxter AG</td>
<td>Intramuscular injection</td>
<td>18 years and older</td>
<td>2 x 0.5 mL at least three weeks apart</td>
</tr>
<tr>
<td><strong>Pumarix</strong></td>
<td>GlaxoSmithKline Biologicals S.A.</td>
<td>Intramuscular injection</td>
<td>18 years and older</td>
<td>2 x 0.5 mL at least three weeks apart</td>
</tr>
</tbody>
</table>

* Vaccines do not have trade names.
* Vaccines have been authorised under “exceptional circumstances” which occurs when the applicant shows that they are unable to provide comprehensive data on the efficacy and safety of the medicine for which authorisation is being sought, due to the rarity of the condition it is intended for, limited scientific knowledge in the area concerned, or ethical considerations involved in the collection of such data.
* Dosage not specified in the European Public Assessment Report for this vaccine.
### Annex 6.2.2: Rapid influenza diagnostics tests

<table>
<thead>
<tr>
<th>Rapid diagnostic test</th>
<th>Manufacturer</th>
<th>Viral strain detection/differentiation</th>
<th>Viral subtype differentiation</th>
<th>Specimen type</th>
<th>Time to result</th>
<th>Regulatory approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Film Array</td>
<td>Biofire Diagnostics, Inc.</td>
<td>A, B</td>
<td>H1, 2009 H1N1, H3</td>
<td>NP</td>
<td>1 hour</td>
<td>US-IVD, CE-IVD Europe</td>
</tr>
<tr>
<td>Liat Influenza A/B</td>
<td>IQuum, Inc.</td>
<td>A, B</td>
<td>No</td>
<td>NP</td>
<td>20 minutes (24 patients in 8 hrs.)</td>
<td>US-IVD</td>
</tr>
<tr>
<td>Liat Influenza A/2009 H1N1</td>
<td>IQuum, Inc.</td>
<td>A only</td>
<td>2009 H1N1</td>
<td>NP</td>
<td>26 min.</td>
<td>EUO, RUO</td>
</tr>
<tr>
<td>QuickVue Influenza A + B</td>
<td>Quidel Corp.</td>
<td>A, B</td>
<td>No</td>
<td>Nasal swab, NA/W, NP</td>
<td>10 min.</td>
<td>US-IVD</td>
</tr>
<tr>
<td>Sofia Influenza A+B FIA</td>
<td>Quidel Fluorescence</td>
<td>A, B</td>
<td>No</td>
<td>Nasal swab, NP</td>
<td>15 min.</td>
<td>US-IVD, CE-IVD</td>
</tr>
<tr>
<td>BinaxNOW Influenza A &amp; B</td>
<td>Alere, Inc.</td>
<td>A, B</td>
<td>No</td>
<td>Nasal swab, NA/W, NP</td>
<td>15 min.</td>
<td>US-IVD</td>
</tr>
<tr>
<td>Clearview Exact Influenza A&amp;B</td>
<td>Alere, Inc.</td>
<td>A, B</td>
<td>No</td>
<td>Nasal swab</td>
<td>15 min.</td>
<td>US-IVD</td>
</tr>
<tr>
<td>Directigen EZ Flu A + B</td>
<td>Becton Dickinson</td>
<td>A, B</td>
<td>No</td>
<td>NA/W, NP, throat swab</td>
<td>15 min.</td>
<td>US-IVD</td>
</tr>
<tr>
<td>BD Veritor System for Rapid Detection of Flu A+B</td>
<td>Becton Dickinson</td>
<td>A, B</td>
<td>No</td>
<td>Nasal swab, NP</td>
<td>10 min.</td>
<td>US-IVD</td>
</tr>
<tr>
<td>Denka Seiken Quick ExFlu</td>
<td>Denka Seiken CO., Ltd</td>
<td>Not disclosed</td>
<td>Not disclosed</td>
<td>Not disclosed</td>
<td>Not disclosed</td>
<td>Japan</td>
</tr>
<tr>
<td>Quick Navi</td>
<td>Denka Seiken CO., Ltd</td>
<td>Not disclosed</td>
<td>Not disclosed</td>
<td>Nasal swab, NA/W, throat swab</td>
<td>8 min.</td>
<td>Japan</td>
</tr>
<tr>
<td>Espline Influenza A&amp;B-N</td>
<td>Fujirebio, Inc.</td>
<td>A, B</td>
<td>Not disclosed</td>
<td>Nasal swab, NA, NP</td>
<td>Japan</td>
<td>Japan</td>
</tr>
<tr>
<td>Rockeby Influenza A Antigen</td>
<td>Rockeby Biomed</td>
<td>A only</td>
<td>H3N2, H5N1</td>
<td>Nasal swab, NA/W, NP, throat swab</td>
<td>10 min.</td>
<td>IVD</td>
</tr>
<tr>
<td>TRU FLU</td>
<td>Meridien Biosciences</td>
<td>A, B</td>
<td>No</td>
<td>Nasal swab/wash, NP swab/aspirate</td>
<td>15 min.</td>
<td>US-IVD, CE-IVD Europe</td>
</tr>
<tr>
<td>Formosa One Sure Flu A/B Rapid</td>
<td>Formosa Biomedical Technology Corp.</td>
<td>Not disclosed</td>
<td>Not disclosed</td>
<td>Not disclosed</td>
<td>Not disclosed</td>
<td>Not disclosed</td>
</tr>
<tr>
<td>artus Influenza A/B RT-PCR kit</td>
<td>Qiagen</td>
<td>A, B</td>
<td>No</td>
<td>NP</td>
<td>Not specified</td>
<td>US-IVD</td>
</tr>
<tr>
<td>Infinity RVP Plus</td>
<td>AutoGenomics</td>
<td>A, B</td>
<td>2009 H1N1</td>
<td>Not specified</td>
<td>Not specified</td>
<td>RUO</td>
</tr>
<tr>
<td>3M Rapid Detection Flu</td>
<td>3M</td>
<td>A, B</td>
<td>No</td>
<td>Nasal swab, NA, NP</td>
<td>15 min.</td>
<td>US-IVD</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>A+B</th>
<th>Manufacturer</th>
<th>Format</th>
<th>Test Type</th>
<th>Result Time</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSOM Influenza A&amp;B</td>
<td>Sekisui Diagnostics, LLC.</td>
<td>A, B</td>
<td>No</td>
<td>Nasal swab</td>
<td>10 min</td>
</tr>
<tr>
<td>Xpect Flu A&amp;B</td>
<td>Thermo Fisher Scientific</td>
<td>A, B</td>
<td>No</td>
<td>Nasal swab, nasal wash, throat</td>
<td>15 min.</td>
</tr>
</tbody>
</table>

* Only nasal swab and NP specimens are CLIA-waived.

Product status unknown: MultiCode-PLx (EraGen Biosciences acquired by Luminex in June 2011)
Annex 6.2.3: Molecular diagnostics tests with longer time to result

<table>
<thead>
<tr>
<th>Molecular diagnostic test</th>
<th>Manufacturer</th>
<th>Viral strain detection/differentiation</th>
<th>Viral subtype differentiation</th>
<th>Specimen type</th>
<th>Time to result</th>
<th>Regulatory approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xpert Flu Assay</td>
<td>Cepheid</td>
<td>A, B</td>
<td>2009 H1N1</td>
<td>Nasal aspirate/wash (NA/W) or nasopharyngeal swab (NP)</td>
<td>75 min.</td>
<td>US-IVD</td>
</tr>
<tr>
<td>xTAG Respiratory Viral Panel (RVP) v1</td>
<td>Luminex Corp.</td>
<td>A, B</td>
<td>H1, H3, H5</td>
<td>NP</td>
<td>96 patients in 8 hrs. (5min/pt)</td>
<td>US-IVD, Health Canada IVD, CE-IVD Europe</td>
</tr>
<tr>
<td>xTAG RVP FAST</td>
<td>Luminex Corp.</td>
<td>A, B</td>
<td>H1, H3</td>
<td>NP</td>
<td>&lt; 4 hrs.</td>
<td>US-IVD, Health Canada IVD, CE-IVD Europe</td>
</tr>
<tr>
<td>Prodesse ProFlu+</td>
<td>Hologic Gen-Probe, Inc.</td>
<td>A, B</td>
<td>No</td>
<td>NP</td>
<td>&lt; 4 hrs.</td>
<td>US-IVD</td>
</tr>
<tr>
<td>ResPlex II Plus Panel PRE</td>
<td>Qiagen</td>
<td>A, B</td>
<td>2009 H1N1</td>
<td>Not specified</td>
<td>&lt; 6 hrs.</td>
<td>RUO</td>
</tr>
<tr>
<td>Prodesse ProFAST+</td>
<td>Hologic Gen-Probe, Inc.</td>
<td>A only</td>
<td>H1, H3, 2009 H1N1</td>
<td>NP</td>
<td>&lt; 4 hrs.</td>
<td>US-IVD, CE-IVD Europe</td>
</tr>
<tr>
<td>Verigene RV+</td>
<td>Nanosphere</td>
<td>A, B</td>
<td>H1, H3, 2009 H1N1</td>
<td>NP</td>
<td>&lt; 2.5 hrs.</td>
<td>US-IVD</td>
</tr>
<tr>
<td>Verigene Respiratory Virus XP</td>
<td>Nanosphere</td>
<td>A, B</td>
<td>H1, H3, 2009 H1N1</td>
<td>Not specified</td>
<td>&lt; 1.5 hrs.</td>
<td>RUO</td>
</tr>
<tr>
<td>Seeplex Influenza A/B One Step Typing</td>
<td>Seegene</td>
<td>A, B</td>
<td>H1, H3, 2009 H1N1</td>
<td>NP aspirate/swab, bronchoalveolar lavage</td>
<td>&lt; 5 hrs. (?)</td>
<td>Health Canada IVD</td>
</tr>
<tr>
<td>RespiFinder 15 and 19</td>
<td>Patho Finder</td>
<td>A, B</td>
<td>H5N1</td>
<td>Nasal swab, NP aspirate/lavage, bronchoalveolar sputa</td>
<td>&lt; 6 hrs.</td>
<td>CE-IVD</td>
</tr>
<tr>
<td>RespiFinder 22 and SMART 22</td>
<td>Patho Finder</td>
<td>A, B</td>
<td>H1N1</td>
<td>Nasal swab, NP aspirate/lavage, bronchoalveolar sputa</td>
<td>&lt; 6 hrs.</td>
<td>CE-IVD</td>
</tr>
<tr>
<td>RealAccurate Respiratory RT PCR v2.0</td>
<td>Patho Finder</td>
<td>A, B</td>
<td>No</td>
<td>Nasal swab, NP aspirate/lavage, bronchoalveolar</td>
<td>2 hrs.</td>
<td>CE mark</td>
</tr>
<tr>
<td>Simplexa Flu A/B/RSV Direct</td>
<td>Focus Diagnostics</td>
<td>A, B</td>
<td>No</td>
<td>NP</td>
<td>&lt; 1 hr.</td>
<td>US-IVD</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Test Name</th>
<th>Manufacturer</th>
<th>Target(s)</th>
<th>Sample Type</th>
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<tr>
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<td>Focus Diagnostics</td>
<td>A only</td>
<td>2009 H1N1 Nasal swabs, NP aspirate/swab</td>
<td>&lt; 1 hr.</td>
<td>US-IVD, CE mark</td>
</tr>
<tr>
<td>Quidel Molecular Influenza A + B</td>
<td>Quidel Molecular</td>
<td>A, B</td>
<td>No Nasal swab, NP</td>
<td>&lt; 75 min.</td>
<td>US-IVD</td>
</tr>
</tbody>
</table>

* Only approved by CE-IVD Europe
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Appendix 6.2.4  Informal Consultation on Technical Specifications for a WHO International H5N1 Vaccine Stockpile
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Background Paper 6.3
Ischaemic heart disease

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Tel +61 2 9993 4557
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1. Introduction

In 2004 Warren Kaplan and Richard Laing wrote the “Priority Medicines for Europe and the World Report”. In this report they placed great emphasis on the background paper written by Bruce Neal titled “Secondary Prevention of Cardiovascular Disease: Fixed Dose Combinations.” (http://archives.who.int/prioritymeds/report/background/cardiovascular.doc). In the 2004 report Kaplan and Laing stated “The simple solution to this deficiency (in the effective treatment of patients with proven cardiovascular disease) is to develop and test a fixed-dose combination (FDC) product of these proven effective medicines. The research agenda proposed in this section is different to that of the other sections because this approach offers the greatest potential short-to-medium term impact of all of the possible research activities in this Report.” (Page 58). This background paper to the 2013 update of the Priority Medicines for Europe and the World reports on the work that has been done since 2004 making the case that what was proposed in 2004 has now been undertaken and that the next stage is to undertake large scale pan European and global clinical trials to understand the place of “polypills” in the treatment of individuals who have suffered from cardiovascular and/or cerebrovascular events. There have been two large scale clinical trials funded in this area. One of these studies (the UMPIRE trial) has since reported positive results as outlined in detail in this background paper. This report updates the information on this topic.

This report updates the potential information on this topic and therefore continues to focus on secondary prevention among patients who have already suffered a cardiovascular event. The majority of such patients have IHD, but a significant minority have cerebrovascular disease or peripheral vascular disease.

In addition to secondary prevention with the polypill, a number of other pharmacological approaches to prevention and treatment of IHD will need to be researched in order to provide more effective, safer and individualized intervention strategies. These include the development of new lipid-lowering drugs; pharmacological means to address novel mechanistic concepts of vessel wall damage and protect against conditions such as chronic inflammation and local angiogenesis; and regenerative medicine/cell therapy approaches. Similarly, new pharmacological treatment strategies need to be developed for heart failure and arrhythmias, frequent consequences of IHD.

2. What is the size and nature of the disease burden?

Detailed analysis of overall global trends in burden of disease is available in Chapter 5, however a summary of disease burden attributable to cardiovascular disease is included here. Each year about 15.6 million deaths (30% of global mortality) occur from cardiovascular disease (CVD) making it the leading cause of death.² Worldwide, ischaemic heart disease (IHD) is ranked as the leading specific cause of death, with 13.3% of total deaths, followed by cerebrovascular disease (11.1%) (Table 6.3.1). Together IHD and all forms of stroke worldwide killed an estimated 12.9 million people in 2010, a quarter of the global total, an increase from one in five deaths worldwide 20 years earlier.²
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Following global trends, the largest single cause of death in the 2010 Global Burden of Disease study in the combined region of Central, Eastern and Western Europe was ischaemic heart disease (26.6% of all deaths), closely followed by cerebrovascular diseases (ischaemic and haemorrhagic and other non-ischaemic stroke) with 11.0% of the total number of deaths (Table 6.3.1).

The most common specific cause of cardiovascular death is IHD which accounts for 45% of global cardiovascular deaths and 54.6% of European cardiovascular death. Cerebrovascular diseases account for 37.6% of cardiovascular diseases globally and 31.4% in Europe. Hypertensive heart disease is the third biggest contributor to this group of diseases with 5.6% of global cardiovascular mortality and 3.7% of the total cardiovascular mortality in Europe.

Table 6.3.1: DALY and mortality data for the most common cardiovascular diseases, for the European regions and the world.

<table>
<thead>
<tr>
<th></th>
<th>Eastern, Western and Central Europea</th>
<th>World</th>
<th>Eastern, Western and Central Europe</th>
<th>World</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DALYs</td>
<td>% of total</td>
<td>DALYs</td>
<td>% of total</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>32 928 727</td>
<td>13.8</td>
<td>129 819 898</td>
<td>5.2</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>16 913 463</td>
<td>7.1</td>
<td>102 232 304</td>
<td>4.1</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>1 857 167</td>
<td>0.8</td>
<td>15 324 193</td>
<td>0.6</td>
</tr>
</tbody>
</table>


* Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Macedonia, the Former Yugoslav Republic of Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia, Belarus, Estonia, Latvia, Lithuania, Moldova, Russian Federation, Ukraine, Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom.
Figure 6.3.1: Distribution of global and European mortality for cardiovascular and circulatory diseases.


In addition, cardiovascular disease causes a large non-fatal global disease burden as a consequence of prevalent disease states such as angina. When the non-fatal disease burden is taken in conjunction with the healthy life years lost due to premature death the total overall disease burden attributable to cardiovascular and circulatory diseases accounted for 11.8% of global DALYs (Disability Adjusted Life Years) in 2010. The major diseases within this group worldwide are, just as with mortality data, ischaemic heart disease (5.2%), cerebrovascular diseases (4.1%), and hypertensive heart disease (0.6%). In Central, Eastern and Western Europe, 13.8% of the total DALY burden can be attributed to IHD, 7.1% to cerebrovascular disease and 0.8% to hypertensive heart disease (Table 6.3.1).

Not only is CVD currently the greatest cause of death and disability worldwide, CVD mortality is predicted to rise to approximately 23.4 million by 2030 with CVD predicted to remain the leading cause of death. Recent data from the Global Burden of Disease study 2010 confirms the likelihood of reaching these predictions. Cardiovascular diseases and more specifically ischaemic heart disease increased by 31.2% and 34.9%, respectively, in terms of absolute deaths in the past two decades. In terms of years of life lost (YLLs), ischaemic heart disease increased in rank from fourth in 1990 to first in 2010, reflecting an increase of 28%. Cerebrovascular disease is currently ranked third globally for YLLs, but in some Asian regions it is ranked first. Ischaemic heart disease is ranked first in almost all regions other than Asia. In addition, from 1990 to 2010, both ischaemic heart disease (IHD) and cerebrovascular disease have risen in their position amongst the top 10 causes of DALYs – IHD from position number four to number one and stroke from position number five to number three, reflecting increases of 29% and 19% respectively. In Europe, ischaemic heart disease and...
stroke have maintained their ranking as the leading and second most common causes of death and YLLs over the past 20 years. In central and eastern Europe they have maintained their respective highest and second highest rankings for DALYs also, however in western Europe, low back pain has now emerged as the foremost cause for DALYs in that region. IHD and stroke come in at numbers two and three.³

Figure 6.3.2 shows the amount of absolute disability-adjusted life years (DALYs) caused by ischaemic heart disease (IHD) by age group for the world, Central, Eastern and Western Europe. The highest burden of disease from ischaemic heart disease, amongst the three European regions, is present in Eastern Europe in all age groups, followed by Western Europe. The amount of DALYs caused by ischaemic heart disease peaks at 80 years and above in all four regions.

Figure 6.3.3: Absolute deaths caused by ischaemic heart disease by age group and region demonstrates the mortality rates for ischaemic heart disease, in absolute death numbers, by age group and region.³ As with the DALYs, Eastern Europe has the highest number of deaths from ischaemic heart disease amongst the European regions in all age groups, except for in the over 80 years age group, where Western Europe has slightly higher numbers of deaths due to IHD. This is remarkable since Western Europe has approximately half the number of deaths in the other age groups, compared to Eastern Europe. Furthermore, it’s striking that Central Europe has less than half the number of deaths due to IHD than Eastern Europe or Western Europe.

More figures for mortality and burden of disease from IHD per region and age group can be found in the annexes of this background paper.
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Figure 6.3.2: Absolute DALYs caused by ischaemic heart disease by age group and region.³


Figure 6.3.3: Absolute deaths caused by ischaemic heart disease by age group and region.³

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Common interests between Europe and the world

Despite the common misperception that CVD is a ‘rich man’s disease’, 80% of CVD deaths occur in low- or middle-income countries (LMIC). These deaths in LMICs are not only occurring more frequently than in high income countries but are also occurring earlier in life causing a greater social and economic impact in these countries. Many of these countries typically are least equipped to deal with this epidemic of CVD due to inadequate health care systems and significant levels of poverty.

The commonality between high income countries and low income countries of risk factors responsible for the identical leading causes of death ensures that any solutions that are found have the potential (within the bounds of adaptation to local conditions) to advantage a broad range of countries across the economic spectrum. Any intervention that has the capacity to affect significant public good in Europe can be applied globally in many different settings. This well documented epidemic of CVD is due to two main factors – ageing of the world’s population, and epidemiological transition in LMIC leading to global exposure to the key risk factors for CVD.

Population Ageing

Chapter 5 provides significant detail on global ageing and will not be repeated here. Figures 5.1 and 5.2 in particular show the predicted ageing of the population globally and particularly in the European Region. Such increases in life expectancy, although showing global ‘successes’ in modernization and improvements in standards of living and health care, mean that more people are living to an age where they are more likely to have a cardiovascular event and if they survive that event, live longer with the disability associated with that event.

Risk Factors

Risk factors associated with CVD are well established through multiple large epidemiological studies which show that CVD is overwhelming preventable. Fifty-seven per cent of CVD deaths (19% of global deaths) can be attributed to just eight risk factors associated with poor diet and low rates of physical activity: high blood pressure, high blood glucose, physical inactivity, being overweight or obese, high cholesterol and low fruit and vegetable intake. The other key risk factor is tobacco use which accounts for nearly 10% of CVD. The 2010 Global Burden of Disease study reported that the two leading risk factors for global disease burden overall were high blood pressure (9.4 million deaths and 7% of global DALYs) and tobacco smoking including second-hand smoke (6.3 million deaths and 6.3% DALYs) both of which are key factors in increasing risk of CVD. The leading risk factor for Europe was also high blood pressure with smoking ranked either second or third (depending on the region of Europe). Detailed proportions of global IHD DALYs attributable to individual risk factors are presented in Table 6.3.2: Proportion of ischaemic heart disease DALYs attributable to individual risk factors, worldwide, 2010. These risk factors are all similarly implicated in other atherosclerotic disease such as stroke.

Of note is the high proportion of IHD DALYs attributable to excessive alcohol use. Although significant, excessive alcohol use and the consequent disease states, treatment options and recommendations for further research are covered in detail in Chapter 6.14: Alcohol use
disorders and alcoholic liver disease and the accompanying background paper. Hence, this will not be addressed in this background paper.

### Table 6.3.2: Proportion of ischaemic heart disease DALYs attributable to individual risk factors, worldwide, 2010.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Disability adjusted life-years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiological risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>High blood pressure</td>
<td>53%</td>
</tr>
<tr>
<td>High total cholesterol</td>
<td>29%</td>
</tr>
<tr>
<td>High body-mass index</td>
<td>23%</td>
</tr>
<tr>
<td>High fasting plasma glucose</td>
<td>16%</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>33%</td>
</tr>
<tr>
<td>Tobacco smoking including second-hand smoke</td>
<td>31%</td>
</tr>
<tr>
<td><strong>Dietary risk factors and physical inactivity</strong></td>
<td></td>
</tr>
<tr>
<td>Diet low in nuts and seeds</td>
<td>40%</td>
</tr>
<tr>
<td>Physical inactivity and low physical activity</td>
<td>31%</td>
</tr>
<tr>
<td>Diet low in fruits</td>
<td>30%</td>
</tr>
<tr>
<td>Diet low in seafood omega-3 fatty acids</td>
<td>22%</td>
</tr>
<tr>
<td>Diet low in whole grains</td>
<td>17%</td>
</tr>
<tr>
<td>Diet high in sodium</td>
<td>17%</td>
</tr>
<tr>
<td>Diet high in processed meat</td>
<td>13%</td>
</tr>
<tr>
<td>Diet low in vegetables</td>
<td>12%</td>
</tr>
<tr>
<td>Diet low in fibre</td>
<td>11%</td>
</tr>
<tr>
<td>Diet low in polyunsaturated fatty acids</td>
<td>9%</td>
</tr>
<tr>
<td>Diet high in trans fatty acids</td>
<td>9%</td>
</tr>
<tr>
<td>Diet high in sugar-sweetened beverages</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Air pollution</strong></td>
<td></td>
</tr>
<tr>
<td>Ambient particulate matter pollution</td>
<td>22%</td>
</tr>
<tr>
<td>Household air pollution from solid fuels</td>
<td>18%</td>
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<tr>
<td><strong>Other environmental risks</strong></td>
<td></td>
</tr>
<tr>
<td>Lead exposure</td>
<td>4%</td>
</tr>
</tbody>
</table>


**Summary:**

From the previously presented data, it is immediately apparent that CVD must be a priority for any attempt to reduce burden of disease at a global level and within Europe. The potential for public health benefit from the development of new or improved medical interventions to address the pandemic of CVD is incontrovertible. Not only would this have a major impact on Europe but would also potentially improve the lives of millions of patients in LMIC as well. The most significant contributors to IHD (and via extrapolation of other CVD) DALYs are amenable to pharmacological intervention i.e. the physiological risk factors and tobacco smoking. Despite much progress in the development of pharmaceutical
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interventions to prevent CVD, there is significant opportunity to further invest in this area, as will be described in the remainder of this background paper.

3. What is the control strategy?

Recommended strategies for prevention of CVD (both primary and secondary) can be categorized into lifestyle versus pharmacological interventions. Most attention in this chapter will focus on pharmaceutical interventions.

3.1 Lifestyle intervention

Since most of the major risk factors for CVD are related to lifestyle; advocacy and promotion at the population and patient level to modify poor lifestyle choices will always be an important and critical method to reduce the burden of CVD. When adhered to by patients not only is it cost-effective but will always be more effective that simply directly recommending pharmaceutical therapy. Smoking cessation has been shown to significantly decrease the smoking-attributable risk of disease and CVD risk return to that of a non-smoker within about five years.\textsuperscript{12,13} Intuitively, modification of diet and activity levels will positively benefit an individual’s cardiovascular risk factor profile. Physical activity and dietary modification have not only been shown to have a significant favourable effect on other major risk factors (including lipids, blood pressure and insulin resistance) but also to have an independent role in prevention of cardiovascular disease.\textsuperscript{14,15,16,17,18} Taken in conjunction, data has shown that adherence to lifestyles guidelines advocating moderate physical activity, cardio-protective diet and abstinence from smoking can reduce the incidence of cardiovascular disease by more than 80% compared to the rest of the population. However, studies have shown that the general population nor (more surprisingly) people with established CVD typically adhere to these recommended guidelines. Recent data from the United States NHANES 2005 to 2010 study\textsuperscript{19} showed that 22.6\% of respondents were current smokers and 24.1\% were former smokers. Thirty-two per cent did not engage in any physical activity with a further 23\% only engaging in intermediate activity (better but still not reaching the ideal level of activity). A total of 77.7\% of people surveyed scored less than two out of out a healthy diet score that included consumption of fruit and vegetables, wholegrains, and fish, and limiting sugar and salt intake. These figures have not changed significantly since previous NHANES surveys.\textsuperscript{19}

It is not only the general population who are failing to follow lifestyle advice. The European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) studies have completed three surveys on lifestyle and risk factor management in patients with coronary heart disease (CHD).\textsuperscript{20,21,22} Each study recruited consecutive patients with first or recurrent diagnosis or treatment for CHD across multiple hospitals in nine to 22 countries and interviewed between six months and three years later to see how many were adhering to recommended lifestyle and treatment measures. Arguably this population should be the most motivated to apply and adhere to lifestyle guidelines, having already experienced CVD and being at high risk of a recurrent event. In the latest round of surveys in 2006 to 2007, the investigators found that 51.9\% of smoking patients persisted after their event and only 51.8\% of obese patients had followed dietary
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recommendations to lose weight, with only 38.2% of obese patients increasing their regular physical activity. Of the overall cohort, only 48% increased their overall physical activity. An impressive 92% of the cohort attempted to change their diet however this subjective reporting is undermined by the objective measures of obesity (35.3%) and central obesity (52.7%). Many of these high risk patients were not taking medicines that have been proven to prevent reoccurrence of cardiac events.

The EUROASPIRE investigators also compared the results of the three different surveys to see if any improvements had been made over time. Disappointingly, between the first and third surveys rates of smoking in younger female patients increased (despite an overall decrease in smoking) and prevalence of obesity increased by 13%. Raised blood pressure increased by 3.4% and reporting of diabetes mellitus increased by 9.3%. Full prevalence data for coronary heart disease risk factors in EUROASPIRE III are shown in Table 6.3.3: Prevalence (%) of coronary heart disease risk factors in EUROASPIRE III, by country, age and diagnostic category.

<table>
<thead>
<tr>
<th>Country</th>
<th>Smoking (%)</th>
<th>Overweight (%)</th>
<th>Obesity (%)</th>
<th>Increased waist circumference (%)</th>
<th>Raised blood pressure (%)</th>
<th>Lipids (%)</th>
<th>Diabetes mellitus (%)</th>
<th>Self-reported diabetes (%)</th>
<th>Undiagnosed diabetes (%)</th>
<th>Diabetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>165/6.4</td>
<td>15.0</td>
<td>80.3</td>
<td>25.5</td>
<td>45.5</td>
<td>51.6</td>
<td>44.5</td>
<td>22.5</td>
<td>26.6</td>
<td>18.6</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>225/11.0</td>
<td>19.0</td>
<td>79.2</td>
<td>30.3</td>
<td>50.4</td>
<td>55.2</td>
<td>63.7</td>
<td>45.6</td>
<td>44.5</td>
<td>28.2</td>
</tr>
<tr>
<td>Croatia</td>
<td>15.1/13.6</td>
<td>14.7</td>
<td>86.6</td>
<td>37.4</td>
<td>78.0</td>
<td>62.3</td>
<td>49.9</td>
<td>34.1</td>
<td>33.3</td>
<td>20.5</td>
</tr>
<tr>
<td>Cyprus</td>
<td>26.1/9.0</td>
<td>23.8</td>
<td>88.0</td>
<td>38.2</td>
<td>45.9</td>
<td>52.6</td>
<td>49.8</td>
<td>51.2</td>
<td>40.4</td>
<td>30.5</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>20.9/13.7</td>
<td>19.4</td>
<td>84.1</td>
<td>36.7</td>
<td>55.6</td>
<td>66.0</td>
<td>46.6</td>
<td>31.2</td>
<td>41.2</td>
<td>31.1</td>
</tr>
<tr>
<td>Finland</td>
<td>13.0/7.6</td>
<td>11.0</td>
<td>74.0</td>
<td>39.6</td>
<td>40.9</td>
<td>66.4</td>
<td>25.8</td>
<td>27.0</td>
<td>26.2</td>
<td>19.8</td>
</tr>
<tr>
<td>France</td>
<td>22.6/15.7</td>
<td>20.5</td>
<td>77.0</td>
<td>35.7</td>
<td>56.7</td>
<td>55.4</td>
<td>41.4</td>
<td>28.4</td>
<td>36.1</td>
<td>35.0</td>
</tr>
<tr>
<td>Germany</td>
<td>172/8.1</td>
<td>15.3</td>
<td>85.8</td>
<td>41.8</td>
<td>52.8</td>
<td>53.7</td>
<td>51.5</td>
<td>27.8</td>
<td>32.1</td>
<td>24.2</td>
</tr>
<tr>
<td>Greece</td>
<td>185/5.0</td>
<td>16.4</td>
<td>75.2</td>
<td>23.1</td>
<td>42.3</td>
<td>32.2</td>
<td>40.7</td>
<td>49.3</td>
<td>21.1</td>
<td>18.3</td>
</tr>
<tr>
<td>Hungary</td>
<td>172/15.6</td>
<td>16.6</td>
<td>84.9</td>
<td>47.3</td>
<td>64.6</td>
<td>53.9</td>
<td>55.4</td>
<td>48.8</td>
<td>44.6</td>
<td>42.4</td>
</tr>
<tr>
<td>Ireland</td>
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<td>17.9</td>
<td>92.4</td>
<td>34.7</td>
<td>47.9</td>
<td>52.2</td>
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<td>32.5</td>
<td>30.6</td>
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<td>64.0</td>
<td>25.3</td>
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<td>40.3</td>
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<td>36.0</td>
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<tr>
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<td>97.2</td>
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<tr>
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<td>92.2</td>
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<td>51.4</td>
<td>55.4</td>
<td>53.2</td>
<td>31.9</td>
<td>34.8</td>
<td>27.2</td>
</tr>
<tr>
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<td>21.6</td>
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<tr>
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<td>84.3</td>
<td>38.9</td>
<td>64.0</td>
<td>58.0</td>
<td>45.6</td>
<td>42.7</td>
<td>26.1</td>
<td>33.4</td>
</tr>
<tr>
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<td>41.2</td>
<td>55.2</td>
<td>48.3</td>
<td>50.2</td>
<td>36.6</td>
<td>27.1</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>227/13.1</td>
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<td>70.6</td>
<td>29.4</td>
<td>45.9</td>
<td>47.4</td>
<td>30.9</td>
<td>39.1</td>
<td>25.7</td>
<td>23.8</td>
</tr>
</tbody>
</table>

Table 6.3.3: Prevalence (%) of coronary heart disease risk factors in EUROASPIRE III, by country, age and diagnostic category.

Source: Kotseva K et al. Eur J Cardiovasc Prev Rehabil, 200922
Update on 2004 Background Paper, BP 6.3 Cardiovascular Disease

These data indicate that, despite public awareness campaigns and educational efforts, population based lifestyle change is not happening. Into this evidence-practice gap fits the opportunity for modification of CVD risk with pharmacological management. The role of cholesterol lowering therapy, blood pressure lowering therapy and anti-platelet therapy is now incontrovertible having been proven effective in large meta-analyses in all three medication categories.

3.2 Lipid-lowering therapy

The role of lipids as a major risk factor for cardiovascular disease has been well established and has been estimated to cause approximately a third of global ischaemic heart disease. Furthermore, the relationship between serum cholesterol and the risk of cardiovascular disease has been shown to be continuous with no defined level below which a person can be considered to be at ‘low risk’. The discovery of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) has dramatically impacted the treatment of cardiovascular risk. Ongoing individual patient data meta-analyses by the Cholesterol Treatment Trialists (CTT) Collaboration of large scale clinical trials of statins have shown with standard statin regimes a consistent reduction in major vascular events over five years of around 20% per 1 mmol/L decrease in LDL regardless of baseline lipid levels or other patient characteristics. This benefit is seen even in those at lowest baseline risk with demonstrated reduction in events greatly exceeding any known hazard of statin therapy.

This raises the possibility that indications for treatment, which are currently aimed at patients at high risk should possibly be widened to include those at 5 to 10% absolute cardiovascular risk over five years. No level has been demonstrated below which reduction in LDL produces an increase in adverse events, demonstrating an acceptable safety profile for intensive treatment regimes capable of further LDL reductions.

The observed benefit from statins improves with the length of time taken with only a 10% decrease in events seen in the first year but up to 28% reduction in events by the third or fourth year. These estimates of benefit are in fact likely to be an underestimate of the true effect of long term benefit from statin therapy due to the problem of long term non-adherence by patients. Full compliance would achieve larger overall reductions in LDL, up to 1.5 – 1.8 mmol/L predicted in some cases which would result in closer to a one third reduction in vascular events overall.

In addition to statins’ role in reducing LDL cholesterol, fibrates (agonists of the peroxisome proliferator receptors selective for the α receptors - PPAR) have a clear role in raising HDL cholesterol and reducing triglyceride concentrations and consequently have recently been shown in meta-analysis to be effective in reducing cardiovascular events in their own right primarily by preventing coronary events. The relative risk reductions shown for fibrates (10% for major cardiovascular events, 13% for coronary events, no effect on stroke) are much less than for statins, however offer the potential for additive effects in risk reduction due to targeting of different cholesterol sub fractions and hence addressing the ‘residual risk’ remaining after treatment with statins particularly those patients with combined dyslipidemia. Despite this, the potential for increased risk of side effects, in particular muscle damage (myopathy) when taken together with statins has somewhat limited concurrent use of these drugs together, in particular gemfibrozil.
Ezetimibe is a newer lipid-lowering agent which inhibits cholesterol absorption from the gut available as monotherapy as well as combination therapy with simvastatin. Although shown to be effective in significantly lowering LDL cholesterol (including an extra 12 to 19% when coadministered with a statin\textsuperscript{35,36}), there is still controversy about its use with three separate trials showing paradoxical results in effect on carotid-artery intima-media thickness and also superficial femoral artery atherosclerosis.\textsuperscript{37,38,39} Results from the ongoing IMPROVE-IT trial (http://clinicaltrials.gov/show/NCT00202878) are required to determine the true value of ezetimibe in CVD prevention.

Two other products of note are niacin and omega-3 fatty acids. Despite marketing approval for nicotinic acid/laropiprant (niacin) being granted in 2008 by the European Medicines Agency to treat adults with dyslipidemia, this approval was suspended in January, 2013 following the preliminary reporting of the HPS2-THRIVE study’s (http://www.thrivestudy.org) primary outcome and safety data which showed no advantage of niacin in addition to statins on the outcome of CVD events and an increase in non-fatal but serious side effects. Omega-3 fatty acids have received widespread publicity and now represent a multi-million dollar industry due to positive findings in prevention of CVD in early trials. Later trials however produced conflicting results. A recent systematic review and meta-analysis did find a significant effect of omega-3 fatty acids on vascular death (RR 0.86, 0.75-0.99) however no significant effect on all other outcomes studied (it was noted that there was significant heterogeneity between the trials which may have impacted the overall results). The authors concluded that although there does seem to be a positive effect on some cardiovascular outcomes, perhaps the public and physician’s expectations of the true benefit should be lowered somewhat.

### 3.3 Blood pressure lowering therapy

Suboptimal blood pressure (systolic >115 mmHg) has been estimated to account for about 62% of global cerebrovascular disease and 49% of ischaemic heart disease globally.\textsuperscript{42} The majority of adult blood pressures are this category, and only about half of the attributable burden occurs among those with ‘hypertension’. This is true for both developing and developed countries although in developed regions blood pressure levels are particularly high.\textsuperscript{11} Major prospective observational studies have shown conclusively that blood pressure (both diastolic and systolic) has a continuous, independent relationship with the risk of cardiovascular disease.\textsuperscript{43,44,45}

Evidence for the effectiveness of blood pressure lowering therapies has led to a plethora of such drugs in multiple classes. All commonly used regimens (including ACE inhibitors, calcium channel antagonists, diuretics and beta blockers) have been shown to reduce cardiovascular risk similarly with larger reductions in blood pressure producing larger reductions in risk.\textsuperscript{46} As is the case for cholesterol lowering, an approximately consistent proportional difference in CV risk (35 to 40% for stroke and 20 to 25% coronary heart disease) is associated with each given absolute reduction in blood pressure (5-6 mmHg of diastolic blood pressure) regardless of the BP at baseline.\textsuperscript{43} It follows then that if the size of the absolute risk reduction is related to baseline untreated risk, then the greatest risk reductions occur in those whose baseline risk is highest.\textsuperscript{47} In Europe, although no particular medication class is recommended for treatment of uncomplicated high blood pressure, certain classes have been recommended in certain clinical conditions (Table 6.3.4) and new guidelines are in development.
Table 6.3.4: Position statement: Antihypertensive treatment: Preferred drugs. European Society of Hypertension and European Society of Cardiology.

<table>
<thead>
<tr>
<th>Subclinical organ damage</th>
<th>Preferred drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH</td>
<td>ACEI, CA, ARB</td>
</tr>
<tr>
<td>Asymptomatic atherosclerosis</td>
<td>CA, ACEI</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>ACEI, ARB</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>ACEI, ARB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical event</th>
<th>Preferred drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous stroke</td>
<td>any BP lowering agent</td>
</tr>
<tr>
<td>Previous MI</td>
<td>BB, ACEI, ARB</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>BB, CA</td>
</tr>
<tr>
<td>Heart failure</td>
<td>diuretics, BB, ACEI, ARB, antialdosterone agents</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>ARB, ACEI</td>
</tr>
<tr>
<td>Recurrent</td>
<td>BB, non-dihydropiridine CA</td>
</tr>
<tr>
<td>Permanent</td>
<td>ACEI, ARB, loop diuretics</td>
</tr>
<tr>
<td>ESRD/proteinuria</td>
<td>CA</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Preferred drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISH (elderly)</td>
<td>diuretics, CA</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>ACEI, ARB, CA</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>ACEI, ARB</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>CA, methyldopa, BB</td>
</tr>
<tr>
<td>Blacks</td>
<td>diuretics, CA</td>
</tr>
</tbody>
</table>

Abbreviations: LVH: left ventricular hypertrophy; ISH: isolated systolic hypertension; ESRD: renal failure; ACEI: ACE inhibitors; ARB: angiotensin receptor antagonists; CA: calcium antagonists; BB: β-blockers


Combination therapy for lowering blood pressure

Hypertension management strategies, such as those endorsed by most practice guidelines including the European Society of Hypertension 49 have traditionally focussed on “tailored therapy” and “stepped-care” approaches. These tend to be time consuming for doctor and patient, only cautiously recognise that contemporary BP targets almost always necessitate additional medication and ignore the auto-regulatory mechanisms that limit responsiveness to a single drug administered alone.

3.3.1 Evidence on potential benefits of regimen simplification and use of two-drug combination pills

Most patients with hypertension require BP lowering medication from two or more classes to achieve adequate control.50 The need for titration of medication and addition of multiple classes of drug requires multiple physician visits and this in itself triggers poor adherence to prescribed medication and poor attendance at scheduled visits.51 The requirement to take multiple medications in complex regimes also results in poor adherence.52 For physicians, the need for repeated up-titrating or adding extra medications can lead to inertia and complicit...
acceptance of inadequate BP control. Dual combination BP lowering medication has been shown to improve achieved BP reductions as well as cardiovascular event rates. Initiating anti-hypertensive treatment with dual combination therapy not only accelerates the time taken to achieve control but also attains a lower final target. For the patient, improved adherence has also been demonstrated without adversely affecting the side effect profile. Further benefits in BP control are also available via simplifying up-titration regimes.

3.3.2 Evidence on hypertension combination pills containing more than two medications

There are sound pharmacological principles to expect the maximum benefit to side effect ratio from low-dose triple combinations. In short, benefits of each component are additive, and low doses typically avoid most side effects while achieving most blood pressure reduction. Thus for example, three half-dose medications would typically lower blood pressure about as much as two full-dose medications, but with fewer side effects.

A number of important questions however remain to be answered. The triple BP lowering pills that have recently become available in western countries, have focussed exclusively on severe hypertension that remains uncontrolled with full dose dual combination therapy. Furthermore, previous trials have been within the mode of traditional stepped care, and have not tested the integration of a low-dose triple combination within a simplified regimen. For example, the recent trial of Exforge® involved patients with baseline BP of 170/107 mmHg, randomised to receive five weeks of treatment with amlodipine/valsartan/HCTZ 10/320/25 mg or one of the three dual therapies indicated previously herein. Perhaps unsurprisingly, this trial showed that patients on triple therapy achieved better BP reductions than patients on dual combination therapy.

To date no clinical trial has tested the benefits or cost-effectiveness of combination therapy with three, low dose BP lowering drugs in hypertension. One such trial, the TRIUMPH (TRIple Pill versus Usual care Management for Patients with mild-to-moderate Hypertension) study (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=363169), a 700 patient randomised controlled trial of a triple low dose blood pressure lowering pill versus usual care is currently starting up in India with the aim of answering these questions.

3.4 Anti-platelet therapy

A meta-analysis by the Antithrombotic Trialists’ Collaboration in 2002 showed that use of antiplatelet agents (primarily aspirin) in patients at high risk due to a pre-existing occlusion or predisposing condition, decreased the occurrence of serious vascular events by one quarter, with a third reduction in non-fatal myocardial infarction (MI) and a quarter reduction in non-fatal stroke. Vascular mortality overall was decreased by one sixth. They concluded that the absolute benefits of antiplatelet therapy substantially outweighed the absolute risks of major extra-cranial bleeding in patients with vascular disease. The balance of benefits and risks is less clear in lower risk populations, and conclusions have been hampered by not recognising the heterogeneity of this “primary prevention” population. A more detailed meta-analysis by the Antithrombotic Trialists’ Collaboration stratified results by estimated cardiovascular risk, and showed that even in medium risk population the number of excess haemorrhagic events (mostly gastrointestinal) was broadly similar to the
number of major vascular events prevented.\textsuperscript{64} However, further modelling and research is required to determine appropriate patient populations, given the emerging evidence showing that aspirin reduces the risk of several major cancers,\textsuperscript{65} and the changing background rates of gastrointestinal haemorrhage and vascular events.

Clopidogrel is the next most commonly used anti-platelet agent, and has similar efficacy to aspirin.\textsuperscript{63} Clopidogrel confers additional benefit when added to aspirin treatment in ST elevation myocardial infarction (RRR 9\%, 3-14)\textsuperscript{66}, non-ST elevation myocardial infarction (RRR 20\%, 10 – 28)\textsuperscript{67} and long-term following percutaneous coronary intervention (RRR 26.9\%, 3.9-44.4).\textsuperscript{68} Prior to coming off patent in May 2012, opinions varied as to the cost-effectiveness of clopidogrel compared to aspirin,\textsuperscript{69,70} and LMIC cost almost certainly would have limited its use significantly. However, now that generic clopidogrel is becoming available, its use in prevention of CVD is likely to increase.

4. Why does the disease burden persist?

4.1 Non-optimal use of existing effective medications

Despite large-scale clinical trial/meta-analyses having demonstrated substantial reductions in the risks of cardiovascular events with antiplatelet,\textsuperscript{63} blood pressure lowering \textsuperscript{46} and cholesterol lowering therapy\textsuperscript{71} in patients with established CVD and those at high calculated risk of CVD current treatment gaps among this patient group are very large. Despite the majority of people with established CVD in high income countries being started on recommended medications, significant numbers of people in high income countries\textsuperscript{23,72-73} and even larger numbers in low and lower middle income countries do not either receive or remain adherent to these treatments long-term,\textsuperscript{74,75,76} (Figure 6.3.4)

Within Europe, the EUROASPIRE III study\textsuperscript{22} showed that the majority of coronary patients that required BP lowering and lipid lowering medications were not receiving them on a long-term basis and if patients were receiving them, they were not reaching their BP and lipid targets (Table 6.3.5) suggesting either poor adherence by the patient or insufficient titration by physicians.
Figure 6.3.4: PURE study: Number of drugs taken by individuals with established cardiovascular or cerebrovascular disease by country economic status.

For coronary heart disease (A), drugs counted were aspirin, β blockers, ACE inhibitors or ARBs, or statins. For stroke (B), drugs counted were aspirin, statins, ACE inhibitors or ARBs, or other blood-pressure-lowering drugs (e.g., β blockers, diuretics, and calcium-channel blockers). ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.76

Table 6.3.5: Percentage of patients reaching BP and lipid targets in EUROASPIRE III

<table>
<thead>
<tr>
<th>Reaching Target (%)</th>
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</thead>
<tbody>
<tr>
<td>On BP lowering medication</td>
</tr>
<tr>
<td>Not on BP lowering medication</td>
</tr>
<tr>
<td>On lipid lowering medication</td>
</tr>
<tr>
<td>Not on lipid lowering medication</td>
</tr>
</tbody>
</table>

Source: Kotseva K et al. Eur J Cardiovasc Prev Rehabil, 200922

Various factors may underlie the suboptimal treatment of high risk patients, such as the need to navigate complex guidelines by doctors, low continuation rates by patients, inequities in health care and resistance to costs by both doctors and patients.

Non-adherence to therapy is one of the main obstacles for the unsatisfactory reduction of risk factors, particularly in developed countries. It is characterized by the premature cessation of treatment together with suboptimal use of medication, and is correlated with an increased risk of mortality.77 Non-adherence is especially relevant in chronic, asymptomatic diseases as cessation of treatment does not lead to symptoms in patients but they remain at high risk of serious micro- and macrovascular complications in the case of atherosclerotic cardiovascular diseases. Patients often do not understand the importance of taking long-term medication for chronic diseases, particularly those that are generally symptom-free. Reported long-term adherence is low with only 70% adherence to aspirin therapy and only 45% to lipid- and BP-
lowering therapy after 12 months.\textsuperscript{78} The main determinants of non-adherence are multiple medications with complex dosing regimens, inadequate knowledge about the medications and cost.\textsuperscript{79,80,81,82,83} Increasing age, established cardiovascular disease and/or type 2 diabetes usually indicate the usage of more than five drugs per day (polypharmacy).\textsuperscript{84} Treating high risk patients often requires polypharmacy even though this is known to be associated with patients’ non-adherence, inadequate prescription of medication by doctors and drug interactions. Therefore the complexity of the prevention of cardiovascular diseases requires simplicity.

The lack of affordability of therapy largely affects treatment gaps in developing countries since in developing countries most healthcare services are paid for out-of-pocket with little or no subsidy through health insurance or the government. The economic burden of secondary prevention of cardiovascular diseases is enormous, especially among the rural and urban citizens. As a month’s treatment costs ranges from 1 to 18 days’ wages of government workers, preventive drugs are unaffordable for the majority of individuals in developing countries.\textsuperscript{85,86} Patients can delay or omit drug doses and not fill prescriptions as strategies for cost reduction. Though the efficacy of preventive strategies may be proven and recognized at a high level, supply and access at the population level remains the major challenge.

Practical and affordable approaches to closing these treatment gaps are required. Combination pills or ‘polypills’ may play a role in closing these treatment gaps in ischaemic and cerebrovascular disease, and their use has been advocated for almost a decade.\textsuperscript{87,88,89} Reducing the complexity, number and costs of medication regimens with a ‘polypill’ containing off patent generic medicines will potentially improve adherence and hence reduce cardiovascular events.

\section*{4.2 New innovative therapies}

Further research into new, innovative therapies for the prevention and treatment of CVD is ongoing particularly amongst the larger pharmaceutical companies. Advancements in the knowledge of the pathophysiology and underlying determinants of the various types of CVD (including advances in genomics and targeted population groups) are constantly opening up new lines of enquiry into the possibility for a newer drug that may perhaps target a more specific mechanism or a targeted clinical population which, when added to the currently available medication options, may offer increased prevention or treatment for CVD. There is clearly a need for development of new medication types as even if all of the previously mentioned available therapies are utilized maximally, patients still have a residual risk of CVD. The reality though is that development of a new drug costs well over a billion US dollars. This scope of research is well outside any publicly funded research scheme and therefore will not be addressed in this background paper. Although new innovative therapies are potentially worthwhile, the most cost-effective measure for preventing CVD currently is improving access and adherence to currently available, generic medications.
5. **What can be learnt from past/current research into pharmaceutical interventions for this condition?**

Research over the last half century involving hundreds of thousands of patients in clinical trials has provided an enormous body of evidence on the efficacy and safety of different blood pressure lowering, statin and antiplatelet agents in the control of cardiovascular disease.\(^88,89\) The large majority of these trials were designed to assess the effects of individual medicines given the understandable clinical, regulatory and commercial requirements to assess the benefits and risks of specific drugs before access and uptake in the market. Hence trials typically involved randomization of a single agent versus placebo, on top of a background of usual care treatments at that time. Systematic reviews of these trials reveal an overall finding of broad relevance to clinical and public health practice, and to development of poly pills: an approximate constancy of relative risk reduction (i.e. lack of interaction or effect modification) of each modality (BP lowering, cholesterol lowering and anti-platelet effect), irrespective of whether the other modality is present or absent.\(^31,90,91\) More specifically, these systematic reviews of clinical trials have shown that proportional reductions in cause-specific outcomes (such as CVD mortality) are closely similar across a wide range of patient populations, with no major differences between agents (after accounting for the extent of risk factor reduction for SBP and LDL) and even when event rates vary tenfold or more. For example, aspirin produces a one-fifth reduction in CHD and ischaemic stroke risk in ‘primary’ and ‘secondary’ prevention, even though event rates differ by an order of magnitude. There is clear evidence that the proportional reductions in major outcomes achieved with each treatment modality are approximately the same in the presence or absence of other interventions and across a range of risk factor levels which is expected given the lack of interaction between treatments in terms of risk factor reduction and the epidemiology of blood pressure and cholesterol joint effects—this is outlined in Figures 6.3.5 and 6.3.6.

Given this consistency in proportional reductions, it is an expectation that combination therapy will have beneficial effects. More specifically, the combined effects are best estimated by multiplying relative risks together, after adjusting for the size of SBP and LDL-cholesterol reductions.
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Figure 6.3.5: Reduction in vascular events with a statin in the Heart Protection Study\textsuperscript{92} and reduction in stroke events with blood pressure lowering in the PROGRESS study\textsuperscript{93} by concomitant treatments and other factors.

Source: Heart Protection Study Collaborative Group. Lancet, 2002
Progress Collaborative Group. Lancet, 2001

Figure 6.3.6: Reduction of serious vascular events with aspirin, by blood pressure and cholesterol levels.

Source: Baigent C \textit{et al.} Lancet, 2009 \textsuperscript{90}
The concept of combining multiple classes of cardiovascular medications into a single pill also has a long history – for example, the term “asp-olol” was coined for an aspirin and atenolol combination in the 1970’s. Patents claiming rights over combinations of various cardiovascular medications had been filed since the late 1990s (for example 94,95,96). The first major scientific meeting on the concept of a fixed dose combination pill for CVD prevention was held in 2001, when the World Health Organization and the Wellcome Trust convened a meeting of experts to discuss evidence-based and affordable interventions for non-communicable diseases.87 A major impetus for the meeting was the potential for fixed-dose combination pills containing aspirin, statin, and BP-lowering agents, noting ‘the use of a single pill could well encourage patients to adhere to treatment as well as seriously reduce the cost of the drugs’. In the medical literature, the concept of a fixed-dosed combination pill was discussed by Yusuf in a Lancet editorial in 2002 88 and effectiveness and cost-effectiveness analyses were conducted in the 2002 World Health Report.97 The term ‘polypill’ itself was introduced with the publication of the Wald and Law’s seminal paper in 2003.89 Wald and Law estimated that the use of a single pill (containing aspirin, a statin, three BP-lowering drugs, and folic acid) in all people aged over 55 years would reduce cardiovascular disease by more than 80%.

Over the ensuing decade several clinical trials in the area of fixed dose combination pills have been conducted. These trials can be broadly grouped into two main areas:

- Comparisons of polypill versus usual care - in patient populations with established indications for all the component medications e.g. previous coronary disease
- Comparisons of polypill versus placebo/no treatment - in patient populations with established indications for none of the component medications e.g. those without hypertension, dyslipidaemia or vascular disease but who are nonetheless at raised cardiovascular risk

The 2004 Priority Medicines for Europe and the World Report1 and its recommendation to prioritize research into fixed dose combinations for the secondary prevention of CVD led to the European Commission funding of the largest Request for Proposal in this area, and hence two of the largest polypill trials: the Use of a Multidrug Pill In Reducing cardiovascular Events (UMPIRE) trial 98 and the Fixed Dose Combination Drug for secondary Cardiovascular prevention (FOCUS) trial 99 and these will be discussed following a review of other trials. While many of the patients involved in these trials suffered from IHD, some of the patients included were suffering from cerebrovascular disease.

5.1 Previous trials – polypill versus placebo or no treatment

These trials are summarized in Annex 6.3.2 and main outcomes in Annex 6.3.3.

5.1.1 Summary of TIPS 1 and 2

The Indian Polycap Study (TIPS)100 was a randomised, partial factorial design trial of Polycap® versus eight other medication combinations including aspirin alone, simvastatin alone and different combinations of hydrochlorothiazide, ramipril, and atenolol (see reference 100) for details of various combinations). Over two-thousand participants with at least one risk factor for CVD (such as hypertension, diabetes, current smoker, raised lipids or raised waist: hip ratio) were randomly allocated to one of the nine groups and followed up for 12 weeks. Outcomes included effect on blood pressure, heart rate, lipids and urine
thromboxane B2 as well as safety and tolerability. The study showed that the BP lowering effect of the Polycap® was comparable to the additive effects of each of the three component BP lowering drugs. A lesser effect on LDL cholesterol than simvastatin alone was noted (0.13 mmol/L) which was significant. Mean changes in blood pressure and LDL are shown in Figure 6.3.7 below.

**Figure 6.3.7: Mean changes in blood pressure and LDL in the TIPS study**

Source: The Indian Polycap Study (TIPS). Lancet, 2009

Error bars indicate 95% CI. Mean changes from baseline in the nine groups in the TIPS trial, and the effects of no blood-pressure-lowering drugs (As, S), one blood-pressure-lowering drug (T), two blood-pressure-lowering drugs (T+R, T+At, or R+At), or three blood-pressure-lowering drugs (T+R+At, T+R+At+S), or the Polycap (P)

### 5.1.2 Summary of Wald and Law trial

Wald and Law \(^1\) conducted a randomised, double-blind, cross-over trial of the polypill studied containing three half-dose BP lowering medications and a statin in 86 participants over the age of 50 with no history of CVD. Each participant took placebo or polypill for 12 weeks sequentially. Mean systolic blood pressure was reduced by 17.9 mmHg (95% CI, 15.7–20.1) on a polypill, diastolic blood pressure by 9.8 mmHg (8.1–11.5), and LDL cholesterol by 1.4 mmol/L (1.2–1.6), reductions of 12%, 11%, and 39% respectively (Figure 6.3.8). These results were almost identical to those predicted from previous trials of individual components. This trial is in effect a large Phase 1 study of the polypills efficacy in patients without cardiovascular disease.
Figure 6.3.8: Observed and expected reduction of blood pressure and LDL-cholesterol in a 2x12 week crossover trial. 101


5.1.3 PILL Collaborative Group

The Pill Pilot study 102 was a randomised, double-blind placebo-controlled trial of a polypill (containing aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg and simvastatin 20 mg) in 378 individuals without an indication for any component of the polypill, but who had an estimated five year cardiovascular disease risk over 7.5%. Over 12 weeks, polypill treatment reduced SBP by 9.9 (95% CI: 7.7 to 12.1) mmHg and LDL-cholesterol by 0.8 (95% CI 0.6 to 0.9) mmol/L.
5.1.4 Other trials

Two other trials have been conducted however have significant issues associated with them meaning that their results must be interpreted very cautiously.

Malekzadeh et al.\textsuperscript{103} conducted a double-blind randomized, placebo controlled trial in Iran in 475 participants over 50 years without CVD. They found a small but significant different in SBP at 12 months (4.5/1.6 mmHg) as well as LDL cholesterol (0.46 mol/L) however a significant difference of 6 mmHg of SBP at baseline between the two groups infers failure of the randomization process. Furthermore, the less than expected effects of the polypill on their outcomes raises concern about the reliability of reported compliance with medication.

Soliman et al.\textsuperscript{104} reported on an open-label, randomized controlled trial of a polypill versus usual care in 216 patients without CVD. No significant difference was found in SBP or total cholesterol after three months which was presumed by the authors to be due to the usual care arm receiving a higher than usual standard of care during the trial than would occur in usual practice. Further, larger than expected reductions in risk factors (e.g. for SBP a decrease

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Figure 6.3.9: Change in BP and LDL cholesterol at 12 weeks in the Pill Pilot study.

of 28.8 mmHg versus 26.9 mmHg in usual care) also raised concerns about standardization of measurement of risk factors.

For the above mentioned reasons, these two studies are not generally considered to be reliable representations of the true effect of polypill care.

5.1.5 Conclusions from previous trials of polypill versus placebo or no treatment

The key conclusions from the previous trials of polypill versus placebo/no treatment are that short term risk factor reductions are of approximately the size expected from individual agents, after taking into account loss to follow-up and non-adherence. The size of the underestimation due to loss to follow-up and non-adherence was very small in some trials (Wald et al, Pill Collaborative Group) and very large in others (Iranian Trial, Sri Lanka trial), with consequent differences in the observed to expected risk factor reductions. The trials provided relatively few data on side effects and tolerability but overall these were consistent with effects known from the separate medications. There were no reliable data on long-term risk factor reductions or cardiovascular outcomes though these would not be expected in such short term small studies.

5.2 Ongoing trials – polypill versus placebo

Several large scale randomized trials have commenced (Annex 6.3.7) which aim to address the question of the effect of a polypill on CVD outcomes (in particular CVD events) in primary prevention. This is a patient population in which perhaps use of a polypill may be considered more controversial as some may argue that the benefits of treatment may not outweigh the risks of treating such patients (particularly in relation to the use of aspirin). Three trials are recruiting/following-up patients who are at moderate risk of CVD in large scale, long-term trials which are powered to assess the risk-benefit ratio of polypsills in primary prevention and particularly the effect on CVD events. The results of these trials will also give an indication of the effect of a polypill on adherence over time in a group of patients who, being asymptomatic without a diagnosis of CVD, may well be less inclined to be adherent to preventive medication.

5.3 Previous trials – polypill versus usual care

5.3.1 FP7-funded UMPIRE trial

The “Use of a Multidrug Pill In Reducing cardiovascular Events” (UMPIRE) trial aimed to assess whether a polypill-based strategy for delivery of medications (aspirin, statin and two blood pressure lowering agents) compared to usual care would improve long-term adherence to guideline-indicated therapy, systolic blood pressure (SBP) and low density lipoprotein (LDL)-cholesterol in people with CVD or at similarly high risk. The trial was a prospective, randomized, open-label, blinded-endpoint (PROBE) clinical trial among 2004 participants from India and Europe. The main eligibility criteria were established CVD or an estimated five-year CVD risk of ≥15%. Participants were randomly assigned (1:1) to a fixed-dose combination POLYPILL-based strategy or usual care. In the POLYPILL group, physicians could use a POLYPILL that contained aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg and atenolol 50 mg or one containing aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg and hydrochlorothiazide 12.5 mg. In the usual care group, treatment continued
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According to physician discretion. Adherence to medication (defined as self-reported use of antiplatelet, statin and ≥2 BP-lowering medications) and changes in SBP and LDL-cholesterol from baseline were the main outcomes. At baseline, mean blood pressure was 137/78 mmHg, LDL-cholesterol was 91.5 mg/dl and 1233/2004 (61.5%) participants reported use of antiplatelet, statin and ≥2 BP lowering medications. Full baseline characteristics are provided in Annex 6.3.4.

Median follow-up was 15 months. Allocation to the POLYPILL group improved adherence by one-third (RR 1.33, [95% CI 1.26, 1.41] p<0.0001), with reductions in SBP (-2.6 mmHg [95% CI -4.0, -1.1] p=0.0005) and LDL-cholesterol (-0.11 mmol/l [95% CI -0.17, -0.05] p=0.0005) that which corresponds to 4.6 patients needing to be treated with the polypill in order to gain one additional adherent patient. These results are shown in Figure 6.3.10.

Figure 6.3.9: Adherence to indicated medications by treatment group over follow-up in the FP7-funded UMPIRE trial

Source: personal communication, S Thom

Legend: Figure shows overall adherence (panel A), statin (panel B), antiplatelet drug (panel C), and ≥2 BP lowering drugs (panel D) by follow-up time in the POLYPILL and usual care groups. M6-M24 are visits at months six to 24.
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Figure 6.3.10: Systolic blood pressure and LDL-cholesterol by treatment group over follow-up in the FP7-funded UMPIRE trial

Source: personal communication, S Thom

Legend: Systolic blood pressure (panel A) and LDL-cholesterol (panel B) values shown at baseline, during follow-up and at end of study (EOS) in the polypill and usual care groups.

There was broad consistency of effects across pre-defined subgroups including cardiovascular history, gender, smoking status, diabetic status, region (Western Europe versus India) and choice of POLYPILL. In addition, there was consistent evidence of larger benefits among patients with lower adherence at baseline i.e. those who were not already receiving antiplatelet, statin and two blood pressure drugs at baseline (Table 6.3.6). It should be noted that the adherence rates of the non POLYPILL control patients was high as compared to the results of normal care as reported in the EUROASPIRE studies described above.

Table 6.3.6: Primary outcomes in UMPIRE trial, according to baseline adherence

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean difference and 95% CI, polypill versus usual care</th>
<th>p-value for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adherent* at baseline</td>
<td>Not adherent* at baseline</td>
</tr>
<tr>
<td>Adherence* (relative risk)</td>
<td>1.04 (1.01, 1.08)</td>
<td>3.35 (2.74, 4.09)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>-1.0 (-2.9, 0.8)</td>
<td>-4.9 (-7.3, -2.6)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>-0.07 (-0.15, 0.01)</td>
<td>-0.17 (-0.27, -0.07)</td>
</tr>
</tbody>
</table>

Source: personal communication, S Thom

* defined as taking statin, antiplatelet and two or more blood pressure lowering agents
In absolute terms, the improvement in adherence was particularly large in the group who were under-treated at baseline (73.4% versus 23.1%) compared to those who were taking medications from all recommended classes at baseline (92.1% versus 88.1%). There were no significant differences in serious adverse events between the groups.

The trial had several strengths, in terms of sample size, duration of follow-up and completeness of data collection. However, there are several issues to be considered when interpreting results from adherence trials in general and this study in particular. Most importantly, the trial likely under-estimated benefits in a general population setting with typical adherence levels, since volunteers for clinical trials tend to be relatively motivated and clinical management in a trial setting tends to be more intensive than usual care. The size of this under-estimation is suggested in the minority of individuals who were not taking indicated medications at baseline, in whom randomization to POLYPILL resulted in a three-fold increase in adherence levels and larger reductions in SBP and LDL-cholesterol. Effects were nonetheless observed in a trial population of whom 82% initially reported use of statin, antiplatelet and blood pressure lowering drug(s), whereas comparable combination treatment rates are around 50% in high income countries and 5 to 20% in low and middle income countries. Furthermore, improvements were observed compared to a usual care group in whom treatment rates rose initially and remained higher than baseline throughout the study, whereas adherence typically reduces over time and in the usual care group, approximately three-quarters of all statin prescriptions were for atorvastatin or rosuvastatin which are newer and somewhat more efficacious statins at the doses used.

Ethics Committees required the researchers to provide the polypill free of charge, whereas the usual care group continued to receive their medications with attendant costs or subsidies. In one sense, this reflects the real impact if the polypill were to be made available at low or zero cost to the patient, for example as part of a universal health care program. Among this trial population, the economic advantage for the polypill group would likely have been modest, both in India given the generally low cost of medicines and relative affluence of participants from tertiary care settings, and in Europe given the prevalence of medication and prescription subsidies. A large United States trial recently showed that elimination of copayments for core cardiovascular medicines improved adherence by about 5% in absolute terms, which is smaller than the treatment effect seen here.

The trial did not identify an effect on cardiovascular events, but with only 85 events it provided little power to detect meaningful differences between groups. Based on observed differences in SBP, LDL cholesterol and aspirin use, relative risk reductions of around 15% in coronary disease and stroke are anticipated after a few years. However, a clinical trial would need to observe over 1 000 events to reliably detect a relative risk reduction of 15%. Among patients who were under-treated at baseline, the observed risk factor reductions would be expected to lead to about a 30% reduction in cardiovascular events.

The main conclusion overall from UMPIRE was that among a well-treated population with CVD or at similarly high risk, long-term provision of indicated cardiovascular preventive medication as a polypill led to improvements in adherence, SBP and LDL-cholesterol.
5.4 Ongoing trials versus usual care (Annexes 6.3.7)

5.4.1 FP7 funded FOCUS trial
The second trial funded by the FP7 program is the Fixed Dose Combination Drug for Secondary cardiovascular Prevention (FOCUS) trial (www.focus-fp7.eu), which includes a multi-country 4 000 patient descriptive non-interventional study aiming to provide a comprehensive analysis of potential factors precluding adequate secondary prevention, including health system characteristics, drug affordability and availability, as well as patient characteristics. The second component will be a 1 340 patient randomised trial of the effect of a polypill on adherence, BP and lipid levels at six to 9 months in participants with established CVD. Phase 2 will also include a prospective economic evaluation. Patient recruitment has commenced in this trial however results are not expected for some time yet.

5.4.2 Kanyini-GAP
The Kanyini guidelines adherence with the polypill (Kanyini-GAP) study is an Australian 623 patient randomised controlled trial of the effect of a polypill on adherence, SBP and total cholesterol in indigenous and non-indigenous populations with established CVD or five year CVD risk of at least 15%. This study was completed in September 2012 and is undergoing analysis of results. Of note, the Kanyini-GAP trial aimed to recruit patients and conduct the trial in as ‘real-life’ a setting as possible. This included:

- Recruitment and follow-up conducted through patient’s usual primary care provider to reflect actual practice once a ‘polypill’ enters the market
- Recruitment in urban, rural and remote settings to accurately reflect the challenges inherent in following up patients in a range of clinical settings
- Patients pay the relevant co-payment amount for their Red Heart Pill (polypill) prescription to reflect actual required payment once the Red Heart Pill is available in the Australian market.

5.4.3 IMPACT
The IMProving Adherence using Combination Therapy (IMPACT) trial is a New Zealand 513 patient randomised controlled trial investigating the impact of a polypill on adherence, SBP and LDL cholesterol in both Maori and non-Maori populations with established CVD or five year CVD risk of at least 15%. The study has completed recruitment and is currently conducting final patient visits with results expected in late 2013. As for the Kanyini-GAP trial, patients were recruited and followed up in as ‘real-life’ a setting as possible including recruitment through general practitioners, in a variety of urban and rural settings and including the relevant medication co-payment that would be required from a patient once a polypill is available on the market.

5.4.4 SPACE Collaboration meta-analysis
The UMPIRE, Kanyini-GAP and IMPACT trials are all part of the Single Pill to Avert Cardiovascular Events collaboration (www.spacecollaboration.org), an international group of investigators who aim:
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1. To facilitate the conduct of independent clinical trials of a fixed dose combination pill containing aspirin, a statin and blood pressure lowering drugs in individuals at high cardiovascular risk
2. To promote the opportunities for such trials in low and lower middle income countries and in marginalized populations in high income countries
3. To ensure as much uniformity between trials as possible to enable subsequent data pooling
4. To undertake IPD meta-analysis at the conclusion of all the trials.

Having individual patient data (IPD) available for meta-analysis will provide the ability to perform more complex analyses (survival and multivariate analyses), investigate the influence of covariates on heterogeneity of treatment effects, both within and between trials, facilitate greater flexibility in the categorization of subgroups and reduce potential biases by allowing consistency checks with individual study results. Results from this IPD meta-analysis are expected in early 2014.

6. What is the current “pipeline” of products that are to be used for this particular condition?

An exhaustive review of the pipeline of all products relevant to cardiovascular disease control is beyond the scope of this Background Paper. A summary of the polypills that are in development is given in Annex 6.3.8. As can be seen, there are several products in the research pipeline that have aspirin, statin and one or more blood pressure lowering agents. There are also a number of ‘semi-polypills’ in development, combining across two therapeutic classes e.g. a statin and an anti-diabetic agent.

7. What are the opportunities for research into new pharmaceutical interventions?

The use of fixed dose combinations in cardiovascular disease has stimulated much discussion and debate in the medical literature. Criticism of the polypill strategy was based on the view that it would largely be applied in the primary prevention of a population at a relatively low absolute risk of cardiovascular disease. It was argued that a large proportion of the population would be medicated unnecessarily. Furthermore, there was concern that the polypill might induce a sense of protection and deflect attention from healthy lifestyle behaviours like low fat diet and physical activity. The counter-arguments however are strong. Although Professors Wald and Law still promote the concept of generic prescription of a ‘polypill’ to all patients in a certain age group, it is worth clarifying that the majority of clinical researchers working in the area of fixed dose combination pills for CVD prevention do not agree with this proposal. Instead, the majority of work conducted so far in this area has focused on proof of concept, placebo-controlled, pharmacodynamics trials, primary prevention for patients with moderate CVD risk versus placebo trials, and polypill versus usual care in secondary prevention and high risk primary prevention population trials.
Several paradigm changes have been proposed in the area of fixed dose combinations, both as and by the Wald and Law papers published in 2003 are involved in the “polypill” concept, as broadly defined in Table 6.3.7.

### Table 6.3.7: Paradigm changes in the field of polypill research.

<table>
<thead>
<tr>
<th>Paradigm change / research question</th>
<th>Relevant trials ongoing</th>
<th>Gaps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use in established indications: do any benefits of fixed combinations of indicated medicines (access, adherence, treatment inertia) outweigh any problems (lack of tailoring, dose titration etc.)</td>
<td>UMPIRE, Kanyini-GAP, IMPACT</td>
<td>None in specific disease areas e.g. diabetes</td>
</tr>
<tr>
<td>Prevention: new approach to preventing CVD (indication not available for separate components)</td>
<td>TIPS-3</td>
<td>High dose – side effects may be too high</td>
</tr>
<tr>
<td>Use of low doses of three BP drugs</td>
<td>TRIUMPH TIPS-4</td>
<td>Sample size may be too small</td>
</tr>
<tr>
<td>Treatment initiation – based on CV risk not risk factor level. In most extreme form age is only risk indicator needed</td>
<td>All trials have entry based on CV risk except Wald (age only)</td>
<td>Not amenable to trials - more analysis and policy</td>
</tr>
<tr>
<td>Treatment monitoring – based only on adherence, not based on risk factor levels, or e.g. hypertension control</td>
<td>None</td>
<td>Trial needed</td>
</tr>
</tbody>
</table>

8. What are the gaps between current research and potential research issues which could make a difference are affordable and could be carried out in a) five years or b) in the longer term?

8.1 Need for large-scale trials among people with established cardiovascular disease and other indications for treatment

There are numerous reasons to focus on people with established cardiovascular disease and other clear indications for future polypill research. From a public health viewpoint, this is a large, easily identified, high-risk patient population among whom almost half of all cardiovascular events occur.\(^{111}\) There are well-established large reductions in cardiovascular events and mortality that can be achieved when patients are prescribed and adhere to recommended preventive medications such as cholesterol lowering,\(^{27}\) blood pressure lowering \(^{112}\) and anti-platelet drugs,\(^{90}\) yet large treatment gaps still persist. Following an acute myocardial infarction, if left untreated, patients with CVD have a persistent 5% risk of
mortality each year. In this context, the ‘low hanging fruit’ of CVD prevention is to make available, prescribe and promote adherence to essential medications in those at highest risk i.e. those who have established CVD. The FP7-funded UMPIRE trial showed that promising improvement in adherence and clinical indicators could be achievement with provision of a polypill in this patient group in different environments. However, a number of research questions remain outstanding, and these include the following questions.

8.2 What are the effects of implementing a polypill strategy on cardiovascular outcomes?

In circumstances in which individual medicines are already proven to be efficacious, there should be no need to doubt or require repeat evidence of the benefit of combined therapy, unless some new interaction or some new issue related to concomitant starting or stopping; or that there perhaps exists benefits for some components and hazards for others. Thus generally improvement in adherence can (and should) be taken as improvement in CV outcomes. However there are legitimate reasons to assess the size of benefits, and risks, of implementing a polypill strategy on a large scale. Many of the factors involved in scale-up are system-level e.g. training, education, task shifting, electronic decision support, and many of the patients, clinicians and environments most in need of adherence-improving strategies are those least likely to join a standard clinical trial. Therefore the area would be well served with a very large implementation trial, or a series of sister trials, with the following features

- cluster or step wedge implementation
- unit of randomisation: primary healthcare facility
- denominator/patient population: individuals with established CVD stratified into different population groups
- numerator/outcome: CV outcomes, and also to assess generalizability in subgroups

The UMPIRE trial showed improvements in risk factor reductions that would be expected to result in a 10 to 15% reduction in CV events in that trial population, but that benefit might be at least twice as great among a group not taking all indicated medications. One would therefore require trials involving several tens of thousands of participants in order to reliably assess CV outcomes, and assess consistency in different patient groups and in different health systems. However if such a trial was successful it would result in the transformation of the standard of care for patients with proven cardiovascular disease and save hundreds of thousands of lives.

Several other pressing research questions exist, which could be addressed as part of the above trial(s), or as separate trials.

8.3 Potential benefits of next generation polypills

8.3.1 Additional benefits from use of newer agents

Several agents have recently come off patent (e.g. atorvastatin, clopidogrel) and could conceivably be included in the next generation of polypills, and other agents will be coming off patent within five years (e.g. rosuvastatin). Research could usefully be directed to assessment of the additional benefits of including these agents for specific patient populations or having them replace agents in the existing polypills.
8.3.2 How many dose versions for each polypill?

The ‘default’ option from a regulatory point of view is to make available all conceivable dose versions, excluding perhaps those that are rarely or never used, whereas the original concept of the polypill was based on a single dose version. An important research question is whether the advantages of therapeutic flexibility outweigh the advantages of regimen simplicity and avoidance of resistance to treatment.

8.3.3 Low dose or high dose polypill components?

The ideal dose(s) of component medications is a topic of intense debate in the area. In the simplest case, there is little doubt that low doses of aspirin are ideal, given that higher doses are associated with more side effects but not greater benefits. Statins have a shallow dose response curve in terms of benefits, with each doubling of dose only leading to about a 7% increase in LDL reduction. However, side effects are low at all doses except maximal ones. In the context of combination therapy, there are surprisingly modest marginal benefits in cardiovascular risk reduction of increased dosages of the blood pressure lowering drugs, at the cost of an increase in side effects. Evidence from a very large number of clinical trials has shown that doubling the dose of a blood pressure agent typically leads to much less than a doubling in blood pressure reduction, but a moderate increase in side effects. The small expected difference in overall cardiovascular event reduction for polypill formulations differing in their extent of BP reduction is shown in Figure 6.3.8.

The recently completed TIPS 2 trial suggests that maximal dose polypill versions will achieve only a few mmHg additional SBP difference at most in the long-term. This trial observed an increased SBP reduction of only 2.8 mmHg after doubling the dose of three blood pressure lowering agents (i.e. one arm taking a single polycap containing ramipril 5 mg, atenolol 50 mg, hydrochlorothiazide 12.5 mg was compared to an arm taking two polycaps). Furthermore, there was attenuation of the already small treatment differences at week 12 compared to weeks two to eight. However increasing blood pressure lowering drugs to maximal doses results in appreciable increases in side effects, which can reasonably be expected to reduce long-term adherence.
Table 6.3.8: Expected reduction in coronary heart disease risk with polypill versions containing different doses of blood pressure lowering agents

<table>
<thead>
<tr>
<th>Modality</th>
<th>Polypill – base case</th>
<th>Polypill versions that achieve incremental additional SBP reductions of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 mmHg</td>
</tr>
<tr>
<td>BP reduction</td>
<td>26%</td>
<td>28%</td>
</tr>
<tr>
<td>LDL reduction</td>
<td>42%</td>
<td>42%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Combination</td>
<td>66%</td>
<td>66%</td>
</tr>
</tbody>
</table>

Data sources and assumptions:
- Polypill “base case” version reduces SBP by 12 mmHg and LDL by 1 mmol/l (39 mg/dL)
- Relative risks provided by systematic reviews of trials of aspirin, blood pressure lowering and cholesterol lowering. Since 1 mmol/L LDL-cholesterol reduction, 10 mmHg SBP reduction and aspirin each individually lower CHD risk by 42%, 22% and 20% respectively (i.e. RRs are 0.58, 0.78 and 0.80 respectively), the expected joint effects of a 1 mmol/L LDL-cholesterol reduction, 16 mmHg SBP reduction and aspirin would be approximately a 69% lower CHD risk (since $0.58 \times 0.78 \times 0.80 = 0.41$, and $(1-0.41) \times 100\% = 69\%$).

8.4 Polypill approach in specific patient populations

The polypill approach can be adapted and adopted for other disease conditions, particularly those with a large disease burden, for which adherence is a major factor. Polypills could be developed in several of these areas, for example:
- a ‘diabetes polypill’, incorporating one or two hypoglycaemic agents as well as a statin and an ACE-inhibitor
- A ‘hypertension polypill’ – incorporating three or even four very low dose medications (see Annex 6.3.6 for current trials assessing this concept).

However, use in these conditions will likely require direct evidence of efficacy to convince regulators and key opinion leaders, requiring trials similar to UMPIRE and FOCUS.

8.5 Expanding the polypill concept to acute care

To date, polypill trials have been conducted among a population with long-established cardiovascular disease. However key issues arise concerning whether treatment should be started sooner after an acute event:
- Are there greater benefits if people are started in hospital soon after an acute event?
- Can benefits accrue in the first year after acute coronary syndrome, when the greatest risk for drop-off in adherence and for another major event are highest?

Therefore, trials of next generation polypills started in acute or semi-acute disease are required.
9. For which of these gaps are there opportunities for pharmaceutical research?

There are considerable formulation challenges in simultaneously achieving bioequivalence, long-term stability and maintaining a size for the polypill that is acceptable to patients. Pharmaceutical research could be usefully directed to developing and testing new ways to develop and manufacture polypills, including with some of the newer ingredients outlined above.

An example of such research is the TI Pharma project “Design quality into products” (http://www.tipharma.com/pharmaceutical-research-projects/production-technologies/dosage.html, Accessed February 22nd, 2013) in which researchers successfully created a production process that achieves homogeneity in drug mixtures, a process which is essential in the creation of polypills as each pill must contain exactly the same dose of each of the component drugs.

10. Conclusion

In the eight years since the last ‘Priority Medicines for Europe and World’ report, much work has been done in the area of medication use for prevention of CVD. However the biggest opportunity to have maximal impact on CVD prevention still remains further research into ensuring widespread availability of fixed dose combination therapy (or polypills) that include medications that have been demonstrated to be highly effective in CVD prevention, are available in cheap generic formulations but are underutilized in almost every clinical setting globally. Development of new medications for CVD prevention still has a role to play but despite ongoing research costing billions of dollars, no new ‘blockbuster’ medication has come to light recently that has the potential for greater effect than ensuring what already exists is available and prescribed globally to patients with established CVD.

The FP7 funded UMPIRE trial has shown that even in a clinical trial population who were already highly adherent at baseline, opportunity exists to improve BP and cholesterol control via improved adherence with a polypill. In patients who were not adherent to all medication classes at baseline, a massive 300% increase in adherence to all recommended classes of medication was seen. If such a polypill were applied across non-adherent patients across Europe the scale of potential prevention of CVD events would be counted in the hundreds of thousands. Extension of this potential to LMIC where the bulk of the disease burden lies extends this to millions of people. Funding from FP7 has contributed significantly to the progress so far in understanding the potential benefit of polypills in CVD prevention however further funding is required to build upon the available evidence.

The scale of funding required to further develop the evidence base that has already been achieved in the area of polypill research is unlikely to be committed to by major pharmaceutical companies as their focus lies in the development of newer patent-protected products which are likely to have higher profit margins. Meanwhile, generic pharmaceutical companies do not have the research budgets that would enable them to invest in such large-
scale clinical trials. Major public funding commitment is therefore needed to ensure that what has been achieved so far is built upon and to provide the evidence necessary for regulatory approval in both Europe and worldwide. The potential benefits of the widespread use of polypills are enormous.

Other issues in this area that require further research include:
- Potential additional benefits from newer agents now off-patent
- Number of dose versions
- Low-dose versus high-dose polypills
- Specific populations (e.g. diabetes polypill, hypertension polypill)
- Use in acute care (e.g. immediately after a heart attack versus use in chronic care).

Other cardiovascular research areas
As mentioned in the introduction, there are many other areas of research into pharmacological approaches to IHD that may need to be supported. These include the development of new lipid-lowering drugs; pharmacological means to address novel mechanistic concepts of vessel wall damage and protect against conditions such as chronic inflammation and local angiogenesis; as well as regenerative medicine/cell therapy approaches. Similarly, new pharmacological treatment strategies need to be developed for heart failure and arrhythmias, frequent consequences of IHD. While these areas have not been investigated in this background paper or the chapter, opportunities for research may exist that are not being addressed by the pharmaceutical industry.
11. Declarations

The authors have received grants from several research charities and national funding agencies for research on cardiovascular fixed dose combination medications, and from Dr Reddys Ltd for co-ordination of the SPACE program (www.spacecollaboration.org). The George Institute for Global Health obtained an exclusive global license in December 2012 for the fixed dose combinations used in the SPACE trials following a decision by Dr Reddy’s Ltd not to proceed with taking the products to market because of uncertainty in regulatory requirements.

References


34 Xydakis AM, Ballantyne CM. Combination therapy for combined dyslipidemia. Am J Cardiol. 2002; 90(10B): 21K-9K.


randomised drug trials in their epidemiological context.[see comment]. Lancet. 1990; 335(8693): 827-38.


54 Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. Hypertension. 2006; 47(3): 345-51.


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89. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. British Medical Journal 2003; 326(7404): 1419.


95 Tobert JA, Merck & Co Inc, inventors; Combination therapy for reducing the risks associated with cardiovascular disease 1997.

96 Wald NJ, Law MR, inventors; Pharmaceutical formulation for the prevention of cardiovascular disease patent GB 2361 185 A.


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Annexes

Annex 6.3.1: Mortality and burden of disease from IHD per age group and per region
Annex 6.3.2: Baseline characteristics of previous randomized controlled trials – versus placebo or no treatment
Annex 6.3.3: Actual versus expected reductions in systolic blood pressure and LDL-cholesterol in trials of ‘polypills’ versus placebo or no treatment
Annex 6.3.4: Baseline characteristics of UMPIRE trial
Annex 6.3.5: Ongoing randomized controlled trials – polypill versus usual care
Annex 6.3.6: Ongoing trials of “hypertension polypills”
Annex 6.3.7: Ongoing trials – polypill versus placebo or no treatment
Annex 6.3.8: Pipeline of polypills
Annex 6.3.1: Mortality and burden of disease from IHD per age group and per region

Update on 2004 Background Paper, BP 6.3 Cardiovascular Disease

**Absolute DALYs due to IHD by age group in Eastern Europe**

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Absolute DALYs</th>
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<tbody>
<tr>
<td>0-1 years</td>
<td>500,000</td>
</tr>
<tr>
<td>1-4 years</td>
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<tr>
<td>75-79 years</td>
<td>8,500,000</td>
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<tr>
<td>80+ years</td>
<td>9,000,000</td>
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</table>

**Absolute DALYs due to IHD by age group in Western Europe**

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Absolute DALYs</th>
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</thead>
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<tr>
<td>0-1 years</td>
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<td>75-79 years</td>
<td>8,500,000</td>
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<tr>
<td>80+ years</td>
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Global mortality for IHD by age group

Mortality for IHD by age group in Central Europe
Update on 2004 Background Paper, BP 6.3 Cardiovascular Disease

Mortality for IHD by age group in Eastern Europe

<table>
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<tr>
<th>Age groups</th>
<th>Absolute deaths</th>
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<tr>
<td>28-364 days</td>
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<td>1-4 years</td>
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<tr>
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<td>70-74 years</td>
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<tr>
<td>75-79 years</td>
<td>0</td>
</tr>
<tr>
<td>80+ years</td>
<td>500,000</td>
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</table>

Mortality for IHD by age group in Western Europe

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Absolute deaths</th>
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<tbody>
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<td>10-14 years</td>
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<td>70-74 years</td>
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<tr>
<td>75-79 years</td>
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<tr>
<td>80+ years</td>
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</table>
## Annex 6.3.2: Baseline characteristics of previous randomised controlled trials – versus placebo or no treatment

<table>
<thead>
<tr>
<th>Included Study</th>
<th>Study population characteristics</th>
<th>Mean age (SD); female gender (%)</th>
<th>Mean SBP(SD)/DBP (SD) mmHg</th>
<th>Mean total cholesterol (SD); LDL (SD) mmol/L</th>
<th>‘Polypill’ contents (dose); n</th>
<th>Comparison; n</th>
<th>Duration of follow-up;</th>
<th>Outcomes assessed;</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malekzadeh et al 2010 3034*</td>
<td>Primary prevention (no previous CVD)</td>
<td>59.1 (6.9); 33%</td>
<td>127.5 (17.3) / 79.8 (10.1)</td>
<td>5.26 (1.01); 2.99 (0.68)</td>
<td>Aspirin (81 mg), Enalapril (2.5 mg), Atorvastatin (20 mg) and Hydrochlorothiazide (12.5 mg); n=241</td>
<td>Placebo; n=234</td>
<td>12 months</td>
<td>SBP, DBP, Total cholesterol, LDL, AEs; Imbalance in baseline checks suggests inadequacy of randomization; Low follow-up rate: 68% in intervention, 78% in control</td>
<td></td>
</tr>
<tr>
<td>Pill Collaborative 2011 121</td>
<td>Primary prevention (no previous CVD)</td>
<td>61.4 (7.2); 19%</td>
<td>134.0 (13.5) / 80.5 (9.0)</td>
<td>5.50 (1.05); 3.65 (0.90)</td>
<td>Aspirin (75 mg), Lisinopril (10 mg) Hydrochlorothiazide (12.5 mg) and Simvastatin (20 mg); n=189</td>
<td>Placebo; n=189</td>
<td>12 weeks</td>
<td>SBP, DBP, Total cholesterol, LDL, AEs; 99% follow-up</td>
<td></td>
</tr>
<tr>
<td>Wald 2012 122</td>
<td>Primary prevention (no previous CVD)</td>
<td>59 (range 51-77); 26%</td>
<td>143.0 (16) / 86.0 (10)**</td>
<td>5.9 (1.0); 3.7 (0.9)**</td>
<td>Amlodipine (2.5 mg) Losartan (25 mg), Hydrochlorothiazide (12.5 mg) and Simvastatin (40 mg); n=86</td>
<td>Placebo; n=86</td>
<td>12 weeks (cross-over RCT)</td>
<td>SBP, DBP, Total cholesterol, LDL, AEs; 98% follow-up</td>
<td></td>
</tr>
<tr>
<td>The Indian Polycap Study ‘TIPS’ 2009 100</td>
<td>Primary prevention (no previous CVD)</td>
<td>53.6 (7.7); 44%</td>
<td>134.3 (12.3) / 85.2 (8.1)</td>
<td>4.7 (0.9); 3.0 (0.8)</td>
<td>Hydrochlorothiazide (12.5 mg), Atenolol (50 mg), Ramipril (5 mg), Simvastatin (20 mg), Aspirin (100 mg); n=412</td>
<td>Aspirin (100 mg); n=205 (Simvastatin 20 mg group added for BP comparison n=202)</td>
<td>12 weeks (some 8-12 weeks);</td>
<td>SBP, DBP, Total cholesterol, LDL, AEs; 85% follow-up in these three arms</td>
<td></td>
</tr>
</tbody>
</table>
Update on 2004 Background Paper, BP 6.3 Cardiovascular Disease

* BP not assessed in meta-analysis as both arms contained an anti-hypertensive; ** Following placebo 12 weeks of cross-over RCT; † Double-blind nine-arm with varying medication components and number of components. Only three arms were used in this meta-analysis: the polycap, aspirin and simvastatin arms;

BP = blood pressure and measured in mmHg; SBP = systolic blood pressure; DBP = Diastolic blood pressure; Total chol. = total cholesterol in mmol/L; LDL = LDL cholesterol in mmol/L; AE = adverse events; TLC = therapeutic lifestyle changes; SD = standard deviation; CVD = cardiovascular disease

### Annex 6.3.3: Actual versus expected reductions in systolic blood pressure and LDL-cholesterol in trials of ‘polypills’ versus placebo or no treatment

<table>
<thead>
<tr>
<th>Trial</th>
<th>Antihypertensive(s)</th>
<th>Standard dose equivalent</th>
<th>Mean baseline SBP (mm Hg)*</th>
<th>Expected reduction in SBP (mm Hg)**</th>
<th>Observed mean difference in SBP (mm Hg)</th>
<th>Observed/expected</th>
<th>Statin</th>
<th>Mean baseline LDL (mmol/l)</th>
<th>Expected reduction in LDL (mmol/l)</th>
<th>Observed control-adjusted reduction in LDL (mmol/l)</th>
<th>Observed/expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malekzadeh, 2010</td>
<td>Enalapril 2.5 mg 0.25</td>
<td>Hydrochlorothiazide 12.5 mg 0.5</td>
<td>Lisinopril 10 mg 1</td>
<td>Hydrochlorothiazide 12.5 mg 0.5</td>
<td>Hydrochlorothiazide 12.5 mg 0.5</td>
<td>Losartan 25 mg 0.5 Amlodipine 2.5 mg 0.5</td>
<td>Hydrochlorothiazide 12.5 mg 0.5</td>
<td>Atenolol 50 mg 1 Ramipril 5 mg 2</td>
<td>Atorvastatin 20 mg 2.99</td>
<td>1.29</td>
<td>0.45</td>
</tr>
<tr>
<td>PILL collaboration, 2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Simvastatin 20 mg 3.65</td>
<td>1.17</td>
<td>0.75</td>
</tr>
<tr>
<td>Wald, 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Simvastatin 40 mg 3.70</td>
<td>1.37</td>
<td>1.4</td>
</tr>
<tr>
<td>The Indian Polycap Study, 2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Simvastatin 20 mg 3.00</td>
<td>0.96</td>
<td>0.72</td>
</tr>
</tbody>
</table>

* rounded to nearest 10 mm Hg; ** based on mean baseline SBP & standard dose equivalence (from Law 2009)\(^{123}\); *mean baseline LDL x percentage reduction in LDL cholesterol for the statin at that dose (from Law 2003)\(^{125}\) estimate: two drugs at half dose therefore an overestimate of likely effect; ** estimate: two drugs at half dose therefore an underestimate of likely effect; 12.7 mmHg for two drugs at standard dose; \(\beta\) estimate: three drugs at standard dose; 15.2 mmHg for three drugs at half standard dose.

---


<table>
<thead>
<tr>
<th></th>
<th>FDC (N = 1002)</th>
<th>Usual care (N = 1002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62.1 (10.4)</td>
<td>61.6 (10.8)</td>
</tr>
<tr>
<td>Male</td>
<td>817 (81.5%)</td>
<td>825 (82.3%)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>137.0 (21.3)</td>
<td>137.7 (21.1)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77.4 (12.0)</td>
<td>78.1 (11.5)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71.0 (15.1)</td>
<td>70.8 (14.6)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.2 (1.0)</td>
<td>4.2 (1.1)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.1 (0.3)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>2.3 (0.8)</td>
<td>2.4 (0.9)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.5 (0.9)</td>
<td>1.5 (0.9)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>6.3 (2.4)</td>
<td>6.3 (2.3)</td>
</tr>
<tr>
<td>Creatinine (umol/L)</td>
<td>89.0 (22.10)</td>
<td>89.7 (22.2)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>131 (13.1%)</td>
<td>144 (14.4%)</td>
</tr>
<tr>
<td>Ever smoked cigarettes</td>
<td>541 (54.0%)</td>
<td>504 (50.3%)</td>
</tr>
</tbody>
</table>

**Medical history**

- Coronary heart disease: 769 (76.7%) vs 759 (75.7%)
- Cerebrovascular disease: 154 (15.4%) vs 157 (15.7%)
- Peripheral vascular disease: 56 (5.6%) vs 43 (4.3%)
- Diabetes mellitus: 283 (28.2%) vs 281 (28.0%)

**Current drug treatment**

**Antihypertensive treatment**

<table>
<thead>
<tr>
<th></th>
<th>FDC</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>76 (7.6%)</td>
<td>66 (6.6%)</td>
</tr>
<tr>
<td>1 BP drug</td>
<td>266 (26.5%)</td>
<td>225 (22.5%)</td>
</tr>
<tr>
<td>≥2 BP drugs</td>
<td>660 (65.9%)</td>
<td>711 (71.0%)</td>
</tr>
<tr>
<td>Statin</td>
<td>882 (88.0%)</td>
<td>878 (87.6%)</td>
</tr>
<tr>
<td>Anti-platelet drug</td>
<td>920 (91.8%)</td>
<td>912 (91.0%)</td>
</tr>
<tr>
<td>Indicated medications(^1)</td>
<td>598 (59.7%)</td>
<td>635 (63.4%)</td>
</tr>
</tbody>
</table>

Data not shown as n (%) are mean (SD).
1 Indicated medications = statin + anti-platelet + ≥2 anti-hypertensive drugs.
FDC = fixed dose combination.
## Update on 2004 Background Paper, BP 6.3 Cardiovascular Disease

### Annex 6.3.5: Ongoing randomised controlled trials – polypill versus usual care

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population characteristics</th>
<th>N</th>
<th>Regions</th>
<th>‘Polypill’ contents (dose); Comparison; Duration of follow-up</th>
<th>Expected results</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanyini-GAP</td>
<td>Established CVD or CVD risk of &gt;15% over five years</td>
<td>623</td>
<td>Australia</td>
<td><strong>RHP version 1c:</strong> aspirin 75 mg lisinopril 10 mg simvastatin 40 mg atenolol 50 mg <strong>RHP version 2c:</strong> aspirin 75 mg lisinopril 10 mg simvastatin 40 mg hydrochlorothiazide 12.5 mg</td>
<td>Usual care</td>
<td>Minimum 12 months Q2 2013</td>
</tr>
<tr>
<td>IMPACT</td>
<td>Established CVD or CVD risk of &gt;15% over five years</td>
<td>513</td>
<td>New Zealand</td>
<td><strong>RHP version 1c:</strong> aspirin 75 mg lisinopril 10 mg simvastatin 40 mg atenolol 50 mg <strong>RHP version 2c:</strong> aspirin 75 mg lisinopril 10 mg simvastatin 40 mg hydrochlorothiazide 12.5 mg</td>
<td>Usual care</td>
<td>Minimum 12 months Q4 2013</td>
</tr>
<tr>
<td>FOCUS</td>
<td>Post-myocardial infarction</td>
<td>1 340</td>
<td>Argentina, France, Italy, Spain, Switzerland</td>
<td>Aspirin 100 mg Simvastatin 40 mg Ramipril (2.5, 5, 10 mg)</td>
<td>Usual care</td>
<td>9 months ?</td>
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</tbody>
</table>
**Annex 6.3.6: Ongoing trials of “hypertension polyps”**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Aims</th>
<th>Patient population</th>
<th>Comparisons</th>
<th>Follow-up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIUMPH</td>
<td>To assess role of a low-dose triple antihypertensive compared to usual care</td>
<td>Newly diagnosed patients with persistent hypertension despite adequate lifestyle advice and/or changes; and/or single drug therapy for BP lowering</td>
<td>Triple pill versus usual care.</td>
<td>Six months</td>
<td>Primary outcome: % achieving target BP at six months; Secondary outcomes: % with BP control at six and 12 weeks; change in BP; tolerance to treatment; use of health care services; self-reported BP lowering medication use; quality of life.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>India</td>
<td>Telmisartan 20 mg, Amlodipine 2.5 mg, Hydrochlorothiazide 6.25 mg or option with double doses; usual care: separate BP lowering medication prescribed completely at the discretion of the treating doctor.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIPS 4</td>
<td>To assess the incremental BP lowering by full doses of - two 3-BP lowering drugs compared to - three 2-BP lowering drugs combinations.</td>
<td>Men or women aged 30 years or older, With SBP 150 to 180 mmHg</td>
<td>1. HCTZ (25 mg) + Amlodipine (10 mg) 2. HCTZ (25 mg) + Atenolol (100 mg) 3. HCTZ (25 mg) + Ramipril (10 mg) 4. Low doses: HCTZ 12.5 mg + rami 5 mg + aten 50 mg or Amlodipine 5mg 5. Full doses: HCTZ 25 mg + ramipril 10 mg + atenolol 100 mg or Amlodipine 10mg 6 Simvastatin 40 mg 7. Atorvastatin 20 mg</td>
<td>Two weeks run-in, eight weeks follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• To assess the impact of adding a statin on lipids to the BP lowering drug combinations.</td>
<td>India, Canada, Italy</td>
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### Annex 6.3.7: Ongoing trials – polypill versus placebo or no treatment

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Population</th>
<th>Intervention</th>
<th>Countries and Sponsors</th>
<th>Outcomes</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Indian Polycap Trial – TIPS3</td>
<td>5 000</td>
<td>Men ≥55 and women ≥60 years with:</td>
<td>Polycap DS (thiazide 25 mg, atenolol 100 mg, ramipril 10 mg, simvastatin 40 mg) +/- aspirin EC 75 g +/- vit D 60 000 IU monthly versus control</td>
<td>China and India, Cadila Pharmaceuticals, Wellcome Trust, Canadian Institutes of Health Research (CIHR), Heart and Stroke Foundation of Ontario</td>
<td>Major CVD events, neurocognitive function</td>
<td>Enrolment started</td>
</tr>
<tr>
<td>Heart Outcomes Protection (HOPE) 3</td>
<td>12 500-2x2 factorial</td>
<td>Primary prevention in men ≥55 years and women ≥65 years with at least one risk factor</td>
<td>Rosuvastatin 10 mg, candesartan 16 mg/HCTZ 12.5 mg factorial</td>
<td>22 countries CIHR and Astra Zeneca</td>
<td>Major CVD events, neurocognitive function, renal function</td>
<td>Follow-up complete 2015</td>
</tr>
<tr>
<td>Poly-Iran</td>
<td>7 000</td>
<td>Men and women between 50 and 79 years old</td>
<td>Aspirin 81 mg, enalapril 5 mg (or valsartan 40 mg), atorvastatin 20 mg and hydrochlorothiazide 12.5 mg</td>
<td>Iran Tehran University of Medical Sciences</td>
<td>CVD events, blood sugar, cholesterol, BP, compliance, tolerability</td>
<td>Enrolment started</td>
</tr>
</tbody>
</table>
### Annex 6.3.8: Pipeline of polypills

<table>
<thead>
<tr>
<th>Company</th>
<th>Name</th>
<th>Active Components</th>
<th>Clinical trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In development</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alborz Darou (Iran)</strong></td>
<td>Polyiran 1</td>
<td>Aspirin 81 mg, Atorvastatin 20 mg, Enalapril 5 mg, hydrochlorothiazide 25 mg</td>
<td>Pilot studies conducted and published</td>
</tr>
<tr>
<td></td>
<td>Polyiran 2</td>
<td>Aspirin 81 mg, Atorvastatin 20 mg, Valsartan 40 mg, hydrochlorothiazide 25 mg</td>
<td>Pilot studies conducted and published</td>
</tr>
<tr>
<td><strong>Cadila (India)</strong></td>
<td>Ramitorva</td>
<td>Aspirin 100 mg, simvastatin 20 mg, ramipril 5 mg, atenolol 50 mg, hydrochlorothiazide 12.5 mg</td>
<td>TIPS program published; FDA application in process</td>
</tr>
<tr>
<td><strong>Cardio-Pharm (USA)</strong></td>
<td>CardiaPill</td>
<td>BP lowering, statin and aspirin 3 components – specifics undisclosed</td>
<td>Uncertain</td>
</tr>
<tr>
<td><strong>CNIC-Ferrer (Spain)</strong></td>
<td>Trinomia Secondary prevention</td>
<td>Aspirin 100 mg, simvastatin 40 mg, ramipril 2.5/5/10 mg</td>
<td>100 patients in trial in Spain; PD studies done in USA and Spain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Large FOCUS trial underway in Italy, Spain, South America; First patient randomized Nov 2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Already available in Guatemala, and in registration process in Latam</td>
</tr>
<tr>
<td><strong>Dr Reddy’s (India)</strong></td>
<td>Red Heart Pill (RHP) 1</td>
<td>Aspirin 75 mg, Lisinopril 10 mg, Simvastatin 20 mg (40 mg), Atenolol 50 mg</td>
<td>SPACE trials underway, UMPIRE completed</td>
</tr>
<tr>
<td></td>
<td>Red Heart Pill (RHP) 2</td>
<td>Aspirin 75 mg, Lisinopril 10 mg, Simvastatin 20 mg (40 mg), hydrochlorothiazide 12.5 mg</td>
<td>PILL trial published; SPACE trials underway, UMPIRE completed</td>
</tr>
<tr>
<td><strong>Polypill Company (United Kingdom)</strong></td>
<td>Polypill</td>
<td>Simvastatin 20 mg; bendroflumethiazide 1.25 mg; losartan 25 mg; amlodipine 2.5 mg</td>
<td>Uncertain</td>
</tr>
<tr>
<td><strong>PolypillRx.com (USA)</strong></td>
<td>Polypill</td>
<td>Customized production of different drugs into a single capsule through registered pharmacies. Not actually a new pill</td>
<td>None</td>
</tr>
<tr>
<td><strong>On the market</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TajPharma (India)</strong></td>
<td>Multiple pill combinations</td>
<td>Atorvastatin 10 mg, aspirin 75 mg, ramipril 5 mg, Atorvastatin 10 mg, aspirin 75 mg, ramipril 5 mg; metoprolol 50 mg (co-packaged),</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atorvastatin 10 mg, aspirin 150 mg, clopidogrel 75 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Torrent (India)</strong></td>
<td>CVPill</td>
<td>Polytorva®. plus co-packaged metoprolol</td>
<td>Marketed by USV Ltd. In India only</td>
</tr>
<tr>
<td><strong>Surien (India)</strong></td>
<td>Polytov™</td>
<td>Atorvastatin 10 mg, Ramipril 5 mg, and enteric-coated Aspirin 75 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Zyduscadiia (India)</strong></td>
<td>Zycad – secondary prevention</td>
<td>Atorvastatin 10 mg, ramipril 5 mg, Aspirin 75 mg, metoprolol 50 mg</td>
<td></td>
</tr>
</tbody>
</table>

*TGIGH has license – see Declarations

**Not developed to GMP standards, registered only on home country and not able to be exported. Only a selection of products shown here.
Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper
Written by Warren Kaplan

Background Paper 6.4
Diabetes

By Warren Kaplan, Ph.D., JD, MPH
February 8 2013
Update on 2004 Background Paper, BP 6.4 Diabetes

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1. Introduction

The word “diabetes” is from the Greek word for “siphon” and sometime in the second century AD, this clinical description was graphically described as:

“Diabetes is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant, like the opening of aqueducts. Life is short, unpleasant and painful, thirst unquenchable, drinking excessive, and disproportionate to the large quantity of urine, for yet more urine is passed…” (Aretaeus the Cappadocian, translated by Francis Adams 1856- Source Book of Medical History, 1960 Dover Publications)

The urine of some people diabetics was described as tasting like honey, sticky, and attractive to ants. The word “mellitus” is the Latin word for honey. Diabetes was first recognized as a metabolic disorder in the eighteenth and early nineteenth centuries, but it was in 1888 when von Mering and Minkowski made the crucial observation that removal of the pancreas would lead to diabetes in dogs. In 1922, Banting and Best published their first paper describing the use of pancreatic extracts to lower glucose levels in dogs that were lacking a pancreas.

The term diabetes mellitus encompasses a group of disorders characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects of insulin secretion, insulin action, or both. Several terms are important to define in this regard:

**Metabolic syndrome**: a name for a group of risk factors that occur together and increase the risk for diabetes and heart disease among other conditions. The two most prevalent risk factors are extra weight around the middle and upper parts of the body and insulin resistance, a condition in which the body uses insulin less effectively than normal. As a result, blood sugar and fat levels rise.

**Impaired glucose tolerance**: two-hour glucose levels of 140 to 199 mg per dL (7.8 to 11.0 mmol) on the 75 g oral glucose tolerance test.

**Impaired fasting glucose**: glucose levels of 100 to 125 mg per dL (5.6 to 6.9 mmol per L) in fasting patients. These glucose levels are above normal, but below the diagnostic level for diabetes. Patients with impaired glucose tolerance or impaired fasting glucose have a significant risk of developing diabetes and thus are an important target group for primary prevention.\(^1\)

Diabetic hyperglycaemia (i.e. excessive blood sugar) is associated with potentially devastating long-term damage, dysfunction, and failure of various organs. The eyes, kidneys, nerves, heart, and blood vessels are especially prone to such complications. Long-term complications include retinopathy with potential loss of vision, nephropathy leading to renal failure, peripheral neuropathy with pain and risk of foot ulcers, and amputation.\(^1\) People with diabetes are also at increased risk of cardiovascular (CVD), peripheral vascular,
and cerebrovascular diseases, thus public health systems cannot approach diabetes without addressing with its associated co-morbidities.

Diabetes profoundly affects quality of life and represents a life-long burden on a patient’s social support system. The impact of diabetes and its sequelae is enormous. In many countries:

- Diabetes is the leading cause of new blindness in people aged 20–74 years
- Diabetes is the leading cause of kidney disease requiring dialysis
- As a result of the effects of diabetes on nerve and peripheral vascular tissue, diabetes is the most common cause of amputation
- People with diabetes suffer heart disease two to four times more frequently than people without diabetes
- Persons with diabetes suffer strokes two to four times more frequently than those without diabetes
- The rate of congenital malformation in offspring of diabetic mothers may be as high as 10 per cent, and fetal mortality occurs in 3 to 5 per cent of pregnancies.¹

1.1 Types of Diabetes

There are several pathogenic processes involved in the most common forms of diabetes that lead to excess blood glucose and account for a continuum of disease progression. These range from autoimmune destruction of the insulin-producing beta cells of the pancreas (leading to insufficient insulin production) to abnormalities resulting in the body becoming resistant to the insulin it produces. This resistance to insulin results from inadequate insulin to meet requirements as a consequence of increasing obesity, and/or diminished tissue responses to insulin. Poor insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality is the primary cause of the high blood sugar levels. The vast majority of diabetes cases fall into two broad categories.

1.1.1 Type 1 Diabetes (T1D):

Type 1 diabetes (T1D) occurs when destruction of the pancreatic islet beta cells, usually attributable to an autoimmune process, causes the pancreas to produce too little insulin or none at all. Markers of autoimmune destruction (autoantibodies to islet cells, autoantibodies to insulin, or autoantibodies to both islet cells and insulin, and to glutamic acid decarboxylase) can be found in 85% to 90% of people with type 1 diabetes.² Beta-cell loss as a result of autoimmune destruction leaves people prone to ketoacidosis due to an absolute lack of insulin.

The definition of T1D excludes those forms of beta-cell destruction for which an alternative cause can be found (e.g. cystic fibrosis, pancreatitis, pancreatic cancer).³ The current prevailing paradigm on the etiology of T1D hypothesizes that environmentally triggered autoimmune destruction of pancreatic beta cells occurs against the background of genetic risk.³

Incidence/Prevalence

The prevalence of T1D is 0.02% in people aged 0 to 14 years, and it is estimated that 479,000 people in this age group have T1D worldwide with annual increase in incidence of 3%.⁴ Each
year, 75,000 new cases are diagnosed in this age group.\textsuperscript{4} Although TID usually accounts for only a minority of the total burden of diabetes in a population, in most resource-rich countries it is the predominant form of the disease in children.

Nearly a quarter of people with diabetes come from the European region.\textsuperscript{4} In 2008, diabetes accounted for about 2\% of the burden of disease (DALYs) in the WHO European Region\textsuperscript{5} and about 1.5\% worldwide. There is a worldwide increase in the incidence of childhood diabetes with age of onset shifting to a younger age group. This younger age onset means the risk of complications and lifelong dependence on insulin impose a heavy burden for diabetics and health services.

**Etiology and Risk factors**

Two main etiological forms of T1D are recognized. The first is autoimmune diabetes mellitus, which results from autoimmune-mediated destruction of the beta cells of the pancreas. The rate of destruction varies, but all people with this form of diabetes eventually become dependent on insulin for survival. Peak incidence of autoimmune diabetes is during childhood and adolescence, but it may occur at any age. The second is a genetic predisposition and people with this type of diabetes may have other autoimmune disorders.\textsuperscript{6} Certain viruses including rubella, Coxsackie B, and cytomegalovirus have been associated with beta-cell destruction. Other environmental factors contribute to etiology of developing T1D, but these are poorly defined and understood. Table 6.4.1 and Figure 6.4.1 (taken from Figure 2.5 International Diabetes Federation (IDF) Atlas 5\textsuperscript{th} edition\textsuperscript{4}) summarizes this information as of 2011.

**Table 6.4.1: T1D Summary Statistics**

<table>
<thead>
<tr>
<th>AT A GLANCE</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total child population (0-14 years. Billions)</td>
<td>1.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TYPE 1 DIABETES IN CHILDREN (0-14 YEARS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children with type 1 diabetes (thousands)</td>
</tr>
<tr>
<td>Number of newly-diagnosed children per year (thousands)</td>
</tr>
<tr>
<td>Annual increase in incidence (%)</td>
</tr>
</tbody>
</table>

*Source: International Diabetes Federation (IDF), Diabetes Atlas, 5th edition*
Figure 6.4.1: Estimated number of children (0-14yr) with T1D in various regions.

Source: International Diabetes Federation (IDF), Diabetes Atlas, 5th edition
Note: WP: Western Pacific; SACA: South and Central America; AFR: Africa; MENA: Middle East and North Africa; NAC: North America and Caribbean; SEA: Southeast Asia; EUR: Europe

1.1.2 Type 2 diabetes:

Type 2 diabetes (T2D) was once referred to as non-insulin-dependent diabetes or adult-onset diabetes. The cause of T2D is a combination of resistance to the action of insulin and an inadequate secretion of insulin as a normal compensatory response to increased blood glucose as well as a decrease in beta cell mass. Initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive in large part because autoimmune destruction of beta-cells does not normally occur. Many patients with T2D are obese and because obesity is the major cause of worsening insulin resistance,

progressive destruction of the B-cell population may occur. Obesity is the major reason for the need to augment glucose-lowering therapy over the years – a critical issue in care and cost of therapy.

Overweight and obesity are the main preventable risk factors for T2D. Cross-sectional and prospective studies have shown a strong association between obesity and T2D with 44% of the burden of diabetes attributable to overweight and obesity.

The risk of developing T2D also increases with age and lack of physical activity. It occurs more frequently in individuals with hypertension or abnormal blood lipids, and its frequency varies in different racial/ethnic subgroups. Diabetes is a leading cause of death, new cases of end stage renal disease, amputations, blindness and cardiovascular disease.7,8,9,10 Type 2 diabetes constitutes about 85% to 95% of all diabetes in developed countries and for an even higher percentage in developing countries. Eighty per cent of people with diabetes live in low and middle-income countries. See Appendix 6.4.1 (International Diabetes Federation (IDF) Atlas 2012. http://www.idf.org/sites/default/files/5E_IDFAtlasPoster_2012_EN.pdf).
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It is now a serious global public health problem with enormous financial and social repercussions.

The International Diabetes Federation (IDF) estimates more than 371 million people have diabetes (primarily T2D) as of 2012. The number of people with diabetes is increasing in every country, and half of people living with diabetes are undiagnosed. In 2012, nearly 5 million people died due to diabetes and its related complications. See Appendix 6.4.1. Diabetes is a considerable cause of premature mortality, a situation that is likely to worsen in low and middle income countries as the demographic transition (i.e. increasing life expectancy), urbanization, rates of overweight and obesity, and diabetes prevalence all increase.

This report is a review of primarily pharmaceutical interventions for diabetes, but it must be recognized that prevention of T2D through changes in behavior, such as diet and physical activity should be the first line of intervention.

2. What Are the Epidemiological Trends for Europe and the World?

Diabetes mellitus (primarily T2D) is a large burden to society. The dramatic rise in new patients with T2D in Western and Central Europe, the USA, Africa, Eastern Mediterranean, and Middle-East (EMME) over the next few decades must be acknowledged.

2.1 Type 1 Diabetes

The key characteristic of T1D is its extreme global variation in incidence and this represents an epidemiological puzzle. The overall standardized incidence varies from 0.1/100 000 per year in the Zunyi region of China to more than 40/100 000 per year in Finland.12 This represents an approximately 400-fold variation in incidence in the over 100 populations/countries studied.

For instance, a marked variation in incidence from 6.0/100 000 per year to 36.9/100 000 per year, was found among the five populations of the relatively small area around the Baltic Sea.13 Figure 6.4.2 is a map of the global trends in T1D incidence. (Map from reference 14 and see also reference 15)
Figure 6.4.2: Map of published incidence rates (per 100 000) of type 1 diabetes in children in 2006.


### 2.2 Type 2 Diabetes: Increasing overall global burden

The pattern of T2D varies considerably according to countries’ economic status. For developed countries the majority of people with diabetes are aged over 60 years. For developing countries most people with diabetes are of working age, between 40 and 60 years. Present global projections are far higher than predictions made around the time of the 2004 Priority Medicines Report.  

In 2012, about one half of the estimated 370 million people globally affected by diabetes lived in the Western Pacific, South Asia, and Eastern Mediterranean regions. See Appendix 6.4.1. Remarkably, this estimate for 2012 is over 60% higher than the 2004 published estimate for the year 2000.\(^\text{16}\) Previously, T2D was predominantly a disease of middle-aged and older people. In recent decades the age of onset has decreased and type 2 diabetes has been reported in adolescents and children worldwide, particularly in high-prevalence populations. Similarly, a recent Global Burden of Disease study, which included a systematic analysis of all available national health surveys and published estimates and amassed data from 2.7 million participants and 370 country-years, estimated that diabetes affects 347 million adults worldwide.\(^\text{17}\) The study noted that the absolute growth in number of people
with diabetes was primarily driven by population growth and age in the world’s largest countries.\textsuperscript{18}

In 2012, the highest regional prevalence was found in the Eastern Mediterranean/Middle-East/North Africa regions where one in nine adults had diabetes. The African region is expected to have the largest proportional increase in adult diabetes numbers by 2030, followed by the Eastern Mediterranean and Middle-East. Every region will have an increase in incidence, well in excess of adult population growth, and total prevalence of people with diabetes are likely to increase by 50% over the next 20 years. See Appendix 6.4.1. Created from recent data assembled by the IDF (Appendix 6.4.2 at IDFAtlas5E_Detailed_Estimates.xls) Figure 6.4.3 shows the diabetes prevalence in 2012 and the estimate for 2030 in various IDF regions, which are not coincident with WHO regions.

**Figure 6.4.3: Diabetes prevalence in 2012 and the estimate for 2030 in various IDF regions**

![Graph showing median regional diabetes prevalence (2012 vs. 2030)](image)

Source: Created from recent data assembled by the IDF

Note: WP: Western Pacific; SACA: South and Central America; AFR: Africa; MENA: Middle East and North Africa; NAC: North America and Caribbean; SEA: Southeast Asia; EUR: Europe

Considering only the countries in which prevalence studies have been conducted, all 10 of the world’s highest national prevalence in 2012 occurred in the Middle-East and the Western Pacific (see Table 6.4.2, created from the data in Appendix 6.4.2) although only Saudi Arabia (19.4\%) is among the 80 most populous countries.

The total predicted increase in numbers of people with diabetes from 2012 to 2030 is about 180 million persons (371.33 million to 551.87 million, respectively), an astonishing increase of 48\% from 2012 at an annual growth of 2.7\%, which is twice the annual growth of the total world adult population. Forty-two per cent of the anticipated absolute global increase of 180 million people with diabetes is projected to occur in India and China alone. See Table 6.4.3
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(Created from the data in Appendix 6.4.2) lists the top 10 league table of numbers of persons with diabetes (20-79 yrs) in 2012 and estimated for 2030.

Table 6.4.2: “Top 10” league table of diabetes prevalence in 2012

<table>
<thead>
<tr>
<th>Country/Territory</th>
<th>IDF Region</th>
<th>National Prevalence (%)</th>
<th>Adult population (20-79) in thousands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronesia (Fed. States of)</td>
<td>WP</td>
<td>31.8</td>
<td>58.3</td>
</tr>
<tr>
<td>Nauru</td>
<td>WP</td>
<td>29.8</td>
<td>6.2</td>
</tr>
<tr>
<td>Marshall Islands</td>
<td>WP</td>
<td>26.9</td>
<td>33.5</td>
</tr>
<tr>
<td>Kiribati</td>
<td>WP</td>
<td>25.2</td>
<td>61.6</td>
</tr>
<tr>
<td>Tuvalu</td>
<td>WP</td>
<td>24.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>MENA</td>
<td>19.4</td>
<td>17582.0</td>
</tr>
<tr>
<td>Vanuatu</td>
<td>WP</td>
<td>18.9</td>
<td>129.5</td>
</tr>
<tr>
<td>Kuwait</td>
<td>MENA</td>
<td>18.9</td>
<td>1922.2</td>
</tr>
<tr>
<td>Bahrain</td>
<td>MENA</td>
<td>18.3</td>
<td>1010.8</td>
</tr>
<tr>
<td>Qatar</td>
<td>MENA</td>
<td>17.6</td>
<td>1590.9</td>
</tr>
</tbody>
</table>

Source: Created from recent data assembled by the IDF

Table 6.4.3: Top ten countries with people aged 20-79 living with diabetes in 2012 and 2030 estimates.

<table>
<thead>
<tr>
<th>Country/Territory</th>
<th>2012 Millions</th>
<th>Country/Territory</th>
<th>2030 Millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>92.2</td>
<td>China</td>
<td>129.69</td>
</tr>
<tr>
<td>India</td>
<td>63.01</td>
<td>India</td>
<td>101.2</td>
</tr>
<tr>
<td>United States of America</td>
<td>24.11</td>
<td>United States of America</td>
<td>29.6</td>
</tr>
<tr>
<td>Brazil</td>
<td>13.35</td>
<td>Brazil</td>
<td>19.6</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>12.69</td>
<td>Bangladesh</td>
<td>16.83</td>
</tr>
<tr>
<td>Mexico</td>
<td>10.6</td>
<td>Mexico</td>
<td>16.44</td>
</tr>
<tr>
<td>Indonesia</td>
<td>7.55</td>
<td>Russian Federation</td>
<td>14.11</td>
</tr>
<tr>
<td>Egypt</td>
<td>7.54</td>
<td>Egypt</td>
<td>12.37</td>
</tr>
<tr>
<td>Japan</td>
<td>7.1</td>
<td>Indonesia</td>
<td>11.8</td>
</tr>
<tr>
<td>Pakistan</td>
<td>6.55</td>
<td>Pakistan</td>
<td>11.4</td>
</tr>
</tbody>
</table>

Source: Created from recent data assembled by the IDF

For low and middle income countries (LMICs), adult diabetes numbers are likely to increase by over 60% from 2012 to 2030 compared to 20% for developed countries. Total adult populations are expected to increase by 36% and 2%, respectively.

Figure 6.4.4 (created from the data in Appendix 6.4.2) shows the fraction of the total population with diabetes (20-79 years) on the Y axis allocated to different age groups for nine countries with the highest diabetes burden in 2012 and projections for these age groups in 2030. For all these high burden countries, decreases in the fraction of total persons with
Update on 2004 Background Paper, BP 6.4 Diabetes

diabetes numbers between 2012 and 2030 are expected for the youngest age group (20-39) and the middle-age group (with the exception of Egypt and Pakistan). For the over 60-year age group, increases are expected for all nine countries.

Figure 6.4.4: Nine countries with the highest diabetes burden in 2012 and the projection for 2030.

Source: Created from recent data assembled by the IDF
Figure 6.4.5 below (Map 2.1 taken from IDF Atlas, 5th edition) summarizes the global prevalence of diabetes, primarily T2D, in the 20-79 year age group.

Figure 6.4.5: Global prevalence of diabetes in 2011.

Map 2.1. Prevalence (%) of diabetes in (20-79 years), 2011


Note: although this map has been updated for 2012 (Appendix 6.4.1), the present map is included for clarity as the 2012 map is more difficult to view.

In view of the burden and associated costs of diabetes, the ongoing epidemic represents a major public health problem requiring effective control. There is currently a large gap between the prevalence of diabetes and treatment rates, with an estimated 30% to 50% of diabetes cases remaining undiagnosed and therefore untreated. 4

2.2.1 The European burden of diabetes is increasing

Type 1 Diabetes in Europe

Scandinavia, particularly Finland, and the United Kingdom have the highest rates of diabetes in Europe. A north–south gradient in incidence has been proposed with the exception being the island of Sardinia, which has the second highest incidence rate in the world. With regard to countries outside Scandinavia, OECD estimates 19 suggest that T1D incidence is highest in the United Kingdom with 24.5 cases per 100 000 population followed by Germany (18 cases), Spain (13 cases), France (12.2 cases), and Italy (8.4 cases). The EURODIAB study 20 registers in 20 European countries (not including France or Italy) all
report annual increases of 3.9% between 1989 and 2003, with a doubling of prevalent cases expected by 2010. These results are supported by other regional studies in Europe.\textsuperscript{21,22,23}

**Type 2 Diabetes in Europe**

Type 2 diabetes incidence is increasing in both children and adults due to rising obesity in the former and rising obesity in an ageing population in the latter. Added dimensions are the effect of socioeconomic status, with higher incidence of T2D in lower socioeconomic strata in Europe\textsuperscript{24} and a greater association with low birth weight and low childhood weight.\textsuperscript{25}

Based on 2012 IDF data (Appendix 6.4.2) diabetes prevalence (20-79 year age group: primarily measured as type 2) is highest in Portugal and in many countries in Eastern Europe and the Baltic. Prevalence are geographically heterogeneous with Malta having the same prevalence in 2012 as Latvia. See Table 6.4.4.

**Table 6.4.4: Top 10 European league table of diabetes prevalence in people aged 20-79 years.**

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portugal</td>
<td>12.8</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>11.6</td>
</tr>
<tr>
<td>Slovenia</td>
<td>11.2</td>
</tr>
<tr>
<td>Poland</td>
<td>10.6</td>
</tr>
<tr>
<td>Cyprus</td>
<td>10.2</td>
</tr>
<tr>
<td>Austria</td>
<td>10.0</td>
</tr>
<tr>
<td>Latvia</td>
<td>9.7</td>
</tr>
<tr>
<td>Malta</td>
<td>9.7</td>
</tr>
<tr>
<td>Lithuania</td>
<td>9.6</td>
</tr>
<tr>
<td>Belarus</td>
<td>9.4</td>
</tr>
</tbody>
</table>

Source: Created from recent data assembled by the IDF

Figure 6.4.6 (Map 3.2 from *IDF Diabetes Atlas, 5th edn*) shows the prevalence estimates for 2011 for primarily T2D in those aged 20-79 years in Europe.
Figure 6.4.6: prevalence (%) estimates for 2011 for primarily T2D in those aged 20-79 years in Europe


For 2012, across the EU5 countries (France, Germany, Italy, Spain, United Kingdom), diabetes (primarily T2D) prevalence in people aged 20-79 years is substantial and is highest in Spain (9.3%) and lowest in the UK (7.4%). See Appendix 6.4.2.

Figure 6.4.7 shows data extracted from the European Health for All Database (HFA-DB) and the European Mortality indicator database (MDB). See Annex 6.4.1. The figure shows temporal trends in mortality, using standardized death rates from 1995-2011 due to diabetes (mostly T2D) among the EU27 countries, those joining the EU prior to May 2004 (EU15), and those joining after 2004 (EU12). The majority of death due to endocrine diseases is due to diabetes, particularly in the EU12 countries. The trend is generally downwards, but not so pronounced in the EU12. The “break” in diabetes mortality rate trend after about 2000 (EU27, EU15) is interesting but any explanation must await a detailed study.
2.3 Specific epidemiologic issues exist with the main types of diabetes

2.3.1 Increases in Type 1 diabetes

Type 1 diabetes seems to be increasing in almost all populations particularly in nations with a previously low incidence of this disease. The incidence of T1D was expected to be about 40% higher in 2010 than in 1997. As mentioned, wide variations exist between the incidence rates in different populations; incidence is lowest in China and Venezuela (0.1 per 100,000 per year) and highest in Finland and Sardinia (37 per 100,000 per year). In most populations girls and boys are equally affected. In general, it was believed that incidence increased with age and peaking at puberty, but this no longer appears to be the case. The fastest rise in incidence is in the under five years age group. After the pubertal years, the incidence rate drops in young women, but remains relatively high in young adult males aged 29–35 years.

These findings support the impressions of healthcare professionals that they are seeing more cases of T1D, especially in younger children. The incidence of T1D shows a trend towards earlier onset. The incidence rate of T1D in European children has increased by about 4% each year, according to registry data collected from 1989 to 2008.

During the past 20 years, 20 of 21 registries in 15 European countries showed substantial rates of increase in the incidence of T1D diagnosed before age 15 years. The trend persisted
when the median rate of increase was estimated for the first half of registry data (1989-1998) and for the second half (1999-2008). In the first five years (1989-93) incidence rates varied from 3.2 per 100 000 in the Former Yugoslav Republic of Macedonia to 25.8 per 100 000 in the Stockholm area of Sweden. In the last five years (2004-2008) these two registries still had the lowest and highest incidence, but rates had increased to 5.8 per 100 000 and 36.6 per 100 000, respectively. During the 20 year period all but one of the 21 registries showed statistically significant rates of increase (median rate of increase 4% per annum) and similar figures were obtained when this median rate of increase was estimated for the first half of the period (1989-1998) and for the second half (1999-2008).

The European childhood T1D incidence rate continues to rise, but the increase is not necessarily uniform with periods of less rapid and more rapid increase in incidence occurring in some registries. This pattern of change suggests important risk exposures differ over time in different European countries. The explanation for these wide disparities in risk within groups probably lies in differences in genes or environment. Strategies for prevention and long-term management will vary as well.26

2.3.2 Increases in Type 2 diabetes in children:

Despite its high frequency, T2D is difficult to quantify since estimates vary according to access to diagnostic facilities, diagnostic definitions, means of ascertainment, nature and age-structure of the population under consideration, ability to distinguish between type 1 and type 2 diabetes, and the longevity of those affected.

Genes that predispose to cardiovascular disease and obesity in Europe and North America are also widespread in other areas. Presumably, as a function of a more sedentary lifestyle such as changes in eating habits and growing affluence, there has been an increase in both T2D, body weight, and obesity in much of the world.30,31,32

Obesity in adults and children causes hypertension, abnormal lipid metabolism, chronic inflammation, and insulin overproduction. This clustering of cardiovascular disease risk factors, known as “insulin resistance syndrome,” has been identified in children as young as five years of age. Being overweight in childhood increases the risk of death from ischaemic heart disease in adulthood two-fold over 57 years.30 Obese children are now at risk of developing T2D. Predictions from the United States imply that adult onset T2D might become the most common form of newly diagnosed diabetes in adolescent youth within 10 years.33

Evidence now exists suggesting a global spread of T2D in children, but incidence data are uncommon.34 Various centers in the United States have recorded dramatic increases in the number of children diagnosed with type 2 diabetes. A 10-fold increase was reported by a center in New York from 1990 to 2000, with 50% of all new cases having T2D in children.35 In Japan, researchers have documented a rise in annual incidence from 1.73/100 000 to 2.76/100 000 over 20 years.36 Evidence is emerging of an increase in urban South-Asian children 37 and children who belong to certain ethnic populations. These data are approximately coincident with the original Priority Medicines Report and there is still little specific geographic information aside from the global views of the IDF Atlas.
Ethnicity appears to be an important factor. In the USA, less than 5% of children of European origin in diabetes clinics have T2D and this percentage is even lower in Europe. As many as 80% of children of African, Hispanic, Asian, and Native American origin have T2D.

3. What is the Control Strategy?

Is there an effective package of control methods assembled into a “control strategy” for most epidemiological settings?

A complete picture of diabetes in this regard would include primary and secondary prevention and to the extent these are discussed, we confine ourselves to pharmacotherapies, not patient education, exercise, or other non-pharmaceutical interventions.

3.1 Type 1 Diabetes:

3.1.1 Primary Prevention: Avoiding the occurrence of T1D

Even though we now understand a great deal about blood glucose regulation and potential health complications associated with long-term T1D, the underlying reasons for this disease remain elusive. Autoantibody combinations conferring a high risk of progression to diabetes typically become established within the first three years of life. Primary prevention should, therefore, be attempted as early in life as possible. Children born to a family affected by T1D, especially those with high risk HLA genotypes (see below), are most appropriate for interventions and such families are likely highly motivated to participate. Safety is the major criterion for any form of primary prevention since only a small percentage of those at risk will be expected to develop diabetes.

Primary prevention might be attempted by avoidance of environmental risk factors if these could be identified with any confidence. For example, unequivocal identification of a viral cause for type 1 diabetes might lead to vaccination against the virus. Alternatively, potential risk factors could be removed from the environment, such as avoidance of cow's milk in early infancy. A major multinational trial known as TRIGR (Trial to Reduce IDDM in the Genetically at Risk) is currently under way to test this hypothesis.  

A brief summary of current approaches to prevent T1D includes:

- Avoidance of environmental triggers of islet autoimmunity such as cow's milk or gluten. Celiac disease provides an encouraging example of autoimmune disease that can be prevented in this way. Alternatively, diet is supplemented with nutrients for which deficiency presumably promotes islet autoimmunity (i.e. n-3 fatty acids or vitamin D).
- Antigen-specific vaccination using islet autoantigens (e.g., intact insulin, altered insulin or proinsulin peptides), GAD, or heat shock protein 60 (HSP60) peptide. The goal is to induce autoantigen-specific tolerance by induction of regulatory T-cells that downregulate immunity to a specific autoantigen as well as promote tolerance to additional autoantigens.
Non-antigen-specific systemic therapies that range from mild modulation with oral nicotinamide or bacille Calmette–Guerin (BCG) vaccination to immunosuppression and cellular therapies. See section below on vaccinations.

Stimulation of β-cell regeneration in conjunction with suppression of apoptosis that is increased in islet autoimmunity to overcome the relapsing-remitting course of pre-diabetes.

Metabolic modifications, such as weight loss and maintenance and increased physical activity.

There is increasing evidence on predictive markers for T1D. Children with multiple islet cell auto-antibodies are at high risk for the development of diabetes. Vaccination can be considered if the child has not yet had a diabetes-causing virus infection. Previous infection can be detected by measuring the neutralizing viral antibodies in serum. Thus, it is possible to identify a focus group of risk individuals for whom a preventive therapy might be used to prevent the development of T1D.

3.1.2 Secondary Prevention: Treating existing T1D before it causes significant morbidity

Metabolic testing can identify those at imminent risk of progression of T1D and helps to stage the disease process. Major studies have demonstrated the feasibility of large-scale control trials in antibody-positive, first-degree relatives of those with diagnosed T1D, but the logistics are difficult and the number of testable interventions is very limited. For this reason, most investigators have opted to look for efficacy in recently diagnosed patients before testing further agents in secondary intervention trials. In addition to the TRIGR trial (above) two other large studies have reported to date:

- The Diabetes Prevention Trial – Type 1 (DPT-1) reported on use of injected insulin therapy. This unblinded trial screened 84,000 first-degree relatives. Parenteral insulin proved ineffective in the prevention of T1D, as did a second trial based on oral insulin administration.

- The European Nicotinamide Diabetes Intervention Trial (ENDIT) was a blinded comparison of high-dose nicotinamide or placebo that required screening of over 30,000 first-degree relatives in 21 countries. Nicotinamide also proved ineffective.

3.1.3 Prevention of Diabetes Complications: Type 1

Untreated, all people with type 1 diabetes, particularly those with autoimmune diabetes mellitus, will experience increasing blood glucose levels that may progress to ketoacidosis and result in coma and death. All people with type 1 diabetes require insulin for survival, and are described as insulin dependent. The long-term effects of diabetes include retinopathy, nephropathy, and neuropathy. People with diabetes mellitus are also at increased risk of CVD, peripheral vascular disease, and cerebrovascular disease. Good glycaemic control can reduce the risk of developing diabetes-related complications.

Aims of intervention include controlling blood glucose levels; maximizing quality of life; preventing diabetes-related emergencies such as ketoacidosis and hypoglycaemia; maintaining HbA1c levels at optimal level in order to slow disease progression and reduce
risk of microvascular and macrovascular complications; and minimizing adverse effects of treatment.\(^2\)

Intensive treatment programmes in adults and adolescents with type 1 seems to improve glycaemic control compared with conventional treatment, and also seem to improve long-term outcomes (such as retinopathy, neuropathy, and macrovascular events), but they require a considerable investment of time and resources and aggressive treatment associated with increased risk of hypoglycaemia. Over the last two decades, the evidence that better glycaemic control (i.e. keeping blood glucose and HbA1c levels as close to normal as possible) reduces the rates of many complications of diabetes has become overwhelming. As a result, diabetes specialists have expended increasing effort to help most people with diabetes achieve blood glucose levels as close to normal as achievable. It takes about the same amount of effort to achieve good glycaemic control with a traditional two or three injection regimen as does with intensive, flexible therapy: frequent glucose monitoring, attention to timing and amounts of meals. Many diabetes specialists no longer think of flexible insulin therapy as intensive or special treatment for a select group of patients, but simply as standard care for most patients with type 1 diabetes. Better glycaemic control is also associated with higher rates of low blood sugar (hypoglycaemia).

While regular self-monitoring of blood glucose is recommended to adults with type 1 diabetes, there are no reliable data on which to base advice about optimum frequency of blood glucose self-testing.\(^2\) However, the use of continuous glucose monitoring, which allows real-time insulin dose adjustments, may improve glycaemic control in adults compared with intermittent, conventional monitoring. Continuous glucose monitoring systems may also be combined with continuous subcutaneous insulin infusion pumps (CSII).\(^2\) Continuous subcutaneous insulin infusion with various pump systems seem effective at improving glycated haemoglobin (A1c) levels and quality of life compared with multiple daily subcutaneous injections.\(^2\)

People using such pumps remain at increased risk of ketosis if the insulin delivery is interrupted for any reason. Annual costs of CSII and multiple daily insulin injections (MDI) were calculated from the perspective of the United Kingdom third party payers. The total annual costs were calculated to be £2 641 (about US$ 4 225) for CSII therapy and £1 482 (about US$ 2,370) for MDI treatment.\(^45\)

A practical limitation on the use of pump systems is the cost as it is not affordable for many. At least in the USA, insulin pumps can cost between $4 500 and $6 500 for individuals without insurance. The price varies depending upon the features, brand, and size of the pump. Though most pumps will come with infusion lines, syringes and batteries, the patient will have to continually replace these items. These items can cost about US$ 1 500 per year.\(^45\)

### 3.2 Type 2 Diabetes:

#### 3.2.1 Primary Prevention

Epidemiological studies have demonstrated that type 2 diabetes results from an interaction between genetic predisposition and lifestyle factors, including patterns of eating and sedentary behavior, that lead to obesity. Fortunately, there is increasing evidence that type 2 diabetes can be delayed or prevented by changes in these lifestyle factors. There is solid scientific basis for advocating preventive measures to slow the onslaught of type 2 diabetes.
Major primary prevention trials in the late 1990s demonstrated that one can prevent or delay 25–60% of new type 2 diabetes. Approximately one case of diabetes can be prevented or delayed for every six to seven patients with impaired glucose tolerance receiving intensive lifestyle supervision over an approximate three year period. Primary prevention of type 2 diabetes has always been centred on control of the energy economy of the body (i.e. achieving a negative calorie balance if weight loss is required and/or optimal intake of carbohydrates and lipids).

3.2.2 Secondary Prevention
The management of hyperglycemia, the hallmark metabolic abnormality associated with type 2 diabetes, has historically taken center stage in the treatment of diabetes. As of 2012, glycaemic management in type 2 diabetes mellitus has become increasingly complex and controversial as a widening array of pharmacological agents are becoming available. With this comes mounting concerns about potential adverse effects and uncertainties regarding the benefits of aggressive glycaemic control on macrovascular complications. See American Diabetes Association (ADA) Consensus document and associated references.

Key points of a recent ADA Consensus document are as follows:
- Glycaemic targets and glucose-lowering therapies must be individualized.
- Diet, exercise, and education remain the foundation of any T2D treatment program. Unless there are prevalent contraindications, metformin is considered the optimal first-line drug and therapies must be changed or altered as beta-cell function almost inevitably declines over time. After metformin, there are limited data to guide optimal therapies.
- Combination therapy with an additional one to two oral or injectable agents is reasonable. Aim to minimize side effects where possible.
- Many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.
- Comprehensive cardiovascular risk reduction must be a major focus of therapy. See Sections below.

3.2.3 Controlling T2D Complications
The first-line preventative therapy for type 2 diabetes is lifestyle change (i.e. weight reduction and increased physical activity). Unfortunately, lifestyle therapy can be difficult to implement, and the T2D risk factors are subject to other influences, such as genetic predispositions. To effectively normalize the risk factors of this metabolic dysfunction it is often necessary to use pharmaceuticals. If pharmacological interventions are needed, several current treatments have proven useful in reducing mortality and morbidity due to complications of the disease. Such strategies and their expected benefits are shown in Table 6.4.5. Therapies directed at coincident features, such as dyslipidemia, hypertension, obesity, and insulin resistance, have been a major focus of research and therapy. Maintaining glycaemic levels as close to the non-diabetic range as possible has been shown to have a powerful beneficial effect on diabetes-specific microvascular complications.
Table 6.4.5: Pharmacological Strategies to alter diabetes co risk factors

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycaemic control</td>
<td>Reduces micro/macro-vascular disease</td>
</tr>
<tr>
<td>Blood pressure control</td>
<td>Reduces macro/micro vascular events and mortality</td>
</tr>
<tr>
<td>Lipid Control</td>
<td>Reduces coronary events/mortality</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>Reduces myocardial infarction in men</td>
</tr>
<tr>
<td>ACE inhibitor/ARB*use</td>
<td>Reduces nephropathy</td>
</tr>
</tbody>
</table>

*ACE inhibitors angiotensin converting enzyme inhibitors /ARB: angiotensin receptor blockers

At present, however, the only available approach is to use separate pharmaceuticals to target each risk factor. Moreover, risk factors such as hyperglycaemia in type 2 diabetes, may themselves require multiple pharmaceuticals to achieve adequate control. Although this approach has the benefit of allowing a physician to titrate and monitor the efficacy of each drug for each risk factor, the disadvantages include greater risk of adverse drug interactions, complicated treatment regimens, and high cost. Therefore, there has been increasing interest in alternative strategies to develop drug therapies that could positively affect several risk factors. One possible strategy is a fixed dose combination ‘polypill’, whereby several risk factors are treated with a single capsule containing a combination of pharmaceuticals, which can be assembled in various ways. Although the polypill cannot be titrated for better risk factor control when used alone, its advantages include simplicity and cost reduction if generic medicines are used.

A second pharmacological strategy to reduce the problems that are associated with polypharmacy for patients with several risk factors is to develop single drugs that have multiple targets or modulate targets that affect several risk factors. A good example of this is the incretins, which are naturally occurring peptides that are pro-glucagon derivatives that have been implicated in the control of appetite and satiety. The class includes glucagon-like peptide-1 (GLP-1). Preliminary evidence suggests that the native GLP-1 peptide, its active metabolites, GLP-1R agonists (exenatide), and analogues (liraglutide, albiglutide) themselves may also have direct cardiovascular (CV) benefits outside of glycaemic control. At present, it is possible to achieve regulatory approval on the basis of targeting specific risk factors such as high blood pressure, high cholesterol levels, and increased blood glucose levels, but not a nonspecific clustering of risk factors.

Although some single-pill combinations of registered pharmaceuticals (i.e. statin for high cholesterol levels and a calcium channel blocker for hypertension) have recently been approved by the USA Food and Drug Administration (FDA), regulatory agencies seem to be setting a higher bar for new anti-diabetic agents. In December 2008, the FDA developed a guidance document asserting that to establish the safety of a new antidiabetic therapy to treat type 2 diabetes, the developer “should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. Meta-analyses should be performed comparing treated patients with control groups to demonstrate absence of excessive cardiovascular risk.” See FDA Guidance Document in Appendix 6.4.3.
3.2.4 Multifactorial interventions- Steno-2 and follow up

The death rate among patients with type 2 diabetes is approximately twice as high as that of persons without the disorder. The risk of vascular complications was reduced by about half in the Steno-2 Study, a prospective, randomized, open-label, blinded trial during an average of 7.8 years of intensified multi-target intervention aimed at concomitant risk factors.\(^53,54\)

Eighty patients were randomly assigned to receive conventional treatment in accordance with national guidelines and 80 to receive intensive treatment; treatment included a stepwise implementation of behavior modification and pharmacologic therapy that targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, along with secondary prevention of cardiovascular disease with aspirin.

Although the number of deaths was lower in the intensive-therapy group in the Steno-2 Study, the relatively small number of patients who reached that end point precluded a determination of whether this approach affected mortality. A follow-up to the Steno-2 Study was designed to address the question of mortality and whether the risk reductions already achieved for both macrovascular and microvascular diseases were maintained during follow-up in a community setting. In the follow-up study, patients were observed for a mean of 5.5 years after the initial trial had ended.

After a mean of 13.3 years (7.8 years of multifactorial intervention and an additional 5.5 years of follow-up), there was an absolute 20% risk reduction for death from any cause among patients with type 2 diabetes and microalbuminuria who received aggressive therapy, as compared with those who received conventional therapy. The absolute risk of death from cardiovascular causes was reduced by 13% among those receiving intensive therapy.\(^54\)

3.3 Diagnostics

Blood tests are used to diagnose diabetes and irregularities in glucose metabolism, as there may be no physical symptoms in the early stages of the disease. All diabetes blood tests involve drawing blood at a health care provider’s office or commercial facility and sending the sample to a lab for analysis. Laboratory analysis of blood is needed to ensure test results are accurate. Glucose measuring devices used in a health care provider’s office, such as fingerstick devices, are not accurate enough for diagnosis though may be used as a quick indicator of high blood glucose. Testing enables health care providers to find and treat diabetes before complications occur and to find and treat pre-diabetes. Early detection or treatment of pre-diabetes can delay or prevent type 2 diabetes from developing. Any one of the following tests can be used for diagnosis:

- A1C test, also called the hemoglobin A1c, HbA1c, or glycohaemoglobin test
- Fasting plasma glucose (FPG) test
- Oral glucose tolerance test (OGTT)

The diagnostic market is heavily segmented in the products needed to perform diagnosis and monitoring: blood glucose testing devices including blood glucose test kit, blood glucose meters/monitors, and diabetes kits, testing supplies including glucose test strips, lancets, lancet devices, and reagent strips, and other supplies including glucose sensors, solutions, and reagents. With regards to these market segments blood glucose test strips constitute the largest segment followed by blood glucose meters or monitors. Portable meters have evolved as the preferred alternative over conventional methods, such as urine testing, in measuring
blood glucose levels in patients. The user-friendliness of these compact glucose meters, coupled with high levels of accuracy, has been fuelling their market growth. The USA and Europe represent the largest regions within the global diabetes diagnostics market, with the two together accounting for more than a 65% share of the global market by value. The region of the Asia-Pacific is expected to grow at the fastest pace, at a compound annual growth rate of more than 12.9% through to 2017. The A1C assay is the test of choice for the chronic management of diabetes and is now being recommended for its diagnosis. However, there are parts of the world where the costs of providing this assay preclude its routine use.

An expert consultation on diabetes testing was conducted at the WHO on 17 May, 2012. See Appendix 6.4.4. The main objectives of the consultation were to review the need for HbA1c testing in low and middle-income countries (LMICs) and the barriers to access. WHO is interested in increasing access to HbA1c tests for diabetes treatment monitoring in developing countries and has facilitated the development of a Preferred Product Profile (PPP) for an HbA1c test suitable for low and middle income countries. WHO is particularly interested in tests that could be locally produced in developing countries. See Appendix 6.4.4.

It is likely that the evolution of regulatory standards will also play an important part in advancing the therapy of the metabolic syndrome beyond the current approach of polypharmacy.

4. What is Known of the Affordability, Feasibility, and Sustainability of the Control Strategy?

4.1 Economic Burden

Diabetes exacts three broad categories of economic cost:

Direct healthcare costs: These include such items as medication and devices, visits to healthcare professionals, both general and specialist and hospitalization both for the condition itself and for its complications.

Indirect healthcare costs: Includes care in nursing homes and informal care by relatives or caretakers. Although difficult to calculate this expense, some studies suggest this constitutes up to half of the cost of diabetes. Societal expectations about the appropriate place of professional and informal care certainly have important economic consequences. Foregone income by caretakers adds to the national cost of diabetes and can be deeply significant at a household level. For example, relatively poor families in developing countries are greatly affected.

Productivity costs: This includes the loss of earnings from mortality, morbidity (i.e. time taken by otherwise economically active individuals with diabetes to treat their condition), and disability associated with diabetes and its complications.

These costs also extend beyond those closely associated with physical condition. In a series of studies, it was found that when controlling for a set of independent variables, individuals
with childhood diabetes had lower levels of attained education and self-assessed health later in life than the general population within the same age group. This indicated that the onset of a chronic condition during childhood or adolescence might be a factor behind both lower education and lower health later in life. In short, individuals with diabetes might be less well-equipped later in life in regards to knowledge and available resources when it comes to making health-related decisions.57

Diabetes is costly to health care systems. People with diabetes have more outpatient visits, use more medications, have a higher probability of being hospitalized, and are more likely to require emergency and long-term care than people without the disease.4 The global health care expenditure attributable to diabetes has been estimated in 2003 and 2006 by the IDF and reported in the second and third editions of the Diabetes Atlas with a recent update in 2010.

The total annual global health expenditure for diabetes in 2010 was estimated between US$ 376.0 and US$ 672.2 billion.58 Remarkably, expenditure on diabetes was estimated to account for 12% of the world’s total health expenditure in 2010. Globally, per capita spending on diabetes ranges from US$ 60 to 90 billion with about 6.9 billion persons in 2010. The expenditure varied by region, age group, gender, and country’s income level.58

The North American region was estimated to spend US$ 214.2 billion, or at least 57% of the total global diabetes expenditure. The European and Western Pacific regions was estimated at US$ 105.5 billion and US$ 38.2 billion, respectively. More than three-quarters of the global expenditure was estimated to be for persons between 50 and 80 years of age and 53% of the total was spent on women. It was estimated that 91% of the total world health expenditure on diabetes was in developed countries while only 9% of the total was in developing countries.

Figure 6.4.8 displays the health expenditure for diabetes in international dollars (ID) and the number of people with diabetes for the 25 countries with the largest numbers of people with diabetes in 2010.6

There appears to be a discrepancy between countries with the largest number of people living with diabetes and countries with the highest expenditures for diabetes care. The country with the highest total expenditure on diabetes, the United States of America, spent 57% of the global expenditure on diabetes. India, the country with the largest population of people living with diabetes, spent an estimated US$ 2.8 billion on diabetes care, or less than 1% of the world total expenditure. The total diabetes spending in the 18 countries in IDF’s African Region was only US$ 1.2 billion, 0.3% of the global total of diabetes spending. In general, developing countries have more people with diabetes but less total diabetes spending. In contrast, developed countries have much higher national diabetes expenditures, but much smaller numbers of people with diabetes.
Figure 6.4.8: Global health expenditure for diabetes for 25 countries in 2010.


The absolute level of health expenditure on diabetes in developing countries is relatively low. Of the top 80 most populated countries, the lowest spending twenty countries spent less than US$ 50 per person per year for managing diabetes and diabetes-related complications. Expenditure at this level cannot even cover the annual wholesale cost of a generic oral agent capable of preventing acute, life-threatening hyperglycaemia. Considering the health services and therapeutic treatments needed to manage diabetes and diabetes-related complications, more health care resources will be required to provide adequate diabetes care in the poor countries of the world.

A proportion of the costs of treating diabetes, and of its broader economic impact on society, comes from attendant complications, including heart disease, kidney disease, amputations, cerebral conditions, and blindness. More than half of the deaths from heart disease occur in people with diabetes, pre-diabetes, or the closely related metabolic syndrome. More frequent than not, diabetes—particularly when it has not yet been diagnosed—is not recorded as the underlying cause of these incidents. The condition’s true cost is, therefore, almost always underestimated.
Economic Burden: EU 5 countries

A recent detailed economic analysis (London School of Economics, January 2012: http://www2.lse.ac.uk/LSEHealthAndSocialCare/research/LSEHealth/MTRG/LSEDiabetesReport26Jan2012.pdf, See Appendix 6.4.5) provides important information. Diabetes record keeping in all EU5 countries is poor for direct diabetes costs, cost of complications, indirect costs, and diabetes outcomes. No diabetes registries exist in any of the EU5 countries. Although none of the EU5 countries record diabetes costs directly, estimates for 2010 suggest the total direct annual cost ranges from €5.45 billion (Spain) to €43.2 billion (Germany). Across EU5 the total direct cost burden of people with diabetes was €90 billion. This figure includes the cost of complications or medical conditions, some of which may not necessarily be caused by diabetes, but can be exacerbated by it. Per patient direct medical costs are more comparable across countries, with some variation (€1,708 in Spain to €5,899 in Germany in 2010) suggesting a key driver behind total diabetes costs is the disease prevalence. Inpatient costs are consistently higher than outpatient costs in all countries due to increased medical care required with diabetes-related complications. Outpatient costs, on the other hand, and diabetes medications can be less than half of inpatient costs due to the relatively low costs of maintaining good glycaemic control via medication and regular monitoring. Expenditure on insulin and oral anti-diabetic medicines ranges between 6.2% and 10.5% of total direct cost. Indirect costs relate to reduced productivity, absenteeism, early retirement, social benefits, and caretaker costs. These costs are significant and having quantified part of these costs for the first time in Europe, they appear to stand at €98.4 billion and can exceed direct costs by at least a factor of 2- or even 3- to-1 depending on the country.

4.2 Affordability

We know that affordability of diabetes medicines is an issue in low and middle-income countries. To illustrate the issue of high prices and unaffordable treatment Health Action International (HAI) (www.haiweb.org/medicineprices) undertook a one day global ‘snapshot’ of the price of insulin. Individuals from 60 countries collected the retail price a patient would have to pay, as opposed to a co-payment amount where reimbursement systems exist, for a 10ml traditional vial of 100 IU/ml soluble human insulin injection (in their closest private retail pharmacy) on 11 May 2010. Prices were collected for insulin manufactured by three multinational companies: Novo Nordisk, Eli Lilly, and Sanofi Aventis, plus the lowest priced insulin in the pharmacy from other manufacturers.

The map on the website (see above citation for URL) shows the price for a 10 ml vial of insulin converted to American dollars using the exchange rate on 11 May 2010 in each location where data was collected. Prices were indicative of what patients would pay if paying the full retail price in those pharmacies on that day. The price a patient would pay for a 10 ml vial of soluble human insulin in the private sector ranged from US$ 1.55 in Iran to US$ 76.69 in Austria, a difference of almost 5000%. Charts showing prices in all 60 countries are available on HAI’s website. The major drivers for these variations appear to be markups and margins in the distribution chain.

Although not the subject of this report, researching how health systems distribute medicines for non-communicable diseases is critical to improve access and quality of care. Access to effective medicines in those who are diagnosed is absolutely essential. Insulin has been widely available in the Western world since its discovery in 1921, but in resource-poor
settings access to insulin is still problematic. Access to insulin alone is not enough for proper diabetes care. In order to improve the lives of people with diabetes, access to medicines needs to be addressed in parallel to creating a health system able to manage all aspects of diabetes care.59

4.3 Feasibility of Control Strategy

Primary prevention of type 2 diabetes requires concerted effort with regard to diet, lifestyle, diagnosis, costs, and access. Cure of diabetes requires intensive basic and applied research into the genetic and metabolic mechanisms. Prevention of diabetes-related complications requires both diet and lifestyle changes, as well as applied and basic scientific efforts.

5. Why Does the Disease Burden Persist?

A number of powerful barriers are preventing change. The more common type 2 diabetes is both preventable and treatable, but key constraints include cultural resistance to healthier diet and lifestyle among the population; a lack of attention devoted to chronic disease by national and international health organizations (although this is changing); a focus on short-term costs rather than long-term implications; and a lack of universal healthcare coverage in many countries. Success in overcoming these barriers requires systemic change and collaboration between a wide range of important stakeholders.

5.1 Type I Diabetes

Type 1 diabetes is not curable at present and the underlying biological, genetic, and environmental reasons for the autoimmunity are not known. We consider there to be a pharmaceutical gap with regard to type 1 diabetes. There is no identified agent capable of affording primary prevention of incident cases.

Few could argue that such a discovery of a preventative or curative agent would represent a milestone for type 1 diabetes. No treatment has been shown to safely prevent type 1 diabetes in humans. We need more insight into basic biology and new therapeutic innovations for insulin delivery and cure. Individuals with type 1 diabetes require daily injections of insulin to sustain life and access to insulin is a problem in many developing countries.

5.2 Type 2 Diabetes

From a pharmacotherapeutic viewpoint, type 2 diabetes persists because there is no cure. Although current medicines are therapeutically effective in controlling blood sugar, we would consider both the lack of curative agent and lack of development of a therapeutic agent capable of achieving glucose and weight control sufficient grounds to say there is at least one pharmaceutical gap with regards to type 2 diabetes.

A significant percentage of patients do not achieve glucose or weight goals and get complications, notwithstanding the fact that blood glucose lowering agents can assist in preventing onset of type 2 diabetes. Indeed, there are additional pharmaceutical gaps with
regard to T2D. One at present is an inability to prevent progressive loss of islet B-cell function/mass and another is the need to deal with managing the rather progressively ineffective glucose-lowering treatments over time, which result in multiple-therapy need and usually insulin after about 10 years.

The key issue is again long term glycaemic control. Current treatment for type 2 diabetes is quite variable and often staged to the progress of the disease. Early on, or in mild forms, diet, weight loss, and exercise are used to improve insulin sensitivity. If this is inadequate, oral hypoglycaemic agents are added. These may act to further improve insulin action, stimulate more insulin secretion or alter the absorption of carbohydrates in the diet. If these steps are unsuccessful, the patient is often placed on insulin. These approaches often have limited success in controlling elevated glucose levels in patients with type 2 diabetes (see Section 6), and in controlling obesity that predisposes patients to this disease as insulin itself can be associated with weight gain in type 2 diabetes.

Current treatment of type 2 diabetes is far from satisfactory. Evidence suggests controlling obesity and increasing physical inactivity can prevent, or at least delay, the development of disease in many genetically susceptible individuals. Success in controlling these risk factors on a large scale has been limited. There are considerable gaps in our understanding of optimal applications of existing and new therapies, particularly since many patients will have co-morbidities that require polypharmacy. Drug interactions and safety of new agents will be of prime concern.

5.2.1 Poor Insulin treatment of Type 2 patients remains a concern, but there is still controversy over how tight the control should be

Recognizing that many patients with T2D go for long time period with glucose levels well above the recognized toxic threshold has led to guidelines suggesting more prompt control of hyperglycaemia by introducing insulin as an early agent in combination therapy with metformin to achieve glucose management goals. However, some believe prompt glycaemic control can be attained with skillful combination of non-insulin therapies. Treatment typically relies upon measurement of HbA1c. Although long-term management is appropriately directed by HbA1c, rapid advancement of pharmacotherapy requires monitoring of fasting glucose status is necessary for initial management. This can reflect day-to-day changes in control versus the 90 to 120-day control window provided by HbA1c monitoring.

Although there is a linear relationship between HbA1c and adverse outcomes in diabetes, recent literature has challenged the concept that lower HbA1c is always better. The UK Prospective Diabetes Study (UKPDS) enrolled participants soon after diagnosis of T2D and did not require them to have other cardiovascular (CV) risk factors. At the end of randomized comparison of aggressive versus standard glycaemic treatment, improvements of microvascular end points were found, but there was no reduction of CV events or mortality. However, the numbers of participants and the rates of CV events were relatively low and thus the statistical power was limited.

Much larger populations were enrolled in the ACCORD trial ($n = 10,251$) and participants had strong CV risk profiles or prior events and thus predictably high future event rates. The mean duration of known diabetes was 10 years in ACCORD. Aggressive glycaemic control
tactics were used, aiming for nearly normal glycaemic control, and ACCORD achieved very good glycaemic control. One or more microvascular end points were improved. However, the primary CV outcomes were not improved by aggressive glycaemic therapy. In ACCORD, a 22% increase of all-cause mortality accompanied aggressive glycaemic treatment.

Results of these trials have been analyzed together with data from the UKPDS. This meta-analysis found a 9% reduction of major CV events accompanying aggressive glycaemic treatment (hazard ratio [HR] 0.91 [95% CI 0.84–0.99]), but no significant effect on all-cause mortality (1.04 [0.90–1.20]) or CV mortality (1.10 [0.84–1.42]). Both of these meta-analyses showed an increased risk of severe hypoglycemia with aggressive glycaemic management (HR 2.48; relative risk 2.03). Two other meta-analyses, which added additional randomized studies to the large trials, concluded that available data show limited and inconclusive evidence of risk reduction for CV end points but confirmed a substantial increase of severe hypoglycemia.

Late-stage, high-risk patients like those selected for ACCORD may be less likely to benefit from glycaemic control after years of hyperglycemia. Earlier treatment may be more effective even though its effects are delayed. The phenomenon of continuing beneficial effects on diabetic complications after a period of improved glycaemic control followed by a return to often worse metabolic control is described as “metabolic memory”. This suggests early, aggressive treatment of new-onset diabetes mellitus aimed at tight glucose control may reduce the risk of microvascular complications and macrovascular disease.

Notwithstanding the issue of tight versus traditional therapy, we note that the American Diabetes Association 2011 position statement has reiterated that HbA1c goals must be individualized. With a widening array of pharmacological agents now available for T2D, there are concerns about their potential adverse effects and uncertainties regarding the benefits of aggressive glycaemic control on macrovascular complications, and the most recent statement of the American Diabetes Association continues to advocate for a patient-centred approach. In a shared decision-making approach clinicians and patients act as partners, mutually exchanging information and deliberating on options in order to reach a consensus on the therapeutic course of action. Whether this interaction happens in practice is an open question.

The accumulated evidence for T2D suggests not everyone benefits from aggressive glucose management. In most T2D patients, the ADA recommends beginning with lifestyle changes, followed by metformin monotherapy at or soon after diagnosis. If the HbA1c target is not achieved after three months, one of the following five treatment options is supposed to be combined with metformin: a sulfonylurea, thiazolidinedione (TZD), DPP-4 inhibitor, GLP-1 receptor agonist, or basal insulin (see Section 6). This choice is supposed to be based on patient and drug characteristics with “… the over-riding goal of improving glycaemic control while minimizing side effects.”

5.2.2 Access to insulin is poor in many LMICs

This report is concerned mainly with priority pharmacotherapeutics for important conditions affecting Europe and the world. Affordability of medicines is an issue in developed countries, in low-income subgroups, and in ethnic minorities. Nonetheless, the rising burden of diabetes around the world is a compelling argument for a brief review of
one factor that causes both individual suffering and health system overload: the lack of access to insulin. Ninety years after its discovery, insulin is not routinely available in many parts of the developing world. Insulin is often unavailable in large city hospitals in Africa and may be unavailable in rural areas. A child with newly diagnosed type 1 diabetes in much of sub-Saharan Africa may live only one more year after diagnosis. In Bamako, the capital of Mali, it was estimated that the average monthly spending on diabetes care for a patient was US$ 21.24, corresponding to nearly 70% of mean income. This includes each month: one blood glucose measurement, eight syringes, one vial of insulin at an average cost of US$ 10.88 in the public sector, one monthly consultation, and travel costs. Other issues identified as limiting access to diabetes care include: lack of clear national policies for diabetes and non-communicable diseases, the important role of traditional healing, the lack of components of a functioning health system including health workers and record systems for chronic disease management, and the limited national health budgets of resource-poor countries. Insulin is a biopharmaceutical, not a small molecule, and it is difficult to manufacture. Instead of focusing solely on access to medicines, attention should be paid to access to treatment. This concept refers to how health systems can ensure access to other factors that affect patient care and outcomes. These elements may include availability of diagnostic tools and the presence of trained health-care workers able to interpret laboratory test results, formulate treatment, and refer patients for specialized attention.

6. What Can Be Learnt from Past/Current Research into Pharmaceutical Interventions for this Condition?

The oral agents metformin, repaglinide, and thiazolidinediones improve glycaemic control to the same degree as older sulfonylureas. Nateglinide and glucosidase inhibitors may have slightly weaker effects on the basis of indirect comparisons of placebo-controlled trials. Incretin-based therapies (i.e. glucagon-like peptide-1 [GLP-1] receptor agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors) have now become fundamental treatment options. GLP-1 receptor agonists and DPP-4 inhibitors each act in distinct ways on the incretin system to regulate glucose homeostasis and represent unique treatment approaches for type 2 diabetes.

Comparative trials show that there are important differences between and among the glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors with respect to glycaemic lowering, weight effects, and effects on systolic blood pressure and the lipid profile. It would appear that GLP-1 receptor agonists are preferred over DPP-4 inhibitors because of the greater reductions in blood glucose.

6.1 A list of available non-insulin and insulin therapeutics

Although insulin is the primary choice for those patients with T1D, there are many possible pharmacotherapeutic interventions for patients with T2D. Table 6.4.6 below is extracted directly from Table 1 of reference 71.
Table 6.4.6: Possible pharmacotherapeutic interventions for T2D.

<table>
<thead>
<tr>
<th>Class</th>
<th>Compound(s)</th>
<th>Cellular mechanism</th>
<th>Primary physiological action(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Activates AMP-kinase</td>
<td>↓ Hepatic glucose production</td>
<td>Extensive experience</td>
<td>Gastrointestinal side effects (diarrhea, abdominal cramping)</td>
<td>Low</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No weight gain</td>
<td>Lactic acidosis risk (rare)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>No hypoglycemia</td>
<td>Vitamin B12 deficiency</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Likely ↓ CVD events (UKPDS)</td>
<td>Multiple contraindications: CK, acidosis, hypoxia, dehydration, etc.</td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>2nd generation</td>
<td>Closes K&lt;sub&gt;ATP&lt;/sub&gt; channels on β-cell plasma membranes</td>
<td>↑ Insulin secretion</td>
<td>Extensive experience</td>
<td>Hypoglycemia</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Glyburide/glibenclamide</td>
<td></td>
<td></td>
<td>↑ Microvascular risk (UKPDS)</td>
<td>Weight gain</td>
<td></td>
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<tr>
<td></td>
<td>Glipizide</td>
<td></td>
<td></td>
<td></td>
<td>? Blunts myocardial ischemic preconditioning</td>
<td></td>
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<tr>
<td></td>
<td>Glimepiride</td>
<td></td>
<td></td>
<td></td>
<td>Low durability</td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide</td>
<td>Closes K&lt;sub&gt;ATP&lt;/sub&gt; channels on β-cell plasma membranes</td>
<td>↑ Insulin secretion</td>
<td>↑ Postprandial glucose excursions</td>
<td>Hyperglycemia</td>
<td>High</td>
</tr>
<tr>
<td>(gliptides)</td>
<td>Nateglinide</td>
<td></td>
<td></td>
<td>Dosing flexibility</td>
<td>Weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>? Blunts myocardial ischemic preconditioning</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Frequent dosing schedule</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone</td>
<td>Activates the nuclear transcription factor PPAR-γ</td>
<td>↑ Insulin sensitivity</td>
<td>No hypoglycemia</td>
<td>Weight gain</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Durability</td>
<td>Edema/heart failure</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ HDL-C</td>
<td>Bone fractures</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ Triglycerides (pioglitazone)</td>
<td>↑ LDL-C (rosiglitazone)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ ↑ CVD events (ProACTIVE, pioglitazone)</td>
<td>↑ ↑ MI (meta-analyses, rosiglitazone)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ Bladder cancer (pioglitazone)</td>
<td></td>
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<tr>
<td>α-Glucosidase inhibitors</td>
<td>Acarbose</td>
<td>Inhibits intestinal α-glucosidase</td>
<td>Slows intestinal carbohydrate digestion/absorption</td>
<td>No hypoglycemia</td>
<td>Generally modest HbA&lt;sub&gt;1c&lt;/sub&gt; efficacy</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Miglitol</td>
<td></td>
<td></td>
<td>Postprandial glucose excursions</td>
<td>Gastointestinal side effects (flatulence, diarrhea)</td>
<td></td>
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<tr>
<td></td>
<td>Voglibose&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>↑ ↑ CVD events (STOP-NIDDM)</td>
<td>Frequent dosing schedule</td>
<td></td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Sitagliptin</td>
<td>Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations</td>
<td>↑ Insulin secretion (glucose-dependent)</td>
<td>Generally modest HbA&lt;sub&gt;1c&lt;/sub&gt; efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vildagliptin&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Glucagon secretion (glucose-dependent)</td>
<td>Untacteraoangioedema</td>
<td></td>
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<tr>
<td></td>
<td>Saxagliptin</td>
<td></td>
<td></td>
<td></td>
<td>? Pancreatitis</td>
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<tr>
<td></td>
<td>Linagliptin</td>
<td></td>
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<td></td>
<td>Alogliptin&lt;sup&gt;b,d&lt;/sup&gt;</td>
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</table>

<sup>a</sup> Meta-analysis suggests moderate HbA<sub>1c</sub> efficacy.
<sup>b</sup> Dose-dependent effects.
<sup>c</sup> Can induce hypoglycemia.
<sup>d</sup> Data available for a single dose in the study.

6.4-32
It is worth noting that the DPP-4 inhibitor Vildaglptin (Galvus®) has limited use in the USA and Europe which is likely due to safety concerns raised during the FDA approval process. The EMA has approved its use in combination with other anti-diabetic medications including metformin, sulfonylureas, and thiazolidinediones. Galvus® is, however, presently approved in 70 countries and has been launched in 37 countries (http://www.drugdevelopment-technology.com/projects/vildaglptin/).

The DPP-4 inhibitor algoliptin failed to secure FDA approval and has not yet been approved in Europe. TZD rosiglitazone (Avandia®) has highly restricted use in the USA due to its cardiovascular effects. Patients are required to be informed of the risks associated with its
use and the drug will be required to be purchased by mail order through specified pharmacies. In September 2010 the EMA decided to suspend the market authorization of rosiglitazone in Europe.

The bile sequestrants, dopamine-2 agonists, amylin mimetics, and α glucosidase inhibitors also have limited use in USA and Europe. Of the latter class, voglibose is not licensed either in the USA or Europe. The sulfonylurea gliclazide is not licensed in the USA though it is approved by the EMA.

6.2 Alternate delivery methods are possible, but none are commercially available

6.2.1 Inhalation Therapy: Failure to perform

Inhalable insulin was available from September 2006 to October 2007 in the United States as a new method of delivering insulin. After the withdrawal of the only inhalable formulation (Exubera®, from Pfizer) all currently available insulin formulations are administered by injection.

In April 2006, the UK’s National Institute for Health and Clinical Excellence (NICE) issued a preliminary statement advising against the use of inhalable insulin on the grounds that the benefits of avoiding injections did not justify the higher monetary cost of the new product. At that time, NICE recommended use of the new drug only in clinical trials.\(^22\)

As of 18 October 2007, Pfizer no longer manufactured or marketed Exubera®. At the time of the discontinuation several other companies including Alkermes working with Eli Lilly, Mannkind Corporation, and Aradigm working with Novo Nordisk were pursuing inhaled insulin. By March 2008, all of these inhaled products had been discontinued except for MannKind’s Afrezza® product. Notably, in January 2011, MannKind received a letter from the US Food and Drug Administration (FDA) concerning Afrezza®. The FDA asked the company to conduct two Phase III trials with the next-generation inhaler. MannKind believes it can complete both trials in the second quarter of 2013 and submit a new drug application by the third quarter of 2013.

6.2.2 Pumps: Closed-loop systems are still in the research phase, but would revolutionize treatment of T1D

Presently, drug delivery pumps are commonly available.\(^73\) What is likely to represent a major milestone for clinical use is the discovery that interstitial (cell-based) glucose reflects blood glucose with a sufficiently short lag time.

Characterized by real-time glucose-responsive insulin administration, closed-loop systems combine glucose-sensing and insulin-delivery components. In the most viable and researched configuration a disposable sensor measures interstitial glucose levels, which are fed into a control algorithm controlling delivery of a rapid acting insulin analog into the subcutaneous tissue by an insulin pump. Research progress builds on an increasing use of insulin pumps and availability of glucose monitors.\(^74\) The clinical utility of these systems is constrained by inaccuracies in glucose sensing, inter and intra-patient variability, and delays
due to absorption of insulin from the subcutaneous tissue, all of which are being gradually addressed.

Closed loop insulin delivery may revolutionize not only the way diabetes is managed, but also patients’ perceptions of living with diabetes by reducing the burden on patients and caretakers and their fears of complications related to diabetes. However, current fast-acting insulin still are not quite fast enough to handle post-meal spikes in blood sugar and this is a barrier for developing a truly closed loop pump as current insulin cannot respond quickly enough to sensor data in a closed-loop system. Once this is dealt with, the next step is confirming the results collected under controlled laboratory settings in real-life conditions. The final step would be a change in the way health systems introduce and maintain use of these devices.

6.3 Vaccines: Encouraging results for T1D?

6.3.1 Use of insulin

Mouse models of auto-immune diabetes have proved very poor predictors of therapeutic success in humans, but mouse models of type 1 diabetes indicate oral or nasal administration of insulin can induce immune tolerance to insulin and protect against autoimmune diabetes. Such evidence was, until recently, lacking in humans. A recent clinical trial was initiated that randomized 52 adults with recent-onset, noninsulin-requiring type 1 diabetes to nasal insulin or placebo for 12 months. Beta cell function declined by 35% overall, and 23 of 52 participants (44%) progressed to insulin treatment. Metabolic parameters remained similar between nasal insulin and placebo groups, but the insulin antibody response to injected insulin was significantly blunted in a sustained manner in those who had received nasal insulin. Although nasal insulin did not retard loss of residual beta-cell function in adults with established type 1 diabetes, evidence that it induced immune tolerance to insulin provides some rationale for its application to prevent diabetes in at-risk individuals.

6.3.2 Use of the TB vaccine

Faustman et al. used prior evidence that the TB vaccine Bacillus Calmette-Guerin (BCG) reverses T1D in an animal model by restoring insulin secretion. Specifically, BCG stimulates innate immunity by inducing the host to produce tumor necrosis factor (TNF), which kills disease-causing autoimmune cells and restores pancreatic beta-cell function through regeneration. Translating these findings to humans, BCG was administered in a double-blind, placebo-control trial of adults with long-term type 1 diabetes (mean: 15.3 years) at one clinical center in North America. BCG-treated patients showed increases in dead insulin-autoreactive T cells. The authors concluded that BCG treatment transiently modified the autoimmunity that underlies type 1 diabetes by stimulating the host innate immune response. This suggests that BCG or other stimulators of host innate immunity may have value in the treatment and possibly prevention of long-term diabetes.

6.3.3 Development of an Enterovirus Vaccine

Certain viral infections have long been suspected to cause type 1 diabetes. One virus group, enteroviruses, has been extensively studied and has shown an association with type 1 diabetes in several reports.
Enteroviruses include more than 100 different virus types and one subgroup, the six coxsackie B viruses, has been the chief suspect. These viruses have been isolated from the pancreas of type 1 diabetic patients and they also cause pancreatitis and diabetes in mice and monkeys. Based on this evidence the interest in making a vaccine against these viruses has increased since it seems to offer an option for primary prevention of type 1 diabetes. Such a vaccine should be possible to produce since another enterovirus vaccine (poliovirus vaccine) has long been on the market and proved to be safe and effective. Wide collaboration between academic and industrial partners (both biotech companies and large vaccine companies) would be needed to fully explore this opportunity.

6.3.4 Antigen-based therapies (Diamyd® and Diapep®)

Diamyd® is an antigen-based diabetes therapy under development. The active substance is the human protein GAD65 (Glutamic acid decarboxylase isoform 65 kDa). The purpose of the therapy is to prevent, delay, or stop the autoimmune attack on beta cells in type 1 diabetes. A Phase II study of 70 children and adolescents with type 1 diabetes published in 2008 showed that Diamyd® significantly slowed the progression of the disease in subjects treated within 18 months of diagnosis.

On 9 May 2011, it was reported that a parallel European Phase III study with Diamyd® did not meet the primary efficacy endpoint of preserving beta cell function at 15 months as measured by meal stimulated C-peptide, though a small positive effect was seen. Treatment did not significantly improve clinical outcomes over a 15-month period. Following consultation with the United States Food and Drug Administration (FDA), the company stopped its Phase III dosing trial in the USA.

DiaPep277® is a synthetic peptide of 24 amino acids derived from the sequence of the human heat shock protein 60 (Hsp60). A 24-month study assessed the safety and efficacy of this treatment for patients with T1D. The results from patients who were treated with DiaPep277® showed that the study met its primary endpoint, defined as the change from baseline in C-peptide levels at the end of the study. The decline in C-peptide levels was more pronounced in the placebo arm than in the treated group. The difference between the arms reached 0.949 nmol/L/20 minutes, (p=0.0374). A further study included 475 patients and is being conducted at 130 medical centers in the USA, Europe, Canada, South America, and Israel. Results of this trial are expected at the end of 2014.

6.3.5 Immunotherapy for T1D

Teplizumab and otelixizumab are monoclonal antibodies (mAbs). Teplizumab was evaluated in a clinical trial involving patients with recent-onset diabetes. This clinical trial demonstrated a single course of treatment led to an improvement of C-peptide response for up to two years after diagnosis. Treated patients also had sufficiently improved metabolic control, demonstrating lower HbA1c levels and reduced insulin usage. A subsequent clinical trial with otelixizumab found that patients had maintained insulin secretion and had lower insulin requirements 18 months after treatment. In addition, statistically significant improvements in C-peptide responses and in HbA1c levels were seen for up to three to four
years after treatment with otelixizumab. However, sponsors announced the Phase III trial of teplixumab (the Protégé trial) failed to meet primary end points at 1 year, as did a Phase III trial of otelixizumab (the DEFEND-1 trial).

Rituximab, a monoclonal antibody (mAb) specific for human CD20 expressed on the surface of B-cells, has been used to treat patients with B-cell–mediated diseases such as B-cell lymphomas, immune thrombocytopenia (ITP), and other autoimmune diseases. It was recently used to treat patients diagnosed with type 1 diabetes. Results of a phase 2 study with rituximab in 87 newly diagnosed type 1 diabetic patients demonstrated that rituximab partially preserved β-cell pancreatic function for over a year.

6.4 Transplantation

Pancreatic transplantation will remain limited to those patients receiving a kidney transplant and immunotherapy. Islet cell transplantation is at an early, though encouraging, stage following the availability of new less toxic immunosuppressive agents. The fundamental concept is that transplantation of pancreatic islets might allow better regulation of insulin delivery to diabetic patients.

In its 2006 annual report, the Collaborative Islet Transplant Registry, which is funded by the United States National Institute of Diabetes and Digestive and Kidney Diseases, presented data from 23 islet transplant programs on 225 patients who received islet transplants between 1999 and 2004. According to the report, nearly two-thirds of recipients achieved insulin independence, defined as being able to stop insulin injections for at least 14 days during the year following transplantation. However, other data from the report showed insulin independence is difficult to maintain over time. Six months after their last infusion of islets, more than half of recipients were free of the need for insulin injections, but at two-year follow-up the proportion dropped to about one-third of recipients.

Broad-based application of this type of surgery to the millions of individuals with insulin-requiring diabetes is also not possible due to the limited number of suitable donor organs, which is estimated to be in the range of several thousand pancreases per year. Furthermore, transplantation requires long-term immunosuppression with its attendant risks in order for the graft to be protected from the immune system.

Over the years, one of the problems associated with islet cell transplants has been the length of time the cells survive in the body after transplant. Various groups are developing cellular structures that mimic the environment of the pancreas that helps preserve islet cells, allowing them to survive significantly longer while also producing much more insulin. These bio-engineered (BI) matrices can be formed in various ways, but often rely on use of natural materials to hold the beta-cells together. The resulting matrix is seeded with donor islet cells and sometimes stem cells, and then transplanted in animals using microsurgical techniques. Recently, murine beta-cell donor islets incorporated into a bio-engineered implant and transplanted into syngeneic mice recipients are revascularized and produce insulin. Significantly, BIs containing 450–500 donor islets reversed diabetes in streptozotocin (STZ)-treated mice.
7. What is the current “pipeline” of products that are to be used for this particular condition?

7.1 Overview: A fiercely competitive market

The rising health threat of diabetes has generated much R&D in the pharmaceutical industry, which is investigating many new compounds and combinations of older medicines to combat diabetes.

Groups face some noteworthy challenges to advance new medicines for diabetes. Regulators demand extensive evidence of safety and efficacy of the medicines, especially after a prior disaster put the FDA and other regulatory agencies on high alert for any safety risks related to diabetes therapies.

In particular, since 2007 experts have argued about GlaxoSmithKline’s Avandia and its potential link to heart attacks and other serious heart problems. The FDA reviewed study data more than once, and in 2010 decided to restrict the drug in the USA. On the same day, European regulators decided to ban it. See also Table 6.4.5.

These growing demands from regulatory bodies have prompted developers to engineer massive clinical trial programs for new diabetes medicines in some cases requiring data not only on how well therapies control blood sugar levels, but also the impacts on cardiovascular risk. The resulting regulatory requirements result in longer clinical trials that are more complicated and more expensive. There is clearly a great and increasing need for new therapies for diabetes patients who often grapple with co-morbidities. The high cost and massive scale of diabetes drug development have left the field mostly to large, well-financed pharmaceutical companies while smaller biotechs avoid the field or rely on deals with larger companies to advance their programmes.

AstraZeneca and Bristol-Myers Squibb’s (BMS) diabetes alliance, which dates back to January 2007, has enabled the partners to pursue new therapies in several of the new classes of medicines. In addition to dapagliflozin, their alliance includes the already approved DPP-4 inhibitor Onglyza® (or saxagliptin) and a form of the drug combined with metformin called Kombiglyze®. This summer the companies added to their alliance two GLP-1 peptides from BMS’ USD 5.3 billion buyout of Amylin Pharmaceuticals.

Eli Lilly and Boehringer Ingelheim are also developing anti-diabetes medicines. Lilly has four programs in Phase III development, covering several of drug classes listed above. Lilly has a novel basal insulin analog, LY2605541. These two companies together are in late-stage development of another basal insulin analog from Lilly called LY2963016 and an SGLT2 inhibitor from Boehringer called empagliflozin. Lilly has a once-weekly GLP-1 analog called dulaglutide. Lilly and Boehringer Ingelheim have received approval for an oral DPP-4 inhibitor liangliptin (See Table 6.4.6) called Tradjenta.

Merck has many DPP-4 inhibitors, particularly the first-in-class therapy Januvia® (sitagliptin- See Table 6.4.6). They are undertaking clinical trials with a next-generation drug in this class called MK-3102, a once-weekly DPP-4 inhibitor that is chemically distinct from
Januvia®, which is taken daily. Merck is in late-stage development of a pill that contains both Januvia and atorvastatin for patients with type 2 diabetes and atherosclerosis.

**Takeda**, the Japanese pharmaceutical company, has been working toward potential approvals of algoliptin, (Table 6.4.6) another DPP-4 inhibitor (Nesina®). Takeda has submitted an amended new drug application for the USA market and the therapy is also under review in Europe. Takeda is the first to reach late-stage trials with a GPR40 agonist for type 2 diabetes. This is a potential first-in-class drug that stimulates glucose-dependent insulin secretion. In February 2012 the company reported that the drug met the main endpoint of besting placebo in lowering A1C levels in a Phase II study without significantly increasing hypoglycemia.

**GlaxoSmithKline** in July 2012 announced that data have been received from a Phase III study and from its assessment of cardiovascular safety conducted for the injectable GLP-1 receptor agonist albiglutide. These data are the final elements required to complete the clinical registration package. GSK intends to commence global regulatory submissions for this drug to treat T2D in early 2013. Albiglutide is not yet approved as a treatment for type 2 diabetes.

**The Oral Antidiabetics Market**

New therapeutic classes of medicines are expected to be introduced in the oral antidiabetics segment. However, metformin still remains the first line of choice for the treatment of diabetes. New forms of co-therapies, GLP agonists, DPP-IV inhibitors, and SGLT inhibitors are expected to be strong competitors or co-therapies in the near future.

**GLP-1 Agonists**

The first product to be approved by the EMA from the GLP-1 pathway is the enzymatically stable GLP-1 analogue, Exenatide (Byetta®). Liraglutide (Victoza®) is the first human GLP-1 analogue with 97% similarity to natural gut hormone. A once-daily dose of liraglutide stimulates the beta cells of the pancreas to release insulin. Various longer acting formulations of GLP-1 analogues are under development. Other agents such as GPR119 agonists and TRG5 are expected to be introduced in the future.

**DPP-IV Inhibitor**

The first DPP-IV inhibitor approved in the United States was sitagliptin (Januvia), and the second was saxagliptin (Onglyza®). Additionally, vildagliptin (Galvus®) is approved for use in Europe, and several other DPP-IV inhibitors are under development.

**SGLT Inhibitors**

SGLT2 inhibitors are another new class of investigational drugs for the treatment of type 2 diabetes. Sergliflozin, Remogliflozin, Dapagliflozin, and other SGLT2 inhibitors improve glycaemic control. They work independently of insulin to help remove excess glucose from the body, a unique mode of action not seen in any other current treatments for type 2 diabetes.
Numerous SGLT2 inhibitors are in clinical testing phases. Canagliflozin is the USA clinical trials sponsored by Johnson & Johnson. The company has filed this year for approvals of the therapy in the USA. If approved, canagliflozin would become the first SGLT-2 inhibitor to enter the USA market. Canagliflozin was also submitted for approval in Europe on 26 June 2012, putting a potential approval sometime in the middle of 2013.

The FDA denied approval of dapagliflozin (Forxiga®: AstraZeneca and Bristol-Myers Squibb) in January 2012 amid concerns about cancer cases and toxicity seen during development of the drug. The agency asked for more clinical data on the treatment. In April 2012, European regulators diverged from the FDA position on dapagliflozin, clearing it for treating diabetes if AstraZeneca and Bristol-Myers Squibb conducted a post-marketing study to further assess a potential cancer risk. In mid-November 2012, the European Commission approved dapagliflozin tablets for the treatment of type 2 diabetes. This is the first medicine in the new SGLT2 class to gain regulatory approval for the treatment of type 2 diabetes.

**GKAs**

Glucokinase activators (GKAs) represent a new class of investigational drugs for the treatment of type 2 diabetes. Several GKAs are in the phase of clinical development. AstraZeneca has a few GKAs in the clinical development space, with AZD1656 in several Phase I and II trials. In addition, AZD6370 is in Phase II and AZD6714 is in Phase I. Merck’s MK-0599 has completed Phase I clinical trial.

**Fierce Competition in the Insulin Market**

The insulin market is dominated by modern insulin and analogues. Long-acting insulin is expected to increase their market share in the future. Competition is likely to increase with the introduction of biosimilars.

**Rapid-acting Insulin Analogues**

Insulin Lispro: Humalog® was the first genetically engineered rapid-acting insulin analogue. It was approved for clinical use in 1996. Besides glycaemic management, Lispro improves the postprandial leptin and grehlin regulation of type 1 diabetic patients and may be used in cases of gestational diabetes.

Insulin Aspart: (NovoRapid®) is a rapid-acting insulin for use at mealtimes. It was introduced in 1999 in the European Union (EU). NovoRapid is used for people with both type 1 and type 2 diabetes and is also approved for women who are pregnant or breast-feeding.

Insulin Glulisine: Apidra® is the most recent rapid-acting analogue introduced in the market in 2004. Apidra® is indicated for the treatment of adults with type 1 and type 2 diabetes. It has a more rapid onset and a shorter duration of action than most fast-acting human insulin.

Ultra-fast insulin: If successful, insulin that act even faster than those listed above could improve quality of life and decrease the risk of acute and chronic complications in persons with T1D and possibly in those with T2D, caused by recurrent glycaemic. Ultra-fast insulin may also decrease or eliminate the need for pre-meal insulin boluses, which can predispose a
person to dangerous extremes of glycemia when the amount of anticipated carbohydrate intake is frequently erroneously estimated even in the most adherent and knowledgeable of patients. Most importantly, improved insulin will enable the development of fully automated closed-loop systems.

**Long-acting Insulin Analogues**

Insulin Glargine: Lantus® was the first long-acting insulin analogue to be introduced in the market and has become a blockbuster product. Lantus® is indicated for once-daily subcutaneous administration in the treatment of adult patients with type 2 diabetes mellitus.

Insulin Detemir: Levemir® is soluble long-acting modern insulin for once-daily use for type 2 diabetes. It was launched in 2004 in the EU. Levemir® joined NovoRapid® and NovoMix® in achieving blockbuster status.

**Novo Nordisk** received approval from a European Union advisory panel for its long-acting insulin degludec (Tresiba®) and has been approved in Mexico. It is slated for an FDA panel review on 8 November 2012. Novo won approval in 2012 for Tresiba® in the Japanese market.

**7.2 Future Opportunities**

**Heat Stable Insulin**

Creation of a truly heat-stable form of insulin (i.e. capable of being stored above 25°C for long periods) would be a major advancement in treatment as the lack of cold chain capabilities in many developing countries lends some urgency in dealing with this pharmacological gap in diabetes treatment. Insulin exhibits an increase in degradation rate of 10-fold or more for each 10°C increment in temperature above 25°C and guidelines call for storage at temperatures below 30°C, preferably with refrigeration. At higher temperatures, insulin undergoes both chemical degradation (changes in covalent structure such as formation of isoaspartic acid, rearrangement of disulfide bridges, and formation of covalent polymers) and physical degradation (non-native aggregation and fibrillation).

Insulin developer, Thermalin Diabetes, has received a US$ 4.5 million grant from the National Institutes of Health (NIH) to continue development of its insulin analogs. The grant is expected to fund Thermalin through the filing of a new drug application for a rapid-acting insulin analog drug candidate. The company is targeting the first half of 2013 for the IND filing. Thermalin’s insulin analogs were engineered at Case Western Reserve University School of Medicine. Preliminary studies of this modified insulin suggest that it is at least 60-fold more resistant than human insulin to degradation at 37°C (http://www.thermalin.com). This discussion of heat stable insulin and developing countries must acknowledge that the issue is also about availability and affordability of insulin. Heat stability will not change anything about the lack of access, something not within the scope of this report.

**Glucose-responsive insulin: The next frontier along with heat-stable insulin?**

At present, all insulin treatments for people with diabetes release the same amount of insulin at fixed times throughout the entire body. However, in people without diabetes the body secretes insulin in proportion to local blood glucose levels, delivering it to the body’s tissues...
and organs at the appropriate times according to their specific needs. This helps the person without diabetes maintain a target blood glucose level throughout the day. A glucose-responsive insulin for people with diabetes could, therefore, be a transformative solution, vastly improving the quality of life of people with insulin-dependent diabetes. In December 2010, Merck paid more than US$ 500 million to acquire SmartCells® and the MIT spinoff’s glucose-sensitive insulin formulation, which at the time had yet to reach human trials. “SmartInsulin” automatically adjusts to fluctuating levels of blood glucose. Theoretically, a single daily injection would offer all the protection needed by a patient without the regular monitoring and dosing that is required today. 

The diabetes market is the fastest growing one in the pharmaceutical industry with an increase in the diabetic population leading to more demand for effective, convenient, and safe medicines. Increased awareness, proper diet, and adequate exercise along with the correct intake of prescription medicines will help restrain and prevent the disease. New kinds of therapeutic classes and combination therapies are likely to be introduced in the near future. Effective insulin analogues and long-acting insulin are expected to see increased demand in the future. Effective medicines with minimal side effects are needed.

8. What is the Current Status of Institutions and Human Resources Available to Address the Disease?

This is a list of websites from other stakeholders working in the fields of diabetes and health at the European level.

Diabetes stakeholders:
- ECD - European Coalition for Diabetes: [www.ecdiabetes.eu](http://www.ecdiabetes.eu)
- Euradia - Alliance for European Diabetes Research: [www.euradia.org](http://www.euradia.org)
- PCDE - Primary Care Diabetes Europe: [www.pcdeurope.org](http://www.pcdeurope.org)
- FEND - Foundation of European Nurses in Diabetes: [www.fend.org](http://www.fend.org)
- ISPAD - International Society for Pediatric and Adolescent Diabetes: [www.ispad.org](http://www.ispad.org)
- EASD - European Association for the Study of Diabetes: [www.easd.org](http://www.easd.org)
- International Diabetes Federation (Europe): [https://www.idf.org/regions/europe](https://www.idf.org/regions/europe)

Health stakeholders
- EPHA: European Public Health Alliance: [www.eph.org](http://www.eph.org)
- EPF: European Patients' Forum: [www.eu-patient.eu](http://www.eu-patient.eu)
- EHN: European Heart Network: [www.ehnheart.org](http://www.ehnheart.org)
- Health First Europe: [www.healthfirsteurope.org](http://www.healthfirsteurope.org)
- EFPIA: European Federation of Pharmaceutical Industries and Associations: [www.efpia.org](http://www.efpia.org)
8.1 Public Funding

8.1.1 Europe

The EU has a current portfolio of more than 100 FP7 ongoing research projects on diabetes and obesity, representing EU funding worth more than €270 million.

For obesity-specific programmes, see Background paper Chapter 6.18. Some examples of diabetes-specific research side (see http://cordis.europa.eu/fp7/home_en.html) include:

EUROCONDOR (early Treatment of Diabetic Retinopathy (http://eurocondor.eu/)
BETA-JUDO: treatment of insulin hypersecretion in young obese subjects (http://betajudo.org/) under the FP7 Health Programme (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:301:0003:0013:EN:PDF), DG SANCO has also financed projects, such as "Better control in paediatric and adolescent diabetes in the EU: working to create Centres of Reference (SWEET), and European Best Information through Regional Outcomes in Diabetes (EUBIROD). See also http://ec.europa.eu/eahc/health/highlights7.html.

The recently completed DIAMAP (http://www.diamap.eu/) program was a European Commission funded project (FP7 200701) with the mission of undertaking a wide survey of the current European diabetes research landscape, from which expert opinion can identify gaps and highlight strengths, to guide the first Road Map strategy for diabetes research in Europe. The DIAMAP report consists of strategic maps and reports and is “… intended to guide investment in diabetes research in Europe for the period 2010-2019 and to suggest means for improved coordination”. There are two public DIAMAP databases which summarize the current landscape of European diabetes research, with information on research activities and funding.

In February 2012, the EU announced four research projects. A total of more than €16 million is being invested in EPI-MIGRANT, MEDIGENE, RODAM, and GIFTS, which bring together 50 leading European and international research organizations. Twelve million Euros will come from the EU’s 7th Research Framework Programme. See Appendix 6.4.6.

Each project is spotlighting the genetic and environmental factors resulting in variations in prevalence and incidence of metabolic disorders in specific well-characterised populations. They all seek to identify novel genetic and other risk factors for diabetes and obesity. The results could play an important role in improving diagnosis and treatment and could lead to the creation of new therapeutic targets.

The four projects on gene-environment interactions in diabetes and obesity in specific populations are forging collaborations between European researchers and colleagues in Asia and Africa, as well as in Oceania. More specifically, €3 million goes to EPI-MIGRANT ('Identification of epigenetic markers underlying increased risk of T2D in South Asians'), which brings together experts from Australia, Finland, India, Italy, Japan, Mauritius, and the
UK. The project partners are evaluating the lifestyle, environmental, genetic, and epigenetic risk factors involved in the particularly high rates of type 2 diabetes in South Asian populations. This team will investigate how these different risk factors interact. See Appendix 6.4.6.

MEDIGENE is another approximately €3 million FP7 project (‘Genetic and environmental factors of insulin resistance syndrome and its long-term complications in immigrant Mediterranean populations’) and is looking at genetic and environmental factors of insulin resistance in immigrant Mediterranean populations (including Tunisia, Algeria, Morocco, Turkey) in Europe. The consortium consists of experts from Albania, Algeria, Finland, France, Greece, Hungary, Italy, Morocco, Romania, Russia, Spain, Tunisia, and Turkey.

RODAM (‘Type 2 diabetes and obesity among sub-Saharan African native and migrant populations: dissection of environment and endogenous predisposition’), with EU funding totalling €2.9 million, started in January 2012. The project partners plan to tackle a number of key issues of type 2 diabetes and obesity in Ghanaian populations who live in Europe and in their home country. Experts from Belgium, Germany, Ghana, the Netherlands, and the United Kingdom are part of the RODAM team. See Appendix 6.4.6.

The GIFTS (‘Genomic and lifestyle predictors of foetal outcome relevant to diabetes and obesity and their relevance to prevention strategies in South Asian peoples’) project, started in February 2012, is set to investigate the prevalence and incidence of diabetes in a number of South Asian populations. It brings together experts from Bangladesh, Germany, Finland, India, Spain, and the UK.

Table 6.4.7 (also Appendix 6.4.7) summarizes the allocation of EU research funds to diabetes and obesity from various sources between 2005 and 2008.

<table>
<thead>
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<th>2005</th>
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<th>2007</th>
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<td>78 841 809</td>
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<td>187 337 072</td>
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<td>691 199</td>
<td>448 072</td>
<td>1 221 340</td>
</tr>
<tr>
<td>Pharmaceutical company</td>
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<td>4 422 257</td>
<td>4 721 257</td>
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</tr>
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<td>Subtotal</td>
<td>244 982 364</td>
<td>254 685 633</td>
<td>336 482 278</td>
<td>292 363 397</td>
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<tr>
<td>Estimated from NIH (USA)</td>
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<td></td>
<td></td>
<td>40 636 367</td>
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<tr>
<td>Grand Total</td>
<td>244 982 364</td>
<td>254 685 633</td>
<td>336 482 278</td>
<td>323 061 844</td>
</tr>
</tbody>
</table>

Source: FP7 Health Programmes (V. Wirtz, personal communication)
8.1.2 The United States: Comparison with Europe

National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) at the National Institutes for Health (NIH) is the primary federal agency responsible for research to prevent, better treat, and find a cure for diabetes. Research supported by NIDDK has led to advancements and improvements in the treatment of diabetes including progress in predicting the risk of developing type 1 diabetes, preventing type 2 diabetes, and combating diabetes complications.

Currently, NIDDK efforts include research to further advance the development of the artificial pancreas and a new clinical trial testing different medications for type 2 diabetes. The budget appropriations for the NIDDK since 2004 are shown in Figure 6.4.9. The narrow scale on the Y axis suggests, notwithstanding annual changes the NIDDK has been essentially level funded for some time at about USD 1.9 billion dollars per year. Between 2005 and 2008, the average budget of the NIDDK (in Euros) is approximately three to four times the average of EU research funds listed above in Table 6.4.7.

Figure 6.4.9: Budget appropriations for the NIDDK since 2004
Update on 2004 Background Paper, BP 6.4 Diabetes

8.2 Private Sector Funding

By 2019, the global market for diabetes is expected to be worth US$ 35 billion and the private sector is investing heavily.

The commercial market for diabetes therapeutics will ensure that there will be no shortage of private research funding for the immediate future.

For this Background paper, most of the information was gleaned from various market research reports, all of them essentially converging on similar numbers. Once such market analysis (Datamonitor \(^1\)) expects the antidiabetics market to grow to US$ 34.8 billion in 2019 for the seven major markets. More specifically, the antidiabetics market in the major markets (the USA, Europe, Japan) is expected to grow from US$ 22 806 million in 2009 to US$ 34 820 million in 2019 with a 4% annual growth. Growth is driven by the epidemiological expansion of the market and fuelled by the obesity epidemic and improved diagnosis rates. New products launched from the highly active antidiabetic pipeline will command 30% (US$ 10 570 million) of the market in 2019. Highest growth will be seen for the GLP-1 agonists.

It is difficult to estimate the total amount spent by the private sector on diabetes R&D as such information is not conveniently located but must be gleaned from individual companies. Most of the new therapies introduced for type 2 diabetes will cluster in just a few drug classes, meaning the market will see a small number of first-in-class launches followed by an avalanche of follower brands. These follower products will face a challenging launch environment if they cannot demonstrate some added value differentiating them from first-in-class products in the eyes of clinical opinion leaders, prescribers, and payers.

9. Ways Forward from a Public Health Viewpoint with Regard to Public Funding

In principle, areas for public funding of diabetes research with regard to pharmaceutical R&D should initially be aligned with the overall goals of Horizon 2020 and should be directed to areas the pharmaceutical industry may not presently be tackling.

Diabetes is an example of a disease with an unmet global medical need and conforms to the "commonality of interest" principle of the Priority Medicines Project. The dramatic increases in diabetes that are projected over the next several decades require a global strategy for prevention, treatment and medicine development.
9.1 Gaps between current research and potential research issues that could make a difference

Gaps in Basic and Applied Research

A. TYPE 1 Diabetes

- Studying the natural history of pancreatic immune cells is an important basic research goal because it represents our best chance of deciphering the underlying disease process of type 1 diabetes.
- We need disease markers that represent islet-damaging or islet-protective events, such as numbers and phenotype of circulating islet reactive immune cells. This is especially important in clinical trials for prevention or cure of type 1 diabetes. For example, surrogate markers may enable identification of transplant rejection at the very earliest stages so it can be successfully treated. Good surrogate markers could identify diabetic patients suitable for clinical trials and could be used to follow the course of disease and test the effectiveness of therapies.
- We need continuing research on T1D preventative vaccine and possible immune intervention.
- There needs more research into the development of a glucose-responsive insulin drug that would work only when the body needs it. Glucose-responsive insulin would deliver the precise amount of insulin needed in response to circulating glucose levels to control and maintain normal blood glucose levels throughout a daily routine with once-daily or less frequent dosing in people with diabetes. The Juvenile Diabetes Research Foundation has initiated a prize in this regard.
- Heat stable insulin was identified as a priority in the 2004 report and the need still remains.
- A functioning and commercially viable closed loop glucose monitoring system is needed.

B. TYPE 2 Diabetes

- Better animal models representative of human type 2 diabetes are needed. Development of atherosclerosis is rare in rodents so small and large animal models of diabetic complications are required.
- We need innovative, non-analgesic therapeutics to reverse or halt nerve damage in diabetic neuropathies.
- More emphasis is needed on geriatric trials. Much of the large effectiveness studies in diabetes are conducted among middle-aged populations and few RCTs have examined the effect of interventions on cognitive or functional decline. See Chapter 7.3.
- We lack comparative clinical trials of existing diabetes treatments as they are not mandated by the existing regulatory framework.
- There is a need for more effective therapeutics that lower blood glucose and afford weight control.
- Lower cost test strips and innovative (e.g. solar powered) monitors should be developed.
Diabetes is a major and increasing public health problem that has induced high levels of funding from the global pharmaceutical industry. Areas of research (i.e. heat stable insulin) remain areas of support for the EC.

From the perspective of this Update, diabetes is a prototypical public health problem. Research into effective delivery of preventive strategies to delay progression of the disease and its complications is needed that integrates individual, clinical, system, and society-level approaches that span the full course of life.

- We need to increase the evidence base for clinical and public health interventions to include a much broader spectrum of disciplines including, for instance, experts in behavioural economics, systems dynamics, political science, and urban planning. Integration of surveillance, clinical and population-based epidemiology, health services research and economics is sorely needed.
- Large, long-term intervention studies are needed to identify effective strategies for reducing barriers to diabetes care and improving adherence to treatment and management regimens.
- The gap is large between scientific and technological progress and its implementation. Europe can help reduce this gap by championing international efforts to assure that children and adolescents around the world do not suffer premature death and disability because their diabetes is mismanaged.
- Although there are effective preventive strategies for type 2 diabetes, the presently identified susceptibility genes do not provide predictive abilities strong enough to warrant genetic screening so research into genetic screening is limited.
- The safety, efficacy, and economic impact of closed-loop control systems are currently unknown and deserve further investigation.
- Translational research, which seeks to understand how advances can be adopted in community-based and often uncontrolled conditions (e.g. resource-poor environments), has received little attention in diabetes. Some of the important questions in translational research cannot be addressed in randomized trials.
- Planning community-based participatory research, issues related to lifestyle, diet, physical activity, and cultural preferences should be explored.
- A diabetes registry that keeps track of glycosylated hemoglobin (A1C) values is one example of linking diabetes with key policy decisions. Such a registry was implemented in New York City.

References

1 Venkat Narayan KM, EW Gregg, A Fagot-Campagna, MM Engelgau and F. Vinicor, 2000, Diabetes—a common, growing, serious, costly and potentially preventable public health problem, Diabetes Res. and Clinical Practice, 50:S77-S84.

2 BMJ Clinical Evidence at http://clinicalevidence.bmj.com.ezproxy.bu.edu/x/systematic-review/0607/background.html

Update on 2004 Background Paper, BP 6.4 Diabetes


11 American Diabetes Association, 2003, Treatment of Hypertension in Adults with Diabetes, Diabetes Care, 26: S80-S82.


Update on 2004 Background Paper, BP 6.4 Diabetes


26 European Health for All Database at http://data.euro.who.int/hfamdb/

27 European Mortality indicator database at http://data.euro.who.int/dmdb/


29 EURODIAB childhood type 1 diabetes incidence registers - results from the first 20 years C.C. Patterson, G. Dahlquist, E. Gyürüs, G. Soltész, EURODIAB Childhood Type 1 Diabetes Registers; EASD 47th Annual Meeting


Update on 2004 Background Paper, BP 6.4 Diabetes


45 S. Roze, W. J. Valentine, K. E. Zakrzewska and A. J. Palmer 2005 Diabetes UK. Diabetic Medicine, 22, 1239–1245 Health-economic comparison of continuous subcutaneous insulin infusion with multiple daily injection for the treatment of Type 1 diabetes in the UK


6.4-51
Update on 2004 Background Paper, BP 6.4 Diabetes


69 Reid T. 2012 Choosing GLP-1 Receptor Agonists or DPP-4 Inhibitors: Weighing the Clinical Trial Evidence Clinical Diabetes 30(1): 3-12 doi: 10.2337/diaclin.30.1.3.


http://www.biomedcentral.com/1741-7015/9/120


79 Ludvigsson et al., 2008 GAD Treatment and Insulin Secretion in Recent-Onset Type 1 Diabetes N Engl J Med 359 (Epub ahead of print 10.1056/NEJMoa0804328)


89 Forxiga™ (dapagliflozin), First-In-Class SGLT2 That Works Independently of Insulin, Now Approved in European Union for Treatment of Type 2 Diabetes at
Update on 2004 Background Paper, BP 6.4 Diabetes

http://www.businesswire.com/news/home/20121114006517/en/Forxiga%E2%84%A2-dapagliflozin-First-In-Class-SGLT2-Works-Independently-Insulin


### Annexes

#### Annex 6.4.1 EU contribution to the DM research (5th – 7th FP)

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**Total diabetes research**

|     | 35 096 398 €       | 25 053 585 €    |                                 |

61.62% 59.18%

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**Total 2002-2005**

| FP6 | 100 078 000 €      | 44 678 000 €    |                                 |

**Total highly specific to diabetes research**

|                 | 44 678 000 €      | 44.64%          |                                 |

**Other programmes**

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6.4-55
## Annex 6.4.2 Diabetes / Obesity/ Physical Activity Research Projects in HEALTH Programme

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<td>Recruitment and activation of brown adipocytes as preventive and curative therapy for type 2 diabetes <a href="http://diabet.org">http://diabet.org</a></td>
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<td>BetaBat</td>
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**Update on 2004 Background Paper, BP 6.4 Diabetes**

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<td>Mechanisms of prevention of type 2 diabetes by lifestyle intervention in subjects with pre-diabetes or at high-risk for progression <a href="http://www.dexlife.eu">www.dexlife.eu</a></td>
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Appendices

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Appendix 6.4.2  IDF Atlas Detailed Estimates.xls
Appendix 6.4.3  Guidance for Industry, Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), December 2008
Appendix 6.4.4  Preferred Product Profile for HbA1c test, WHO
Appendix 6.4.5  Diabetes expenditure, burden of disease and management in 5 EU countries, Panos Kanavos, Stacey van den Aardweg and Willemien Schurer, LSE Health, London School of Economics
Appendix 6.4.6  FP7 including ERC + PEOPLE + DGINFSO +NMPP.xls
Appendix 6.4.7  Diabetes / Obesity/ Physical Activity Research Projects in HEALTH Programme.xls
Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper
Written by Warren Kaplan

Background Paper 6.5
Cancer and Cancer Therapeutics

By Warren Kaplan, Ph.D., JD, MPH
April 2013
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What’s new since 2004

• Targeted therapies: While previous research on targeted therapies has identified a number of single agents that are safe and can shrink tumours, research during 2004/2005 showed that an increasing number of targeted therapies – in combination with chemotherapy – are effective against common cancers.
  o Now targeted agents have also shown benefit as monotherapy. One such example, is anaplastic lymphoma kinase (ALK) gene-mutated, non-small cell lung cancer, where the pace of research progress in this area has been remarkable.
  o One agent, vismodegib, marks the first FDA approval of a drug that targets the hedgehog signaling pathway, which plays an important role in tissue growth and repair. The drug is also being tested in clinical trials for colorectal, stomach, and pancreatic cancers.

• A potentially useful strategy for conquering resistant tumors is to attack more than one target in a molecular pathway that is critical for tumor survival and growth. This can be achieved through use of multi-targeted drugs, such as the new agents regorafenib, which has benefited patients with treatment-resistant GI stromal tumors (GISTs) and metastatic colorectal cancer; crizotinib, which has shown promising activity against neuroblastoma and anaplastic large-cell lymphoma (ALCL) in children; and cabozantinib, which seems to slow progression of medullary thyroid carcinoma. An alternative approach is to treat patients with two or more drugs that target the same pathway.

• FDA approves first vaccine to prevent HPV infection The most significant advance in 2005 was the U.S. Food and Drug Administration (FDA) approval of the first vaccine to prevent infection with human papillomavirus (HPV), a virus present in virtually all cervical cancers. The vaccine, Gardasil®, was shown to be 100% effective in preventing HPV 16- and 18-related cervical precancers in women who were not previously exposed to these strains of the virus. These strains together account for approximately 70% of cervical cancer cases worldwide. In January 2013, the GAVI Alliance announced it would provide HPV vaccine as part of its portfolio.

• Reductions in breast cancer incidence appear to be associated with the declining use of hormone replacement therapy (HRT) in menopausal women. The use of HRT declined beginning in 2002, following a report from the National Institutes of Health-sponsored Women’s Health Initiative that linked the use of estrogen plus progestin during and after menopause with a number of adverse effects, including an increased risk for invasive breast cancer.

• The monoclonal antibody bevacizumab (Avastin®) has been an important treatment for patients with advanced colorectal and non-small cell lung cancers. In February 2008, the FDA approved the drug—in combination with the chemotherapy drug paclitaxel (Taxol®)—for women with previously untreated metastatic breast cancer. The US breast cancer approval was conditional and the approval was recently withdrawn for this indication. Avastin is still approved for breast cancer in the EU but since the US FDA questioned its risk/benefits profile and asked for withdrawal of
Update on 2004 Background Paper, BP 6.5 Cancer

the marketing application for this indication, Avastin utilization for the treatment of breast cancer in the EU has decreased.

- First targeted treatment for gastric cancer: In 2009, Herceptin®, which is widely used to treat HER2-positive breast cancer, was proven effective in stomach cancer. A large clinical trial found that adding trastuzumab to standard chemotherapy for advanced gastric (stomach) cancer increased survival by 26 percent in patients whose tumours overexpressed the HER2 receptor.

- Vaccine Approved for Treating Advanced Prostate Cancer: In 2010, the FDA approved Sipuleucel-T (Provenge®), a cancer vaccine for metastatic hormone-refractory prostate cancer. Unlike a preventative vaccine, which is given to stimulate the immune system to fight off infections and prevent disease, this is a true therapeutic vaccine that boosts the body’s immune system to attack cancer cells in the body. See also Section 7.4.

- The entire cancer therapeutics field is moving more toward targeted therapies and immunotherapy. The monoclonal antibody ipilimumab was approved by the FDA in March 2011 to treat patients with late-stage melanoma that has spread or cannot be removed by surgery. This is an area of high unmet medical need. On 1 February 2012, Health Canada approved ipilimumab for "treatment of unresectable or metastatic melanoma in patients who have failed or do not tolerate other systemic therapy for advanced disease." [http://en.wikipedia.org/wiki/Ipilimumab - cite_note-8] Ipilimumab was approved in both the UK and European Union (EU), for second line treatment of metastatic melanoma in November 2012.

- Those needing further information should review the American Society of Clinical Oncology annual “Progress against Cancer” brochures at [http://www.cancerprogress.net/latest_advances.html](http://www.cancerprogress.net/latest_advances.html)
Executive Summary

Burden of Disease
It has been estimated that over one-quarter of the global burden of cancer incidence occurs in Europe, despite the fact that persons living in Europe comprise only approximately one-eighth of the world’s population. Within Europe, for all the countries considered, improvement in age-adjusted death rates are more marked in men than women, with however notable disparities. There is a disparity in cancer mortality between central European post-2004 accession countries (particularly Poland) and countries of the EU15. This was seen in the early 2000s and is not projected to have closed, at least in proportional terms, over recent years.

The global burden of cancer doubled between 1975 and 2000 and is expected to double again by 2020 and nearly triple by 2030. Cancer burden in many countries in societal and economic transition from a communicable to a non-communicable epidemiology and demography is a net burden between reductions in infection-related cancers and increases in new cases that are more associated with reproductive, dietary, and hormonal factors.

Treatment Options
The wide range of cancer treatments and associated services reflects the biological diversity of cancer. For most solid tumours if the cancer is at a relatively early stage of development, surgery is the most standard and effective form of initial cancer treatment, but this is largely augmented by radiation therapy to the tumour bed and some form of systemic therapy. As cancers progress, treatments typically include radiation, combination chemotherapy regimens, in hormone-regulated tumours, hormone ablation therapy, and where appropriate targeted therapies. The stage of cancer at diagnosis, the rate of progression, and the treatment options vary significantly with the type of cancer a patient presents with.

Pipeline of Potential Products
- The therapeutic pipeline is dynamic and significant private sector funding is being put into the cancer R&D system.
- The distribution of therapeutics in clinical trials across cancer types seems to correlate with the incidence of those cancer types reasonably well, suggesting that the pharmaceutical industry is appropriately matching its resources to the size of the market. Recent regulatory approvals significantly impacted approaches to management of lung cancer and increased treatment options in several cancers that have been previously hard to treat such as colorectal cancer. The emerging group of targeted therapies has opened up opportunities for a personalized approach to cancer treatment based on the characteristics of the individual tumour at the time of diagnosis. This area represents a significant focus of current research initiatives and ongoing clinical trials, raising the question of how this may impact future clinical trials design as well as regulatory approval processes.
Introduction to the Background Paper

When the original (2004) Background paper was written, malignant tumours were responsible for 12% of the nearly 56 million deaths worldwide from all causes and over 6 million died specifically from some type of malignant tumour. Indeed, cancer had emerged as a major public health problem in developing countries, matching its effect in industrialized nations. In the European Union (EU) at that time, lung cancer was the principal cause of death in men (25% of all male cancer deaths) followed by colorectal and prostate cancers. In women, the three major causes of death were breast cancer (16% of all female deaths), colorectal (12%) and lung cancer (9%).

At that time, there was a large and dynamic pipeline of products. Further, at that time, the distribution of therapeutics in clinical trials across cancer types seems to correlate with the incidence of those cancer types reasonably well, suggesting that the pharmaceutical industry is appropriately matching its resources to the size of the market. The European Union did not match the private or public funding levels of the United States with regard to cancer therapeutic research and development.

1. Introduction to cancer

Cancers are caused by combined genetic and non-genetic changes induced by environmental factors that trigger inappropriate activation or inactivation of specific genes leading to neoplastic transformations, or abnormal cell growth. There is a lack of information about key cellular events that occur in early stages of cancer development as well as environmental factors and internal cues that trigger these changes.

Advances in molecular epidemiology are allowing researchers the possibility of simultaneously identifying multiple changes affecting the genome and extra-genomic environment of normal, precursor and cancer cells as well as their link to the environment. It should be now possible to define which genetic and other alterations, or combinations thereof, can be interpreted as reliable biomarkers of exposures. By identifying changes associated with tumour cells and surrogate tissues associated with specific known and suspected environmental risk factors, it may be possible to identify particularly high-risk individuals and potentially design an efficient strategy for cancer prevention.

2. Introduction to cancer therapeutics

Cancer is therefore a generic term used to describe a group of at least a hundred diseases that occur when malignant forms of abnormal cell growth develop in one or more body organs. Cancer arises after a series of genetic mutations remove the normal checks on cell growth. These cancer cells continue to divide and grow to produce tumours. Cancer cells can invade adjacent structures and spread via the lymph or blood to distant organs. Some of the
biological mechanisms that change a normal cell into a cancer cell are known while others are not yet known.

Cancer differs from most other diseases in that it can develop at any stage in life and in any body organ. No two cancer cases behave exactly alike. Some may follow an aggressive course, with the cancer growing rapidly. Other types grow slowly or may remain dormant for years. Very high cure rates can be achieved for some types of cancers, but for others the cure rates are disappointingly low and await improved methods of detection and treatment. The wide range of cancer treatments and associated services reflects the biological diversity of cancer. The most common stage of cancer at diagnosis, the rate of progression, and the treatment options vary significantly with the type of cancer a patient presents.

It is estimated that about 80% of cancers are due to environment or lifestyle, and therefore are potentially preventable.\(^1\) The risk factors for some cancers have been clearly identified, but for others further research is needed. Based on current evidence, at least 30% of future cancer cases are preventable by comprehensive and carefully considered action, taken now.\(^2\)

The cancer treatment that a patient receives is determined by the stage of cancer at diagnosis, the type and location of the cancer, the standard medical practices and treatment guidelines in the patient’s country,\(^3\) and the ability of the patient to pay for treatment (through national or private insurance or otherwise). For most solid tumours, if the cancer is at a relatively early stage of development, surgery is the most standard and effective form of initial cancer treatment. This is often combined with radiation therapy to the tumour bed and systemic therapy as the goal is curative treatment. As cancers progress, treatments typically include radiation, chemotherapy, in hormone-regulated tumours, and hormone ablation therapy. Targeted therapy is becoming increasingly available in appropriate cases. See Section 7.3.

Multiple metastases (in various locations) and the overall tumour load ultimately limit surgical removal and the effectiveness of anti-cancer drugs. When cancers recur and spread beyond the initial site or region, systemic treatment is necessary and the goal of this treatment is no longer curative. Chemotherapy is the most prevalent form of systemic treatment, because it can reach and destroy cancer cells throughout the body, although the blood-brain barrier often limits effectiveness in the case of brain metastases. Chemotherapy may be used alone or in combination with other forms of treatment such as radiation therapy to specific metastatic sites. Hormone-regulated tumours, such as certain breast and prostate cancers use the body’s natural hormones to grow, and they are often more responsive to hormone-based treatments that chemotherapy. As in the case of chemotherapy, tumours can become increasingly resistant to standard treatments. Certain cancers can be resistant to systemic treatments at the time of diagnosis. Other cancers become resistant over a period of months or years. Overall, 30% to 80% of cancers can become refractory.\(^4,5,6\)

As there are over 100 cancer types, when discussing specific cancers in this updated Background Paper, we will concentrate on breast cancer, lung cancer, colorectal, and prostate cancers, which are the top four highest incidence cancers in Europe (combined men and women). See Figure 6.5.3.
3. What are the Epidemiological Trends for Europe and the World?

3.1 Cancer in Europe

It has been estimated that over one-quarter of the global burden of cancer incidence occurs in Europe, despite the fact that persons living in Europe comprise only approximately one-eighth of the world’s population.7

The most recent comprehensive data we have is for 2008 (http://eu-cancer.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=930). The WHO GLOBOCAN project, the aim of which is to provide contemporary estimates of the incidence, mortality, and prevalence from major type of cancers at national level, for 184 countries of the world will update their 2008 data in mid-2013 (too late for publication of this Report). Nevertheless, for the EU27 in 2008, a “league table” for men ranked by incidence (age-standardized per 100 000 persons) is shown in Figure 6.5.1, for women the league table ranked by incidence is Figure 6.5.2 and the combined (men and women) league table ranked by incidence is shown in Figure 6.5.3.

Figure 6.5.1: Incidence, mortality, and prevalence from major type of cancers for the EU27 men in 2008

Figure 6.5.2: Incidence, mortality, and prevalence from major type of cancers, for the EU27 women in 2008


Figure 6.5.3: Incidence, mortality, and prevalence from major type of cancers, for the EU27 men and women combined in 2008

In 2012, in the EU-27 over 700 000 men and over 550 000 women were estimated to have died of cancer. These numbers are slightly higher than those recorded for 2007 (increase in 1.5% in men and 2% in women). The age-adjusted cancer mortality rates are expected to substantially improve (in a positive trend) between 2007 to 2012 from 153.5/100 000 men in 2007 to 138.7/100 000 men in 2012 (drop of 9.6%) and from 90.6/100 000 women to 84.7/100 000 women (drop of 6.5%).

In men, improvements in age-adjusted mortality rates (between 2007 to 2012) are also expected significant reductions for five cancer sites: stomach (-20%), leukemias (-11%), lung and prostate (-10%), and colorectal (-27%) cancers. In women in the same five-year period, mortality rates from these individual sites considered are predicted to decline in the following cancers: stomach (-23%), leukemias (-12%), uterus and colorectum (-11%), and breast (-29%), while increases in lung (+7%) and pancreatic (+3%) cancer mortality rates are expected.

Within Europe, for all the countries considered, improvement in age-adjusted death rates are more marked in men than women, with however notable disparities. In men, estimated improvements in the period from 2000 to 2012 were 21% in France, Germany, and Italy, 18% in Spain, 15% in the UK, and 11% in Poland.

There is a disparity in cancer mortality between Central European post- 2004 EU accession countries (particularly Poland) and countries of the EU15. This was seen in the early 2000s and is not projected to have closed, at least in proportional terms, over recent years. See Figure 6.5.4 (where “EU 12” represents approximately the central EU accession countries post-2004). Data from the European Detailed Mortality Database (http://data.euro.who.int/dmdb/).
For women, the improvement in all-cancer mortality rates in the period 2000–2012 was estimated to be 15% for Germany, 11%–12% for France, Italy, Spain and the UK and 7% in Poland. Thus, for women also, the disparity between the already higher rates in countries like Poland and the other EU15 countries is likely to widen.

From trends in mortality rates by cancer site from 1970 onward for various countries considered, some patterns emerge, although disparities in mortality continue to persist. For instance:

- There is a generalized unfavorable trend in pancreatic cancer mortality rates, with a leveling off in recent periods, at least in men;
- The contrasting trends between sexes in lung cancer mortality rates, with increases in women and improvements in men from the 1990s onward, and the exceptionally high rates in certain EU 12 countries;
- The continuing steady declines in (cervix) uterine cancers, without evidence of closing the gap between the higher rates in certain EU 12 countries and the other countries;
- The declines in prostate cancer rates with again a less favorable picture for men in some EU12 countries.
Despite improvements in breast cancer mortality over most recent periods in Europe and the United States, breast cancer is still the leading cancer mortality in women in the EU as a whole, as well as in France, Germany, Italy, and Spain, while lung cancer is the leading cancer mortality site in the UK. In relative terms, younger women (20–49 years) are those who have shown the greatest reductions in breast cancer mortality rates between 2000 to 2004 and 2005 to 2009 (minus 13%) in the EU.\textsuperscript{6,11,12}

The interpretation of the favorable pattern in breast cancer rates in the EU has raised several controversies, in particular as concerns the role of mammographic screening. In general, many important risk factors for breast cancer, including menstrual and reproductive factors, physical activity, and obesity have not changed favorably. This and the spread of mammographic screening, either spontaneous or organized, have led to increases in breast cancer incidence rates up to the early 2000s. Subsequent declines in incidence rates have been attributed, at least in part, to decreased use of hormone replacement therapy. Apart from lung cancer in women and pancreatic cancer, the fall in mortality from major cancers in major European countries and the EU essentially reflects the decline in tobacco smoking in men and the continuing progress in cancer prevention, early detection, and treatment.\textsuperscript{8}

### 3.1.1 Rare cancers

In Europe, any spotlight on high impact cancers such as breast, lung, prostate and colorectal cancers must keep in focus also the rare cancers. There are about 500 000 new cases per year in the EU27 of “rare cancers” (For definitions see \url{http://www.rarecare.eu/default.asp}). About 4 300 000 patients are living today in the European Union with a diagnosis of a rare cancer - 24% of the total cancer prevalence. Five-year survival rates become worse as the patient gets older. Across all ages, five-year survival is 48% for rare and 64% for more common cancers.\textsuperscript{13} About 30% of Europeans with a rare cancer have one of the particularly rare forms that affect less than one per 100 000, and this is important because low incidence is a major obstacle to conducting clinical trials to develop effective treatments.\textsuperscript{13} See also Chapter 6.19 on Rare Diseases.

### 3.1.2 Paediatric/childhood Cancers

All paediatric cancers are rare diseases and fall under the Commission policy framework on rare diseases. The strategic objectives are described in Commission Communication COM(2008)679/2 on Rare diseases: Europe’s challenges (\url{http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf}) and Council Recommendation of 8 June 2009 on an action in the field of rare diseases (\url{http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF}). Each year 15 000 children and adolescents in Europe are diagnosed with cancer. One third of all childhood cancers are leukaemias, of which acute lymphocytic leukaemia (ALL) and acute myelogenous leukaemia (AML) are most common. Brain and other nervous system cancers make up about one fifth of childhood cancers. Although over the past 50 years the progress in the treatment of childhood cancers has been enormous, still around 25% of all patients die of their disease. See Appendix 6.5.1

In the period from 2006 to 2010, on average three in 100 000 children died from cancer in the EU, but in most countries in Northern and Western Europe, childhood cancer mortality is below this level. In the countries in Southern and Eastern Europe, the ratio is higher.
Update on 2004 Background Paper, BP 6.5 Cancer

Romania has the highest childhood cancer mortality rate. The comparison between the various countries in Europe only includes malignant types of cancer.

Figure 6.5.5 (extracted from a Dutch publication Statistics Netherlands, at http://www.cbs.nl/en-GB/menu/home/default.htm) shows the death rate (per 100,000 children: 0-14 yrs) in the EU, 2006-2010

Figure 6.5.5: Child mortality rate (per 100,000 children: 0-14 years) in the EU, 2006-2010

Survival rates have improved to 80% with the latest treatment regiments in developed countries. However, 60,000 children in developing countries die each year from cancers that are often curable. Overall survival for children in 1990s was 64% in Eastern and 75% in Western Europe with differences between regions for all tumour groups. A study showed that the annual government health care expenditure per capita correlated well with the estimated survival rates of children with cancer. The survival rates were calculated as 5% to 50%, 50% to 70% and more than 70% in those which spend less than US$ 100, US$ 100, and
more than US$ 1000, respectively. Access to care and research in childhood cancer as a “rare” tumour is also highly critical to closing the gaps in survival in children with cancer at European and global level. In this context, for both adults and children, there is a need for research in survivorship issues as the long-term side-effects of cancer therapies is an important research subject. In addition, quality of life issues such as end of life care and palliative therapy are worthy of research.

Each year 175,000 childhood cancers are expected at global level. A recent report surveyed European paediatric oncologists. Briefly, we summarize the findings as follows:

- Countries with a larger oncology burden, such as those in Eastern Europe, tended not to collaborate in research with those with a better developed research structure, and this in turn affected the care they were able to give young patients.
- National situations with regard to paediatric oncologic facilities, resources, research grants for young scientists, and hospital space were quite different.
- In Italy, nearly 50 centres specialized in paediatric haematology and oncology, and there was a lack of coordination between research laboratories and clinics.
- The authors also found large differences in the provision of information on childhood cancer, with variations in the involvement of parental organizations, the use of digital media, and the adoption of a common national standard for information provision.
- The authors called for adequate long-term EU funding to support a Europe-wide clinical trials network for paediatric oncology.

3.1.3 Trends in cancer survival

Trends in cancer survival vary across the EU. Berrino et al determined that as of 2009, the relative excess risk of death was 28% higher in Eastern Europe (based on data from the Czech Republic) than Central Europe (based on data from Austria, Belgium, France, Germany, the Netherlands and Switzerland); the relative excess risk of death was 60% higher for patients aged 55–99 years than those aged 15–54 years, and male cancer patients had a significantly higher risk of dying than women. Such data are inherently subject to interpretation and controversy. It is possible that differences between Eastern and Western States have persisted largely because of fewer resources for healthcare services and recent dysfunction in health care systems of Eastern States. Survival differences for relatively uncommon treatable cancers such as testicular cancer and Hodgkin’s disease, and for cancers with very poor prognosis, tend to be less marked than the disparities observed for common breast, cervical, and colorectal cancers.

As an example of the data generated, Coleman et al. collected data from population-based cancer registries in 12 jurisdictions in Australia, Canada, Sweden, Norway, Denmark, and the UK for 2.4 million adults diagnosed with primary colorectal, lung, breast (for women), or ovarian cancer during 1995–2007, with follow-up to 31 Dec 31 2007.

Relative survival improved during 1995 to 2007 for all four cancers in all jurisdictions. Survival was persistently higher in Australia, Canada, and Sweden, intermediate in Norway, and lower in Denmark, England, Northern Ireland, and Wales, particularly in the first year after diagnosis and for patients aged 65 years and older. Trends in cancer incidence and mortality were broadly consistent with these trends in survival. It was asserted that these patterns were consistent with later diagnosis or differences in treatment, particularly in Denmark and the UK, and in patients aged 65 years and older.
The idea of using cancer survival as a means of measuring the effectiveness of health care systems is a major topic of research and discussion and is somewhat challenging. We will not dwell on this subject for the Report but note the following brief points:

- It appears that when factors likely to influence survival statistics are similar across medical facilities, or when data on these factors are available, survival statistics might bring insights into the respective roles of detection and treatment. When comparing countries, it would be prudent to collect country-specific cancer survival data as well as incidence and mortality data.
- One should also consider the multiple factors unrelated to health system performance that could influence survival data. It may well be that joint interpretation of survival, incidence, prevalence, and mortality is the best guide to policy for prevention, screening, treatment, and the organization of health care systems.
- When countries are compared, because of the complexity and intricacy of factors influencing survival statistics (including the fact that health systems differ in many ways), many factors not associated with performance can influence variations in survival.

**Incidence-related factors:** Earlier detection of cancer from which patient will die (lead-time bias); detection of non-life-threatening cancer (length-time bias and over-diagnosis); and detection of cancer precursor lesions.

**Cancer registries:** Cancer definition (e.g. classification used); population coverage; completeness of cancer case ascertainment; registration of newly diagnosed cases; cases registered after death from cancer and unknown date of diagnosis (death certificate only); and registration of cancer recurrence instead of cancer diagnosis.

**Patient-related factors:** Age, gender, genetic background; socioeconomic status, education; race, ethnic origin; comorbidity; and mortality from other causes (competing causes of death).

**Cancer-related factors:** stage at diagnosis; anatomical site of cancer; and dancer capacity to invade surrounding and distant tissues.

**Health system factors:** ability of early detection methods and screening programmes to prevent cancer occurrence and/or occurrence of advanced cancer; alertness of health professionals (attention to signs and symptoms possibly associated with cancer); and availability, access to, and quality of diagnostics, classification of cancers, supportive and follow-up care.

**Organizational efficiency:** speed and quality of work-up of positive early detection (screening) tests, clinical signs, and symptoms; referral to specialized services; and health facility’s patient load.

Survival differences could also be due to differences in exposure to cancer risk factors. For instance, obesity is associated with breast cancers of worse prognosis that are less sensitive to treatment. If the prevalence of obesity in adult women in one country is twice as high as in another, this might play a role in the dissimilarity in breast cancer survival.
3.2 Global Perspective

We note the comprehensive global and regional examination of cancer to date is the World Cancer Report, updated for 2008. We also note the WHO GLOBOCAN project, the aim of which is to provide contemporary estimates of the incidence, mortality, prevalence, and disability-adjusted life years (DALYs) from major type of cancers at national level, for 184 countries of the world.

The 2008 World Cancer Report shows that the global burden of cancer doubled between 1975 and 2000 and is expected to double again by 2020 and nearly triple by 2030. The report estimates that there were some 12 million new cancer diagnoses worldwide in 2008, based on the most recently available data, and that an estimated seven million people will die from the disease. The projected numbers for the year 2030 are 20 million to 26 million new cancer diagnoses and 13 million to 17 million cancer deaths. In large measure, this a function of increased life expectancy generally and of better and earlier diagnostic procedures. There are interesting relationships between cancer and country development index (CDI). In the highest human development index (HDI) regions in 2008, cancers of the female breast, lung, colorectum, and prostate accounted for half the overall cancer burden; whereas in medium HDI regions, cancers of the oesophagus, stomach, and liver were also common, and together these seven cancers comprised 62% of the total cancer burden in medium to very high HDI areas.

In low HDI regions, cervical cancer was more common than both breast cancer and liver cancer. Nine different cancers were the most commonly diagnosed in men across 184 countries, with cancers of the prostate, lung, and liver being the most common. Breast and cervical cancers were the most common in women.

In medium and high HDI settings, decreases in cervical and stomach cancer incidence seem to be offset by increases in the incidence of cancers of the female breast, prostate, and colorectum. See Figure 6.5.6, taken from Bray et al.

If the cancer-specific and sex-specific trends estimated in this study continue, an increase in the incidence of all-cancer cases is predicted from 12.7 million new cases in 2008 to 22.2 million by 2030. This data on the cancer-HDI association suggest that cancer burden in many countries in societal and economic transition from a communicable to a non-communicable epidemiology and demography is a net burden between reductions in infection-related cancers and increases in new cases that are more associated with reproductive, dietary, smoking and hormonal factors. Targeted interventions can lead to a decrease in the projected increases in cancer burden through effective primary prevention strategies, alongside the implementation of vaccination, early detection, and effective treatment programmes.
3.3 Specific cancers

The high impact cancers of the EU with respect to incidence, prevalence, and mortality are summarized in Figures 6.5.1-6.5.3 above.

3.3.1 Tobacco-driven Lung cancer: Europe and the World

Tobacco is the primary driver for development of lung cancer. Within the 27 countries of the European Union, the highest European age-standardized incidence rates for 2008 are
estimated to be in Hungary for men (around 115 cases per 100 000) and Denmark for women (around 51 cases per 100 000), while the lowest rates are in Sweden for males (around 27 cases per 100 000) and Cyprus for females (around 7 cases per 100 000).  

Lung cancer has been the most common cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total). The majority of the cases now occur in the developing countries (55%). Lung cancer is still the most common cancer in men worldwide (1.1 million cases, 16.5% of the total), with high rates in Central-Eastern and Southern Europe, Northern America, and Eastern Asia. Very low rates are still estimated in Middle and Western Africa. In females, incidence rates are generally lower, but worldwide lung cancer is now the fourth most frequent cancer of women (516 000 cases, 8.5% of all cancers) and the second most common cause of death from cancer (427 000 deaths, 12.8% of the total).

The highest incidence rate is observed in North America (where lung cancer it is now the second most frequent cancer in women), and the lowest in central Africa (15th most frequent cancer). Because of its high fatality (the ratio of mortality to incidence is 0.86) and the lack of variability in survival in developed and developing countries, the highest and lowest mortality rates are estimated in the same regions, both in men and women.  

3.3.2 Breast cancer: Europe and the World

Within the 27 countries of the European Union (EU27), the highest female breast cancer European age-standardized mortality rates for 2008 were estimated to be in Ireland (31.1 deaths per 100 000 women), while the lowest were in Spain (18.4 deaths per 100 000 women). Non-metastatic breast cancer is by far the most frequent cancer among women with an estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all cancers), and ranks second overall (10.9% of all cancers). Incidence rates vary from 19.3 per 100 000 women in Eastern Africa to 89.7 per 100 000 women in Western Europe, and are high (greater than 80 per 100 000) in developed regions of the world (except Japan) and low (less than 40 per 100 000) in most of the developing regions. As a result, breast cancer ranks as the fifth cause of death from cancer overall (458 000 deaths), but it is still the most frequent cause of cancer death in women in both developing (269 000 deaths, 12.7% of total) and developed regions, where the estimated 189 000 deaths is almost equal to the estimated number of deaths from lung cancer (188 000 deaths).

Metastatic or advanced breast cancer is the presence of disease at distant sites such as the bone, liver, or lung. The true prevalence of metastatic disease is high because some women live with the disease for many years. Since 1990, there has been an overall increase in incidence rates of about 1.5% annually. It is considered incurable. In women who receive no treatment for metastatic disease, the median survival from diagnosis of metastases is 12 months.
3.3.3 Prostate cancer: Europe and the World

Prostate cancer is the second most frequently diagnosed cancer of men (899,000 new cases, 13.6% of the total). Nearly three-quarters of the registered cases occur in developed countries (644,000 cases). Within the 27 countries of the European Union (EU-27), the highest European age-standardized incidence rates for 2008 are in Ireland (183.2 new cases per 100,000) and the lowest in Greece (27.9 cases per 100,000).

Incidence rates of prostate cancer vary by more than 25-fold worldwide, the highest rates are in Australia and New Zealand (104.2 per 100,000), Western and Northern Europe, and Northern America largely because the practice of prostate specific antigen (PSA) testing and subsequent biopsy has become widespread in those regions. Within the era of PSA testing, an estimated 16% of men will receive a diagnosis of prostate cancer sometime during their lifetime and about 2.2 million American men are estimated to be living with prostate cancer. The lowest age-standardized incidence rate is estimated in South-Central Asia (4.1 per 100,000). Incidence rates are relatively high in certain developing regions such as the Caribbean, South America, and sub-Saharan Africa. The likelihood of prostate cancer increases with age, particularly starting at around age 45 years. Autopsy studies found that as many as 75% of men 85 years and older have prostate cancer at the time of death. With an estimated 258,000 deaths in 2008, prostate cancer is the sixth leading cause of death from cancer in men (6.1% of the total).

Because PSA testing has a much greater effect on incidence than on mortality, there is less variation in mortality rates worldwide (10-fold) than is observed for incidence (25-fold), and the number of deaths from prostate cancer is almost the same in developed and developing regions. Mortality rates are generally high in predominantly black populations (26.3 per 100,000 for the Caribbean and sub-Saharan Africa), very low in Asia (2.5 per 100,000 in Eastern Asia) and intermediate in Europe and Oceania.

3.3.4 Colorectal Cancer: Europe and the World

Colorectal cancer incidence rates have overall increased in Britain since the mid-1970s. For men, European age-standardized incidence rates have increased by 27% between 1975 and 1977 and 2007 and 2009, with most of this increase occurring between the mid-1970s and late 1990s. For women, the rise is much smaller, with rates increasing by 8% between 1975 and 1977 and from 2007 to 2009.

Within the 27 countries of the European Union, the highest European age-standardized incidence rates for 2008 are estimated to be in Slovakia for men (around 91 cases per 100,000) and Denmark for women (50 cases per 100,000), while the lowest rates are in Greece for both sexes (around 24 cases per 100,000 for men and 17 per 100,000 for females). The incidence rate varies up to 10-fold between countries with the highest rates and those with the lowest rates. It ranges from more than 40 per 100,000 people in the United States, Australia, New Zealand, and Western Europe to less than 5 per 100,000 in Africa and some parts of Asia.

Colorectal cancer is a major cause of morbidity and mortality throughout the world. It accounts for over 9% of all cancer incidence.
It is the third most common cancer worldwide and the fourth most common cause of death. It affects men and women almost equally. Countries with the highest incidence rates include Australia, New Zealand, Canada, the United States, and parts of Europe. The countries with the lowest risk include China, India, and parts of Africa and South America. The developed world accounts for over 63% of all cases.30

Much of the geographical variation in incidence across the world can be attributed to differences in diet, particularly the consumption of red and processed meat, fibre and alcohol, as well as excess bodyweight and lack of physical activity. Countries that have had a rapid ‘westernization’ of diet, such as Japan, have seen a rapid increase in the incidence of colorectal cancer. 31 Epidemiological studies report a rapid increase in risk for colorectal cancer in migrants moving from low- to high-risk countries.30,31

4. What is the Control Strategy? Is There an Effective Package of Control Methods

Assembled Into a “Control Strategy” for most Epidemiological Settings?

In 2008, the World Health Assembly passed resolution WHA61.14 endorsing the Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases. 32 The Action Plan set out six objectives, actions to be implemented over the six-year period from 2008 to 2013, and performance indicators to guide the work of WHO at national, regional, and global levels with a particular focus on low - and middle-income countries and vulnerable populations. Member States have committed to national non-communicable diseases (NCD) plans by the end of 2013.

Cancer control is a population-based public health strategy. The aim of cancer control is a reduction in both the incidence of the disease and the associated morbidity and mortality where possible, as well as improved quality of life for cancer patients. Significant advances in our ability to diagnose, screen and detect cancers earlier as well as improved understanding of the etiology and biology of cancer have led to significant improvements in cancer survival over the past decades. This had led to increasingly effective cancer therapies, which add to the ability to tackle more cancer types and individual cancers in a more targeted manner. Advances continue to be made across the disciplines of surgery, radiation therapy and systemic therapy; for example, the development of the human papillomavirus vaccine (HPV), immunotherapy (ipilimumab for melanoma), and survival improvements in patients with chronic myelocytic leukemia using imatinib mesylate (Gleevec ®). 33 See below for more recent advances in this area, Section 7.

We searched the WHO Global Health Observatory data repository, which provides access to over 50 datasets on priority health topics.34 At the national level, many countries have established comprehensive national cancer control programs. The Communication from the Commission of 2009 on Action against Cancer pledges that by the end of the Partnership in 2013 all EU Member States will have adopted integrated cancer plans.35
A recent systematic assessment of the National Cancer Control Plans available in Europe in 2009 showed that despite the growing number of plans in Europe (19 in the 31 countries studied), significant differences remain between them. A major source of concern is the fact that in many cases, elements crucial to a health systems approach and to the efficacy of the plans such as financing, resource allocation, or governance were missing or inadequate. For those interested in national cancer control programmes, see https://spiral.imperial.ac.uk/bitstream/10044/1/4204/1/Cancer%20Control%20vf2.pdf.

In developing countries in particular, where a large proportion of cancers are detected late in the course of the disease, efforts to achieve earlier diagnosis and delivery of adequate palliative care and pain relief deserve urgent attention. A comprehensive national cancer control strategy would be required for any country for the following reasons:

- People are going to continue to develop cancer and die from it
- Cancer control is unique in its complexity, involving a range of diseases and a diversity of service providers – it cannot be achieved by any single organization or by government alone
- Effective and efficient use of limited resources is crucial
- Establishing an alliance of organizations and health professionals, both government and non-government, is critical if action is to be cost-effective
- It is important to act now, before the full impact of the ageing population is felt by the health care system

### 4.1 Prevention

Cancer prevention should be a key element in all cancer control programs. Cancer prevention focuses not only on factors that increase a person’s chances of developing cancer (such as smoking), but also on protective factors such as a healthy diet and physical activity. Exposure to risk factors (e.g. increase in melanoma incidence and the need to avoid sunburn) is generally the result of a complex range of behavioral, social, economic, environmental, and cultural factors that are not easy to change so that efforts to reduce the incidence of lifestyle-related cancers require a comprehensive approach.

Geographical patterns of cancer arise because the prevalences of risk factors differ in a given population. Studies of geographical differences and of migrant populations (i.e. their adoption of the cancer patterns of the host country) provided a cornerstone that established the role of environmental and lifestyle factors in the causation of cancer. Nevertheless, cancer differs from other noncommunicable diseases in that specific risk factors for a number of major cancer sites remain poorly defined.

It is important to recognize that cancer in low- and medium-HDI countries (See Figure 6.4.5 above) is not simply due to their adoption of the social and behavioral conditions found in the high- and very high-HDI countries. Perhaps the best example for which cancer-specific actions are needed is chronic infections. Infections are estimated to explain approximately 16% of cancers globally; however, in developing countries infections explain 22.9% of cancers. The major contributors to cancer are infections with hepatitis B and C viruses (HBV and HCV), HPVs, and *Helicobacter pylori*. Consequently, several of the most common cancers (e.g. liver, stomach, and cervix) in Africa, Asia, and South America are related to an infection.
Ignoring the substantial cancer burden related to infection would be a failure to address preventable causes of cancer in many parts of the world. Other infections that are of lesser global significance can have a serious impact on a local or regional level. These infections can also be addressed by available interventions including the combined role of Kaposi sarcoma herpes virus and HIV in Kaposi sarcoma in sub-Saharan Africa and the role of liver flukes in cholangiocarcinoma in parts of Asia.39

Other categories of risk factors can also be addressed.38 These include environmental and occupational agents: reduction in exposure to aflatoxins, indoor air pollution, radon, arsenic, and excess sunlight; and regulatory protection of workers in certain industries.40 Such preventive measures will be priorities in some regions even though the impact on global cancer incidence will be comparatively modest.

The shared environmental and behavioral risk factors for noncommunicable diseases make an important contribution to the global cancer burden. In addition to the global impact of tobacco on cancer in multiple organs, alcohol is associated with cancers of the liver, larynx, esophagus, pharynx, breast, and colorectum. Also, reducing the consumption of sugar should help control obesity and overweight, which are risk factors for cancers of the esophagus, breast, colorectum, endometrium, kidney, and pancreas. As mentioned above, for some cancers, the challenge is to implement established interventions, and for other cancers the research priority should be to identify prevention strategies. Tobacco consumption probably remains the most important avoidable cancer risk. In the twentieth century, approximately 100 million people worldwide died from tobacco-associated diseases (cancer, chronic obstructive lung disease, heart disease and stroke).

### 4.2 Early Detection and Screening

Early detection means detecting cancer prior to the development of symptoms or as soon as is practicable after the development of symptoms. Its aim is to detect the cancer when it is localized to the body organ of origin, before it has time to spread to other parts of the body.

Early detection is only part of a wider strategy including diagnosis, treatment, and follow-up which can involve strategies to promote early presentation, including education about signs and symptoms and improved access to primary care.27 Early detection of cancer prior to the development of symptoms occurs through screening.

### 4.3 Diagnosis and Treatment

Diagnosis involves clinical assessment and a range of investigations, such as endoscopy, imaging, histopathology, cytology, and laboratory studies. Diagnostic tests are also important in identifying the extent to which the cancer may have spread (known as 'staging'). Cancer staging is necessary for determining options for treatment and assessing likely prognosis.

The cancer treatment that a patient receives is determined in large part by the stage of cancer at diagnosis. For most solid tumours, surgery is the most standard and effective form of initial cancer treatment. As cancers progress, treatments typically include radiation, chemotherapy, and in hormone-regulated tumours, hormone ablation therapy.
Update on 2004 Background Paper, BP 6.5 Cancer

A comprehensive review would also focus on support, rehabilitation and palliative care but this Priority Medicines Report concentrates on pharmacotherapies and these vitally important subject cannot be reviewed here. For further information see Review of Rehabilitation Intervention in Palliative Care for Cancer Patients.41

It is just as challenging to summarize an enormous literature on treatment options in this short review. We use the summaries provided by the United States National Cancer Institute (NCI) as a (US-FDA centric) template for this overview. See http://www.cancer.gov/cancertopics/factsheet/cancer-advances-focus.

Overall:

- Combination chemotherapy is now standard in the treatment of many cancers and has contributed to increasing survival and cure rates. For example, the introduction of combination chemotherapy containing cisplatin led to cure rates for testicular cancer of approximately 95%. Treatment for this disease has become so effective that 80% of patients with metastatic testicular cancer can now be cured. Thirty-five years ago, 95% of these patients died, usually within 1 year of diagnosis.
- Thus far, three cancer prevention vaccines have been approved by the U.S. Food and Drug Administration (FDA). One of these vaccines, the hepatitis B virus vaccine, has the potential to prevent some forms of liver cancer. The other two vaccines are directed against human papillomavirus (HPV) types 16 and 18 and have the potential to prevent approximately 70% of cervical cancers and some other HPV-associated cancers. Significantly, responding to demand from developing countries, the GAVI Alliance announced in November 2011 that it would take the first steps towards the introduction of human papillomavirus (HPV) and rubella vaccines in developing countries. In December 2012, GAVI announced the price for the vaccines at US$ 5 per dose, which is significantly lower than the general retail price of US$Error! Hyperlink reference not valid.. See GAVI FAQ: Appendix 6.5.2
- In 2010, the FDA approved the first cancer treatment vaccine. This vaccine can be used to treat advanced prostate cancer. Several other cancer treatment vaccines are being tested in large-scale clinical trials, including vaccines for the treatment of non-small cell lung cancer, pancreatic cancer, ovarian cancer, melanoma, and multiple myeloma.
- Therapies that target the specific molecular changes that cause cells to become cancerous and processes that are required for continuous cancer cell growth and survival are in use. To date, the FDA has approved approximately 30 molecularly targeted agents for cancer-related indications, including trastuzumab and three different aromatase inhibitors for breast cancer; imatinib mesylate for chronic myelogenous leukemia and gastrointestinal stromal cell tumours (GIST); sunitinib for advanced kidney cancer and imatinib-resistant GIST; bevacizumab for advanced colorectal, non-small cell lung, and kidney cancers; and bortezomib for multiple myeloma and a type of non-Hodgkin lymphoma. See Section 7.
- Refined radiation therapy techniques, such as three-dimensional conformal radiation therapy, stereotactic radiosurgery, and brachytherapy (radioactive seeds), which are designed to deliver high doses of radiation to tumours while minimizing the doses delivered to nearby healthy tissue, are now widely used. These advances have resulted in greater tissue, organ, and limb preservation.
- Effective therapies to control the side effects of cancer and its treatment, including pain, mouth sores, nausea, and vomiting are available.
4.3.1 Tobacco related cancers: Lung cancer

The following summaries are extracted from Autier et al. 2011, and Gatta et al. 2011.12,13 There are some seemingly basic questions that still remain unanswered.

- We do not know whether intensifying the chemotherapy dose increases survival in small cell lung cancer, and it may increase treatment-related toxicity.
- First-line platinum-based regimens improve survival in people with unresectable non-small cell lung cancer compared with older, non-platinum agents, but we do not know whether platinum-based chemotherapy is more effective than non-platinum third-generation chemotherapeutic agents.
- Adding chemotherapy to thoracic irradiation may improve survival at 2 to 5 years in people with unresectable non-small cell lung cancer compared with thoracic irradiation alone, but increases adverse effects.
- Targeted therapy with gefitinib or erlotinib does not increase survival when used as first-line palliative therapy in people with unresectable non-small cell lung cancer. But there are now subgroups defined who can be treated initially with targeted agents alone.
- Adding thoracic irradiation to chemotherapy improves survival in people with limited-stage small cell lung cancer, but may increase complications.

4.3.2 Breast Cancer (non-metastatic)

- Breast-conserving surgery (lumpectomy) followed by local radiation therapy has replaced mastectomy as the preferred surgical approach for treating early-stage breast cancer.
- Combination chemotherapy is a standard of care in the adjuvant treatment of operable breast cancer. The goal of this systemic therapy is to eradicate cancer cells that may have spread beyond the breast. Neoadjuvant chemotherapy, or chemotherapy given before surgery to reduce the size of the tumour and to increase the chance of breast-conserving surgery, is also an option.
- Hormonal therapy with selective estrogen receptor modulators (SERMs)1 (such as tamoxifen) and aromatase inhibitors is now standard in the treatment of women with estrogen receptor-positive breast cancer, both as adjuvant therapy and in the treatment of advanced disease. Aromatase inhibitors block estrogen production by the body.
- Tamoxifen and another SERM, raloxifene, have been approved by the FDA as treatments to reduce the risk of breast cancer in women who have an increased risk of developing the disease.
- The monoclonal antibody trastuzumab is an accepted treatment for breast cancers that overproduce a protein called human epidermal growth factor receptor 2, or HER2. This protein is produced in abnormally high amounts by about 20% of breast tumours. Breast cancers that overproduce HER2 tend to be more aggressive and are more likely to recur. Trastuzumab targets the HER2 protein specifically, and this antibody, in conjunction with adjuvant chemotherapy, can lower the risk of recurrence.

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1 Selective estrogen receptor modulators block the effects of estrogen in the breast tissue. If estrogen isn’t attached to a breast cell, the cell doesn’t receive estrogen’s signals to grow and multiply. There are three SERMs: tamoxifen (also called tamoxifen citrate; brand name: Nolvadex) Evista (chemical name: raloxifene) Fareston (chemical name: toremifene)

6.5-25
recurrence of HER2-overproducing breast cancers by about 50% in comparison with chemotherapy alone.

- Several breast cancer susceptibility genes have now been identified, including BRCA1, BRCA2, TP53, and PTEN/MMAC1. Approximately 60% of women with an inherited mutation in BRCA1 or BRCA2 will develop breast cancer sometime during their lives, compared with about 12% of women in the general population. Women with inherited BRCA1 or BRCA2 gene mutations also have an increased risk of ovarian cancer.

- The prevalence of ductal carcinoma in situ (DCIS) has dramatically increased since the widespread adoption of screening mammography. Because DCIS is considered to be a potential precursor of invasive breast cancer, it has been treated aggressively with local therapy. The potential for pre-operative (neoadjuvant) therapy is being actively explored using a variety of agents (e.g. lapatinib U.S. clinical trials: NCT00555152).

4.3.3 Metastatic breast cancer

- Hormonal treatment using tamoxifen or progestins may be preferable to chemotherapy as first-line treatment in women with estrogen receptor-positive disease.

- First-line chemotherapy is associated with an objective tumour response in 40% to 60% of women, of median duration of 6 to 12 months. Complete remission may occur in some women, whereas others show little or no response.

- The optimum duration of chemotherapy is unknown. Increasing the dose may increase serious adverse effects without prolonging survival.

- Taxane-based chemotherapy may increase tumour response and survival compared with some non-taxane regimens as second-line treatment. No clear benefit has been found in first-line treatment.

- Targeted therapies as m-TOR inhibitors (i.e. everolimus) are now being used in combination with other therapies (e.g. exemestane) to treat metastatic breast cancer

4.3.4 Prostate Cancer/ PSA Screening

Due to the widespread implementation of prostate specific antigen (PSA) screening in the United States, more than 90 percent of all prostate cancers are diagnosed at an early stage. Whether this earlier detection actually reduces the number of prostate cancer deaths was studied in two randomized clinical trials in the NIH-sponsored Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trial and the European Study of Screening for Prostate Cancer (ERSPC). The PLCO trial had at least 44% of participants in the control arm already PSA-tested prior to being randomized into the study. This United States study has been unable to demonstrate any difference in prostate cancer mortality between the two arms of the study. The ERSPC trial has published its 11-year follow-up results (New England Journal of Medicine, 15 March 2012). They demonstrate, as they had in their original findings, that screening does significantly reduce death from prostate cancer by at least 20% but that PSA-based screening “was associated with a high risk of overdiagnosis”.

However, this benefit came at a cost because many more cancers were diagnosed and treated in the screened group than in the control (unscreened) group. These findings suggest that PSA screening can lead to the diagnosis and treatment of some prostate cancers that will not cause symptoms or threaten a man’s life, phenomena known as overdiagnosis and overtreatment (i.e.
unnecessary treatment). The major side effects of prostate cancer treatment include urinary incontinence and sexual impotence.

Summary of progress in prostate cancer:

- Advances in the treatment of prostate cancer include new surgical approaches and improvements in radiotherapy. In addition, laparoscopic and robot-assisted surgical methods are also widely used, although evidence of their superiority to open prostatectomy is lacking. Furthermore, clinical researchers have refined a radiotherapy technique known as brachytherapy, which involves the implantation of small sources of radioactivity (radioactive seeds) into the prostate.

- Advances in hormonal therapy for prostate cancer have included the development of gonadotropin-releasing hormone (GnRH) agonists, which inhibit the pituitary gland’s ability to stimulate the testes to make testosterone. Other GnRH agonists used today include goserelin, triptorelin, and histrelin. Additional prostate cancer treatments that interfere with the production or activity of male hormones and are used today include the drugs degarelix, flutamide, bicalutamide, nilutamide, and ketoconazole.

- Recent progress in our understanding of the pathogenesis of advanced prostate cancer has heralded a new era in treatment. Numerous agents now populate the treatment landscape (i.e. hormonal treatments for advanced disease - abiraterone and elazutamide- and an impressive number of novel agents are in development.

- Advances have also been made in chemotherapy for prostate cancer. In 2004, results from two large NIH-sponsored clinical trials showed that use of the drug docetaxel can prolong the survival of men who have advanced prostate cancer that no longer responds to hormonal therapy. Another drug, cabazitaxel, approved in 2010, improves the survival of men whose prostate cancer no longer responds to docetaxel.

- In 2010, the FDA approved sipuleucel T, a cancer treatment vaccine that improves the survival of men with advanced prostate cancer. This vaccine is created using a patient’s own immune cells. The cells are removed from the patient’s body, activated, and then infused into the patient’s bloodstream to boost the immune response to his cancer.

- In 2003, the NIH-sponsored Prostate Cancer Prevention Trial demonstrated that hormonal therapy with finasteride, a drug approved for the treatment of benign prostatic hyperplasia (a noncancerous enlargement of the prostate), reduced the risk of developing prostate cancer by 25%. This was the first study to show that a drug could be used to prevent this disease. In 2010, a similar drug, dutasteride, was also found to reduce the risk of prostate cancer in men at higher than average risk for the disease.

4.3.5 Colorectal Cancer:

- Colorectal cancer surgical techniques and survival after surgery have improved over the past 15 years. Surgery can cure about 90% of colorectal cancers when they are found early.

- Researchers began testing drug combinations with fluorouracil (5-FU) as early as the 1980s, and, in the mid-1990s, the combination of 5-FU and leucovorin became standard adjuvant treatment for patients with stage III colon cancer. The addition of oxaliplatin to 5-FU and leucovorin was later found to improve survival compared with 5-FU and leucovorin alone. A newer drug, capecitabine, is an alternative to 5-FU.
and leucovorin. Capecitabine is sometimes combined with oxaliplatin as well. Capecitabine is taken by mouth, whereas 5-FU must be given intravenously. For some patients whose cancer has metastasized, the drug irinotecan may also be part of chemotherapy.

- Radiation therapy is not standard treatment for patients with colorectal cancer, but patients with stage II or stage III rectal cancer may receive neoadjuvant radiation plus chemotherapy in addition to adjuvant chemotherapy. If a patient does not receive neoadjuvant radiation therapy, he or she may be treated with adjuvant radiation therapy plus chemotherapy.
- The targeted therapies cetuximab and panitumumab can extend survival or slow tumour growth, respectively, for some patients with advanced colorectal cancer. Recent genetic studies have identified a subset of patients who do not benefit from these drugs, sparing them unnecessary treatment.
- The targeted therapy bevacizumab (Avastin®) blocks the growth of new blood vessels to tumours. Studies have shown that bevacizumab can help extend survival for some patients with metastatic colorectal cancer.

4.4 Histology and segmentation

By necessity, the Background paper is focused on therapeutic interventions, including targeted therapies. Nonetheless, understanding cancer growth, classification, and prognostic factors requires new methods in tumor segmentation and histology. In part this is because many tumours are a complex intermixing of cellular tissue types: incorporating cancer cells, fibroblastic stromal tissue, and inactive fibrosis. Quantitative proportions and distributions of the various tissue types are useful to understand in some detail. Any review of this subject is well beyond the scope of the Background paper. We cite two examples.

Scanning hardware and viewing software can digitize samples of stained pathological tissue excised from a patient. Image analysis algorithms can be employed to assist in analyzing these digital samples, increasing the speed and efficiency with which pathology samples are examined in the clinic. Traditionally these algorithms have focused on simple quantification (e.g. cell counting or stain enhancement), but the most recent developments have focused on developing quantitative disease signatures for different tissue types.

In conventional pathological diagnosis even with serial sections of a good quality, it is difficult, if not impossible, to grasp the three-dimensional (3D) structure of cancer lesions in a complex microenvironment under a microscope. Recent advance in 3D imaging technology allow clinicians to inspect the details of tumor architecture. 45
5. **What is Known of the Affordability, Feasibility, and Sustainability of the Control Strategy?**

5.1 **NCD Global monitoring framework**

A draft comprehensive global monitoring framework, including indicators, and a set of voluntary global targets for the prevention and control of noncommunicable diseases was developed from a WHO meeting of Member States in November 2012 [http://apps.who.int/gb/NCDs/pdf/A_NCD_INF1-en.pdf](http://apps.who.int/gb/NCDs/pdf/A_NCD_INF1-en.pdf). Many of the proposed sets of monitoring indicators are relevant for our present purpose.

The global monitoring framework including the proposed set of indicators, is intended to provide internationally comparable assessments of the status of NCD trends over time and help to benchmark the situation in individual countries against others in the same region or in the same development category.

Some of these indicators might be rated “best buys” as being very cost-effective. For instance, it is estimated that 2.3 million deaths annually, or 3.8% of all global deaths, are attributed to alcohol consumption, from which more than half are due to NCDs including cancers and cardiovascular diseases. Tracking alcohol consumption is important as the risk of most alcohol-attributable health conditions is correlated with the overall levels of alcohol consumption with no evidence of a threshold effect for cancers and hypertension.

Tracking dietary fat intake is important as this has been linked to increased risk of obesity, coronary heart disease and certain types of cancer. Tracking inadequate consumption of fruit and vegetables is important as adequate amounts reduces the risk for cardiovascular diseases, stomach cancer, and colorectal cancer. Tobacco smoking is estimated to cause about 71% of lung cancer deaths. Hepatitis V virus (HBV) results in liver cirrhosis and in total it is estimated that 600 000 people die each year from chronic HBV infections, mainly from cirrhosis and liver cancer. A safe effective vaccine to prevent chronic infection with HBV is available and is recommended by the WHO to be included in national infant vaccination programmes. Preventing liver cancer via hepatitis B vaccination is classified as a “best buy” by the WHO. Human papilloma virus (HPV) vaccination to prevent cervical cancer is potentially very cost effective if it can be made available at below US$ 10 per vaccinated girl.

5.2 **Overall Economic Burden: Europe and the World**

Cancer costs European countries €124 billion (£99 billion) every year, according to the first estimate of the full economic burden of the disease in the EU. *Lung cancer incurred the biggest total cost, amounting to €19 billion (£15 billion). This was mostly the result of losses caused by patients dying prematurely. For healthcare alone, the most expensive disease was breast cancer. At €6 billion (£5 billion), it was responsible for 13% of cancer healthcare costs. Direct healthcare costs were also calculated for each of the 27 countries included in the research.*

Data shows that Lithuania spent the least on cancer healthcare, around €7550 (£6026) per patient with a per capita cost of €32 (£25.50) per person per year. Germany had the highest healthcare cost, spending an average of €28 269 (£22 563) on every cancer case. It had a per-
capita expenditure of €165 (£132). The UK spent €17 619 (£14 062) per case and €88 (£70) per head of population. See also Figure 6.5.7.

Figure 6.5.7: Cancer healthcare costs in various European countries as cost per person (left hand figure) and cost per incident cancer (right hand figure)


In 2008, researchers gathered global burden of disease data from the WHO for 17 different types of cancer, and 15 foremost causes of death. Death and disability is responsible for the loss of 85 million DALY years. To reduce this death toll by one DALY, the WHO recommends investing as much as three times per capita Gross Domestic Product (GDP) to make an intervention cost-effective. Cancer has the largest economic impact from premature death and disability when compared to all global causes of death. 47 Cancer accounted for close to US$ 1 trillion in economic losses from premature death and disability in 2009. The economic burden from cancer, at US$ 895 billion, is nearly 20% more than heart disease’s toll (US$ 753 billion). These figures do not include direct medical costs, which might double the amounts.

It has recently been estimated that it would cost US$ 1.8 billion to reduce exposure to key risk factors like smoking, drinking, and poor diet (US$ 0.6 billion for smoking/ US$ 0.4 billion for diet/exercise and US$ 0.8 billion for alcohol). 48

Alone, cancers of the bronchus, lung and trachea already cost the global economy nearly US$ 180 billion annually. It is estimated that 8 million people will die prematurely because of tobacco smoking by 2030, with four-fifths of these deaths occurring in low- to middle-income countries - approximately 30% of those deaths will be from cancer. It is estimated that passive smoking (second hand smoke) in the workplace kills about 200 000 people annually. 47,49
In the United States alone, based on growth and ageing of the United States population, medical expenditures for cancer in the year 2020 are projected to reach at least US$ 158 billion (in 2010 dollars) — an increase of 27% over 2010.\textsuperscript{50} If newly developed tools for cancer diagnosis, treatment, and follow-up continue to be more expensive, medical expenditures for cancer could reach as high as US$ 207 billion. In 2010, medical costs associated with cancer were projected to reach US$ 124.6 billion, with the highest costs associated with breast cancer (US$ 16.5 billion), followed by colorectal cancer (US$ 14 billion), lymphoma (US$ 12 billion), lung cancer (US$ 12 billion) and prostate cancer (US$ 12 billion).

5.3 Affordability /Availability

More than 70% of all cancer deaths occurred in low- and middle income countries (LMICs). The high cost and poor availability of cancer treatment are significant barriers to access in many LMICs. See Appendix 6.5.3. The issue is not restricted to LMICs. In the context of a National cancer control policy (See above, Section 5.1), a commitment to monitor availability and possibly affordability would be very much needed. The high cost of cancer medicines generally remains a significant question related to the future of healthcare management and its impact on pharmaceutical pricing strategies for emerging treatments that are focused on precision, targeted agents (See Section 7.3) and often times in combination with other novel or existing treatments.

5.3.1 The complex issue of “Companion diagnostics”

The cost of diagnostics is a major issue and challenge for many of the new “personalized” treatments. Regulators and insurers are asking cancer medicine developers to market, or at least use, companion tests to pinpoint which patients are most likely to benefit from a drug, thereby sparing other patients from needless side effects and expense.

The U.S. FDA issued guidance to the industry on companion diagnostics in July 2011, asserting that if safe and effective use of a therapeutic depends on a diagnostic, then FDA generally will require approval or clearance of the diagnostic at the same time that FDA approves the therapeutic.\textsuperscript{51} As of January 2013, the final FDA guidance on this subject has not yet been formulated. The European Medicines Association (EMA) has yet to put forth specific guidance regarding companion diagnostics.

There are numerous economic, scientific and regulatory obstacles to developing companion diagnostics. As the diagnostic may not often be reimbursed in many markets around the world and if the patient cannot access the diagnostic, they will not be able to access the treatment. It is a significant gap that will need to be addressed to ensure that the right patient is benefiting from the right medicine reducing overall healthcare costs to payers and national healthcare systems.

Also, it may not be known what to test for to predict a drug’s effectiveness, or this information is not available and they don’t find out until near the end of the drug’s clinical trials. Moreover, coordinating development and approval of a drug and a test — by two separate companies reviewed by two FDA divisions — can raise the cost of drug development if not done well. Pharmaceutical companies can spend hundreds of millions of dollars to develop a drug, then can reap billions of dollars a year in sales with high profit margins. Diagnostic companies typically spend several million dollars to develop a test, with
annual revenues also around that level, and low profit margins. For pharmaceutical companies, the risk is that a test can lower sales of their drugs by restricting use to a fraction of potential patients. For diagnostic companies, there is a risk of developing a test in advance for a drug that may never reach the market.

5.3.2 Essential NCD medicines and basic technologies to treat major NCDs

The draft comprehensive global monitoring framework, including indicators, and a set of voluntary global targets for the prevention and control of noncommunicable diseases mentioned previously (http://apps.who.int/gb/NCDs/pdf/A_NCD_INF1-en.pdf) contains a comprehensive monitoring framework, one of the indicators being “availability of basic technologies and generic essential medicines required to treat major NCDs in public and private sector facilities, including primary care facilities.” The minimum list of medicines would include: medicines (at least aspirin), a statin, an angiotensin converting enzyme inhibitor, thiazide diuretic, a long acting calcium channel blocker, metformin, insulin, a bronchodilator, and a steroid inhalant. Technologies would include at least a blood pressure measurement device, a weighing scale, blood sugar, and blood cholesterol measurement devices with strips and urine strips for albumin assay.

6. Why Does the Disease Burden Persist?

Cancer is a multidimensional condition, and it is caused by both hereditary and environmental factors. Changing, and disparities in, incidence must be set against the backdrop of improvements in health and life expectancy, the changing demographics and public health improvements in hygiene, sanitation, and combating infectious diseases.

Since many cancers are due to environment or lifestyle, increases in certain cancer types (primarily lung, oral, and pharyngeal cancers) can be anticipated in countries where smoking and obesity has not been controlled. Common to many NCDs, including cancer, is the fact that many of the preventative measures involve behavioural change and these are, by their very nature, difficult to implement and sustain in a population-based manner.

A serious challenge for the future is the ageing of the population, with dramatic increases in the number of people over the age of 65 as well as increases in the number of people over the age of 80, a population that has received little attention. Due to the increase in the total population, as well as the increased cancer risk associated with ageing, we would expect the number of cancer diagnoses in Europe to continue to increase, while there will be concomitant declines in cancer mortality rates. To be sure, ageing is not the only reason why cancer incidence might rise over time. Heightened efforts in screening, diagnosis, education, basic research, tobacco control (especially among women), and other public health interventions will be required.
7. What can be Learned from Past/Current Research into Pharmaceutical Interventions for this Condition?

7.1 Vaccines

Cancer chemoprevention refers to the use of pharmacological agents to inhibit, delay, or reverse the multi-step process of carcinogenesis. Epidemiological studies suggest a protective role of several agents in reducing the risk of cancer. Vaccines targeting infections with hepatitis B virus, a risk factor for hepatocellular cancer, and human papillomavirus, a risk factor for cervical cancer, are considered major clinical cancer chemoprevention successes.

Nevertheless, the broad translation of chemoprevention to the clinic is not yet a reality. Cancer is a comparatively infrequent event, and clinically overt cancer usually takes many years to develop. Clinical trials to test the effectiveness of chemopreventive agents therefore require large study populations and a long-term commitment of resources. The availability of biomarkers as surrogate end points for clinical disease would allow smaller trials of shorter duration, facilitating clinical research into chemoprevention. In this regard, it is useful to talk about the risk benefit ratio of vaccines and of cancer therapeutics generally.

In Europe, part of the mandate of the Committee for Medicinal Products for Human Use (CHMP) is to assess risks and benefits of authorized medicines on behalf of the European Medicines Agency (EMA). In 2007, the CHMP revised its guidance and included quantitative risk-benefit analyses in the regulatory agenda. Although no specific method was recommended, several risk-benefit analysis (RBA) features were noted as being of value, including 1) all important benefits and medically serious risks are identified; and 2) the risks and benefits are weighted according to their relative importance and the strength of the evidence available.

Many payers now use health technology assessments (HTAs) to weigh the additional expense of a new drug against the increase in effectiveness it delivers over the current standard of care. The standard bearer for such assessments has been the UK's National Institute for Health and Clinical Excellence (NICE), which uses the quality-adjusted life year, or QALY, to compare the value and/or health gain of a new product against a comparator drug. Drugs that NICE considers to have a QALY of over £30 000 (US$ 49 000) rarely receive reimbursement.

7.2 Personalized medicine and biomarkers

Genomic technologies, especially next-generation or massively parallel sequencing, has allowed study designs involving understanding gene sequences to be done more quickly while potential lowering the cost and increased the throughput of analyzing tumors. There exists also an information technology structure that allows massive amounts of data to be processed and managed. Arguably, this “era” of personalized medicine in cancer began when in 1998 the FDA approved the use of trastuzumab in metastatic breast cancer patients whose tumors were human epidermal growth factor receptor (HER) 2-positive. The FDA has approved at least 11 tests that either predict response to specific medications or risk of recurrence in malignancies like non-small cell lung cancer (NSCLC), colon, breast, and...
gastric cancer, and chronic myelogenous leukemia. The tests, using a variety of methods, can identify a host of biochemical changes in cancer, including somatic and inherited mutations, polymorphisms, gene expression, amplification or copy number variations, and protein over-expression, loss, mutations and copy number variations as well as other biomarkers.

As an example of how “personalized medicine‘ is changing the regulatory environment, the FDA in 2011 approved Roche’s vemurafenib to treat patients with metastatic or inoperable melanoma whose tumors test positive for a specific gene mutation (BRAF V600E mutation). FDA coupled approval of the drug with a companion diagnostic. Also in 2011, Pfizer’s crizotinib was approved to treat late stage lung cancer, along with a diagnostic to detect abnormal anaplastic lymphoma kinase (ALK) gene expression.

Implementation of these “personalized” medicines is very complex from a drug development as well as from a regulatory perspective and pharmaceutical companies will have to factor in development of diagnostics for identified predictive biomarkers as an investment in this approach.

7.3 Targeted Therapy

Today’s emerging targeted therapies are designed to destroy specific cancerous cells and leave healthy cells intact. Targeted therapies are per definition likely to be more effective at earlier stage where the driver for the tumour growth is the particular target. At later stage disease many mechanisms drive growth. One of the more recent examples includes imatinib mesylate

(Gleevec® in the United States, Glivec® outside the United States), which is a specific inhibitor for tyrosine kinase in Philadelphia chromosome positive chronic myeloid leukemia (CML) and gastrointestinal stromal tumours (GIST). Gleevec® serves a defined but small population, and this is the case with targeted therapies. Thus, the trend in targeted therapy is towards many niched treatments rather than sweeping standard therapies as we have had with chemotherapy. Other drugs work in a similar way, including erlotinib (Tarceva®) for a form of lung cancer, bevacizumab (Avastin®) for breast, colorectal and other cancers, and sunitinib (Sutent®) for renal cell carcinoma and gastrointestinal sarcoma.

In principle, targeted therapies can be tailored to the genetic mechanisms responsible for a particular patient’s tumour. Therefore, one could control a particular cancer’s runaway growth properties, thus controlling the growth of the malignancy in the body and causing the cancer to exist chronically within the body. There are, however, tremendous hurdles to overcome. Most tumours grow by multiple mechanisms so that preventing one such mechanism might not be enough and since cancer cells mutate rapidly, tumours can evolve resistance, sometimes very quickly, and neighboring cells in a tumour might be different and not susceptible to the same drug. The vemurafenib/crizotinib examples, cited above in Section 7.2, show that ‘personalized medicines’ might overcome this issue, given the importance of specific genetic biomarkers.

The first molecular target for targeted cancer therapy was the cellular receptor for the female sex hormone estrogen, which many breast cancers require for growth. When estrogen binds to the estrogen receptor (ER) inside cells, the resulting hormone-receptor complex activates the expression of specific genes, including genes involved in cell growth and proliferation.
Research has shown that interfering with estrogen’s ability to stimulate the growth of breast cancer cells that have these receptors (ER-positive breast cancer cells) is an effective treatment approach. Several drugs that interfere with estrogen binding to the ER have been approved by the FDA for the treatment of ER-positive breast cancer. These include selective estrogen receptor modulators (SERMs), including tamoxifen and toremifene (Fareston®), which bind to the ER and prevent estrogen binding.

Another drug, fulvestrant (Faslodex®), binds to the ER and promotes its destruction, thereby reducing ER levels inside cells. Aromatase inhibitors (AIs) are another class of targeted drugs that interfere with estrogen’s ability to promote the growth of ER-positive breast cancers. The enzyme aromatase is necessary to produce estrogen in the body. Blocking the activity of aromatase lowers estrogen levels and inhibits the growth of cancers that need estrogen to grow. Aromatase inhibitors are used mostly in women who have reached menopause because the ovaries of premenopausal women can produce enough aromatase to override the inhibition. Three AIs have been approved by the FDA for the treatment of ER-positive breast cancer: Anastrozole (Arimidex®), exemestane (Aromasin®), and letrozole (Femara®).

### 7.3.1 A note on Immunotherapy

We briefly only mention a few points about this subject, as a review of this type cannot be fully comprehensive. One of the new trends in the development of cancer therapy has been the involvement of the body’s immune system, which is our primary defense mechanism against disease. The general idea is to develop new therapies that direct our immune system response against cancer cells, which results in their destruction through a natural and highly effective system. This is in contrast to chemotherapy, which destroys normal and cancer cells.

Provenge (sipuleucel-t) in Section 7.3, is but one example. Another is ipilimumab (see Table 6.4D), a monoclonal antibody inhibitor of a protein call CTLA-4 which keeps Cytotoxic T lymphocytes "in check" through one of the body's mechanisms. Through its mechanism of action, it frees one of the natural restrictions put on the immune system to allow for targeting of malignant melanoma cells to great success.

Adoptive cell therapy (ACT), which is the administration of a patient’s own (autologous) or donor (allogeneic) anti-tumour lymphocytes following a lymphodepleting preparative regimen, has emerged as an effective treatment for patients with metastatic melanoma. Studies have demonstrated that normal human lymphocytes can be genetically engineered to recognize cancer antigens and mediate cancer regression in vivo has opened opportunities for enhancing and extending the ACT approach to patients with a wide variety of cancer types. 54

Therapeutic antibodies (Table 6.4A) currently provide clinical benefit to patients with cancer and have been established as 'standard of care' agents for several highly prevalent human cancers. The next generation of unconjugated antibody therapies will undoubtedly yield many effective new treatments for cancer over the next decade. These advances will arise from the identification and validation of new targets, the manipulation of tumour–host microenvironment interactions, and the optimization of antibody structure to promote the amplification of antitumour immune responses. 55
7.3.2 Examples of targeted therapies

Some targeted therapies block specific enzymes and growth factor receptors involved in cancer cell proliferation. These drugs are sometimes called signal transduction inhibitors. See Table 6.4.A. Note that all the names of the medicines in the following Tables are hyperlinked to the NCI clinical trial database at www.cancer.gov.

Table 6.5.1a: Signal Transduction Inhibitors in clinical trials (as of March 2013)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indication (FDA)</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib mesylate</td>
<td>variety of cancers</td>
<td>targets several members of a class of proteins called tyrosine kinase enzymes that participate in signal transduction</td>
</tr>
<tr>
<td>(Gleevec®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dasatinib</td>
<td>approved to treat some patients with chronic myelogenous leukemia (CLL) or acute lymphoblastic leukemia (ALL)</td>
<td></td>
</tr>
<tr>
<td>(Sprycel®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nilotinib</td>
<td>approved to treat some patients with CML</td>
<td>small-molecule tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>(Tasigna®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosutinib</td>
<td>CML</td>
<td>small-molecule tyrosine kinase inhibitor.</td>
</tr>
<tr>
<td>(Bosulif®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>certain types of breast cancer</td>
<td>antibody that binds to the human epidermal growth factor receptor 2 (HER-2). HER-2 antigen-binding domain</td>
</tr>
<tr>
<td>(Herceptin®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>used in combination with trastuzumab and docetaxel to treat metastatic breast cancer that expresses HER-2</td>
<td>Antibody likely prevents HER-2 from sending growth signals and induces the immune system to attack HER-2-expressing cells.</td>
</tr>
<tr>
<td>(Perjeta™)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>advanced or metastatic breast cancer.</td>
<td>small-molecule drug inhibits several tyrosine kinases, including the tyrosine kinase activity of HER-2.</td>
</tr>
<tr>
<td>(Tykerb®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td>advanced non-small cell lung cancer.</td>
<td>inhibits tyrosine kinases of epidermal growth factor receptor (EGFR).</td>
</tr>
<tr>
<td>(Iressa®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>metastatic non-small cell lung cancer and pancreatic cancer</td>
<td>inhibits the tyrosine kinase activity of EGFR,</td>
</tr>
<tr>
<td>(Tarceva®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td>squamous cell carcinoma of the head and neck or colorectal cancer</td>
<td>Antibody binds to the external portion of EGFR, thereby preventing the receptor from being activated by growth signals,</td>
</tr>
<tr>
<td>(Erbitux®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panitumumab</td>
<td>metastatic colon cancer.</td>
<td>Antibody binds to EGFR and prevents it from sending growth signals.</td>
</tr>
<tr>
<td>(Vectibix®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>advanced renal cell carcinoma.</td>
<td>specific inhibitor of a serine/threonine kinase called mTOR that is activated in tumour cells</td>
</tr>
<tr>
<td>(Torisel®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>advanced kidney cancer</td>
<td>binds to a protein called immunophilin FK binding protein-12, forming a complex that in turn binds to and inhibits the mTOR kinase.</td>
</tr>
<tr>
<td>(Afinitor®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vandetanib</td>
<td>metastatic medullary thyroid cancer</td>
<td>binds to and blocks the growth-promoting activity of several tyrosine kinase enzymes,</td>
</tr>
<tr>
<td>(Caprelsa®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>inoperable or metastatic melanoma.</td>
<td>blocks the activity of a permanently activated mutant form of the serine/threonine kinase BRAF (known as BRAF V600E).</td>
</tr>
<tr>
<td>(Zelboraf®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crizotinib</td>
<td>locally advanced or metastatic non-small cell lung cancer.</td>
<td>inhibits the tyrosine kinase activity of a fusion protein called EML4-ALK, resulting in decreased tumour cell growth,</td>
</tr>
<tr>
<td>(Xalkori®)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Other targeted therapies modify the function of proteins that regulate gene expression and other cellular functions. (Table 6.5.1.b)

Table 6.5.1.b: Regulators of gene expression and cell function in clinical trials (as of March 2013)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indication (FDA)</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vorinostat (Zolinza®)</td>
<td>cutaneous T-cell lymphoma (CTCL)</td>
<td>inhibits the activity histone deacetylases (HDACs), HDAC inhibitors can induce tumour cell differentiation, cell cycle arrest, and apoptosis.</td>
</tr>
<tr>
<td>Romidepsin (Istodax®)</td>
<td>CTCL</td>
<td>inhibits members of one class of HDACs and induces tumour cell apoptosis.</td>
</tr>
<tr>
<td>Bexarotene (Targretin®)</td>
<td>CTCL</td>
<td>retinoids, which are chemically related to vitamin A. Bexarotene binds selectively to, and thereby activates, retinoid X receptors. Once activated, these nuclear proteins act in concert with retinoic acid receptors to regulate the expression of genes that control cell growth, differentiation, survival, and death.</td>
</tr>
<tr>
<td>Alitretinoin (Panretin®)</td>
<td>cutaneous lesions in patients with AIDS-related Kaposi sarcoma</td>
<td>binds to both retinoic acid receptors and retinoid X receptors.</td>
</tr>
<tr>
<td>Tretinoin (Vesanoid®)</td>
<td>induction of remission in certain patients with acute promyelocytic leukemia.</td>
<td>retinoid binds to and thereby activates retinoic acid receptors.</td>
</tr>
</tbody>
</table>

Other targeted therapies block the growth of blood vessels to tumours (angiogenesis). To grow beyond a certain size, tumours must obtain a blood supply to get the oxygen and nutrients needed for continued growth. Treatments that interfere with angiogenesis may block tumour growth. Table 6.5.1.c.
Table 6.5.1.c: Angiogenesis and growth factor antagonists in clinical trials (as of March 2013)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indication (FDA)</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (Avastin®)</td>
<td>glioblastoma. non-small cell lung cancer, metastatic colorectal cancer, and metastatic kidney cancer.</td>
<td>binds to VEGF and prevents it from interacting with receptors on endothelial cells,</td>
</tr>
<tr>
<td>Ziv-aflibercept (Zaltrap®)</td>
<td>metastatic colorectal cancer</td>
<td>By binding to VEGF, ziv-aflibercept prevents it from interacting with receptors on endothelial cells,</td>
</tr>
<tr>
<td>Sorafenib (Nexavar®)</td>
<td>advanced renal cell carcinoma and some cases of hepatocellular carcinoma</td>
<td>blocks an enzyme that is involved in cell growth and division.</td>
</tr>
<tr>
<td>Sunitinib (Sutent®)</td>
<td>metastatic renal cell carcinoma, gastrointestinal stromal tumour</td>
<td>small-molecule tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>Pazopanib (Votrient®)</td>
<td>advanced renal cell carcinoma and advanced soft tissue sarcoma</td>
<td>small-molecule inhibitor of several tyrosine kinases,</td>
</tr>
<tr>
<td>Regorafenib (Stivarga®)</td>
<td>metastatic colorectal cancer</td>
<td>small-molecule inhibitor of several tyrosine kinases that are involved in angiogenesis and tumour cell growth,</td>
</tr>
<tr>
<td>Cabozantinib (Cometriq™)</td>
<td>metastatic medullary thyroid cancer.</td>
<td>small-molecule inhibitor of several tyrosine kinases</td>
</tr>
</tbody>
</table>

Some targeted therapies act by helping the immune system to destroy cancer cells. Table 6.5.1.d

Table 6.5.1.d: Immunomodulators in clinical trials (as of March 2013)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indication (FDA)</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab (Rituxan®)</td>
<td>B-cell non-Hodgkin lymphoma chronic lymphocytic leukemia (CLL).</td>
<td>CD20 that is found on B cells. When rituximab binds to these cells, it triggers an immune response that results in their destruction.</td>
</tr>
<tr>
<td>Alemtuzumab (Campath®)</td>
<td>B-cell CLL.</td>
<td>antibody directed against CD52, a protein found on the surface of normal and malignant B and T cells and many other cells of the immune system. Binding triggers an immune response that destroys the cells.</td>
</tr>
<tr>
<td>Ofatumumab (Arzerra®)</td>
<td>CLL</td>
<td>antibody is directed against the B-cell CD20 cell surface antigen.</td>
</tr>
<tr>
<td>Ipilimumab (Yervoy™)</td>
<td>metastatic melanoma</td>
<td>By inhibiting CTLA-4, ipilimumab stimulates the immune system to attack melanoma cells.</td>
</tr>
</tbody>
</table>
Another class of targeted therapies includes monoclonal antibodies that deliver toxic molecules to cancer cells specifically. Table 6.5.1.e

### Table 6.5.1.e: Site-specific targeted monoclonal antibodies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indication (FDA)</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tositumomab and 131I-tositumomab (Bexxar®)</td>
<td>B-cell non-Hodgkin lymphoma.</td>
<td>mixture of monoclonal antibodies that recognize the CD20 molecule. Some of the antibodies in the mixture are linked to a radioactive substance called iodine-131.</td>
</tr>
<tr>
<td>Ibritumomab tiuxetan (Zevalin®)</td>
<td>B-cell non-Hodgkin lymphoma</td>
<td>monoclonal antibody directed against CD20 that is linked to a molecule that can bind radioisotopes such as indium-111 or yttrium-90.</td>
</tr>
<tr>
<td>Denileukin diftitox (Ontak®)</td>
<td>CTCL</td>
<td>interleukin-2 (IL-2) protein sequences fused to diphtheria toxin. The drug binds to cell surface IL-2 receptors, directing the cytotoxic action of the diphtheria toxin to these cells.</td>
</tr>
<tr>
<td>Brentuximab vedotin (Adcetris®)</td>
<td>systemic anaplastic large cell lymphoma and Hodgkin lymphoma</td>
<td>monoclonal antibody directed against a molecule called CD30, which is found on some lymphoma cells, linked to a drug called monomethyl auristatin E (MMAE).</td>
</tr>
</tbody>
</table>

Nevertheless, targeted therapies have some limitations. Chief among these is the potential for cells to develop resistance to them. In some patients who have developed resistance to imatinib, for example, a mutation in the BCR-ABL gene has arisen that changes the shape of the protein so that it no longer binds this drug as well. In most cases, another targeted therapy that could overcome this resistance is not available. It is for this reason that targeted therapies may work best in combination, either with other targeted therapies or with more traditional therapies.

### 7.4 Tumour Vaccines: Therapeutic versus preventive vaccines

Anti-tumour vaccines are effective in preventing a subsequent tumour challenge in animals — this is a well-substantiated observation established through tumour-challenge animal model experiments in which, immunization against a tumour antigen (e.g., a protein) is followed by a challenge with a lethal dose of a transplantable tumour. Vaccines being tested in these models range from those consisting of live, irradiated or genetically modified tumour cells, proteins, peptides or naked DNA. In mice, effective immunity is often elicited and a successful pre-immunization against almost any kind of tumour seems to be feasible as a preventative measure.56

The U.S. Food and Drug Administration (FDA) has approved two vaccines, Gardasil® and Cervarix®, that protect against infection by the two types of HPV—types 16 and 18HPV types 16 and/or 18 also cause some vaginal, vulvar, anal, penile, and oropharyngeal cancers. In addition, Gardasil® protects against infection by two additional HPV types, 6 and 11,
which are responsible for about 90 percent of all cases of genital warts in males and females but do not cause cervical cancer. The FDA has also approved a cancer preventive vaccine that protects against HBV infection. The following are links to the NCI site listing the various clinical trials for preventative vaccines against Cervical Cancer and Solid Tumours.

However, therapeutic immunization in the setting of established, chronic disease such as breast cancer, colorectal cancer and the like has been much less successful. Transfer of experimental results with preventative vaccines to the clinical setting and the prospect of curing cancer with therapeutic vaccines are in principle seen as feasible goals. There are many clinical trials but the results achieved so far, however, have been poor; partial responses are rare and complete responses extremely rare. Only in a few patients has the progression of previously growing tumours been halted and prolonged survivals observed.57

The FDA has approved immunotherapeutic cancer treatment vaccine for certain men with metastatic prostate cancer called Sipuleucel-T (Provenge®). This vaccine is made specially for each man – it is not mass produced. To make it, white blood cells are removed from the patient's blood over a few hours while he is hooked up to a special machine. The cells are then sent to a lab, where they are exposed to a protein from prostate cancer cells called prostatic acid phosphatase (PAP). The cells are then sent back to the doctor’s office or hospital, where they are given back to the patient by vein (IV). In the body, the cells help other immune system cells to attack the prostate cancer.

Researchers are developing treatment vaccines against many types of cancer and testing them in clinical trials. Cancer treatment vaccines are designed to work by activating B cells and killer T cells and directing them to recognize and act against specific types of cancer. They do this by introducing one or more molecules known as antigens into the body, usually by injection. An antigen is a substance that stimulates a specific immune response. An antigen can be a protein or another type of molecule found on the surface of or inside a cell. The list below shows the types of cancer that are being targeted in active cancer prevention or treatment clinical trials using vaccines. The names are linked to the NCI clinical trials website www.cancer.gov.

Active Clinical Trials of Cancer Treatment Vaccines by Type of Cancer:

Brain Tumours; Breast Cancer; Cervical Cancer; Hodgkin Lymphoma; Kidney Cancer; Leukemia; Lung Cancer; Melanoma; Multiple Myeloma; Non-Hodgkin Lymphoma; Pancreatic Cancer; Prostate Cancer; Solid Tumours.
8. The Cancer pipeline

More oncology drugs are available in the United States, and the costs for a higher share of these medicines are reimbursed. The evidence-based approach, which includes health technology assessment, adopted by European systems has improved the affordability of drugs in Europe that are considered to be cost-effective. Regulatory approval in Europe does not imply reimbursement, as the evidence threshold for reimbursement is higher than in the United States. In general, regulatory approval for oncology drugs is faster in the United States than in Europe.58

We looked at the United States pharmaceutical industry association (PhRMA) website 59 and tallied the total number of therapeutics for all types of cancer. We had found 317 distinct drugs in 2003. The pharmaceutical industry now has 887 distinct cancer drugs in development, which is over 30% of its entire portfolio of new drug candidates according to PhRMA.60 The industry is putting much research and development resources in cancer therapeutics.

However, the business reality is that since there are fewer cancer patients than there are people with chronic conditions like elevated cholesterol. Moreover, many cancer patients unfortunately do not live very long, therefore the prices of medicines needed to support the industry’s oncology sector current size, structure and profits must be substantially higher. Therefore, pressures on health systems in light of the ageing population and increase in prevalence of NCDs means that countries will need to develop robust mechanisms for assessing relative benefit to society. The national cancer control policies (See above, Section 4) provides a useful framework for governments to set priorities.

Figure 6.5.8 shows the total number of medicines for various cancers in the U.S. pipeline as of 2012 (PhRMA). Many medicines are found in more than one cancer category. The majority of medicines are for approximately 10 cancers: leukemias, breast, prostate, colorectal, melanoma, ovarian, pancreatic, kidney, liver, and lymphomas. This cross-sectional ‘snapshot’ shows that there are more medicines in Phase II trials than Phase I and, as expected, less in Phase III. As one might also expect, the number of medicines in the pipeline generally for some cancers (CNS, nasopharyngeal, orofacial and so on) are quite low. See Annex 6.5.1.
Do these myriads of cancer medicines bear any relationship to the size of the cancer market? One could expect that, regardless of whether supported by the public or private sectors, the number of therapeutics are ultimately driven by the size of the cancer market.

However, possibly the opposite is going on – with our increasing learning on mutations that can be targeted, the patient population with specific mutations will be small, much smaller than the formerly developed cytotoxic drugs that were given to all patients with a cancer in one specific organ. This is true also for small cancer types that are increasingly being targeted by the pharmaceutical industry with specific drugs.

We ranked various cancers according to their mortality in the United States (combined male and female, all races: mortality per 100 000 persons average between 2004 and 2009 and age adjusted to the 2000 USA standard population.  

Using the PhRMA dataset, above, for a given cancer type we predicted the number of medicines in the pipeline by scaling the total number of medicines in Phase I, II or III to a measure of the aged-adjusted mortality of the that cancer type. Specifically, our scalar was:

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(adjusted mortality rate of cancer \( \times \) total mortality rate of all cancers). Thus, if the total number of medicines for all cancers in Phase I is 100, and the breast cancer mortality scalar is 0.10, we predict there should be 10 medicines for breast cancer (100 * (0.10)) in Phase I if cancer research and development (R&D) is driven entirely by the “market” (i.e. the integrated death rate of breast cancer averaged over several years).

Figures 6.5.9, 6.5.10, and 6.5.11 show the actual number of cancer medicines in the three phases and the predicted number of cancer medicines based on the total cancer medicines in each phase and the scalar (mortality rate of cancer \( \times \) total mortality rate of all cancers). The qualitative prediction, aside from lung cancer, appears quite good for Phase I but then becomes progressively less predictive in Phase III. Remarkably and consistently, there seem to be fewer medicines for lung cancer than one would predict from knowledge of the lung cancer mortality rate.

Figure 6.5.9: Actual number of medicines and predicted number based on mortality rate of different cancers

![Medicines in Phase I](source: U.S. Clinical Trials Database at [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov))

have used mortality data, however, because cancers are often, but not invariably, fatal and it was more readily available than prevalence.
Figure 6.5.10: Actual number of medicines and predicted number based on mortality rate of different cancers

![Medicines in Phase II](image)

Source: U.S. Clinical Trials Database at [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Figure 6.5.11: Actual number of medicines and predicted number based on mortality rate of different cancers

![Medicines in Phase III](image)

Source: U.S. Clinical Trials Database at [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)

We repeated this using the United States clinical trials database\(^2\) and would expect similar results.

Figure 6.5.12 shows the relationship between the actual number of cancer trials as of late 2011 (X axis: total cancer trials = 14 058; all phases) in the database for various cancers and
the predicted number of clinical trials (scaled based on the United States mortality rates, as cited above) for these cancers.

Figure 6.5.12: Actual and predicted number of cancer trials

![Graph showing actual and predicted number of cancer trials](image)

Source: U.S. Clinical Trials Database at [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)

The relatively “poor showing” for lung or bronchus cancers is, unsurprisingly, consistent with the analysis of medicines in the pipeline. We are not able to explain this apparent discrepancy between the high mortality for lung cancer and the relatively few clinical trials and new medicines for this condition. We cannot distinguish between targeted therapies and more generalized chemotherapies in this analysis.

The principal, and rebuttable, presumption of this brief analysis is that mortality rate is a proxy for “market size” and these Figures in particular show a remarkably consistent relationship between the number of medicines (whether targeted or “personalized” or chemotherapeutic) in clinical trials for a given cancer and mortality rate (e.g. size of the market) of that cancer—a proposition that makes intuitive sense. The glaring exception is lung cancer.

It appears from this crude analysis that the pharmaceutical industry is correctly judging their efforts and that overall drug development for most cancers in the public and private sectors is roughly congruent with the mortality (e.g. “market”) for that cancer. Various cancers might

---

These figures show the data as a continuous function but they are not, as the data are discrete and could also be shown as a series of vertical bar graphs. The connected points are, however, easier to visualize. The clinical trials are [interventional trials only](http://www.clinicaltrials.gov) but may include procedures and devices as well as pharmaceuticals. We made no attempt to exclude trials for devices and procedures.
be underrepresented or overrepresented (melanoma, pancreas) based on “market” but the limits of the data cannot suggest a more nuanced statement.

Text Box: Transforming Treatment of Cancer

Gleevec®, also marketed internationally as Glivec and sometimes referred to by its chemical name imatinib, was initially approved for use by the U.S. Food and Drug Administration (FDA) in 2001 for the treatment of chronic myelogenous leukemia (CML), a rare form of cancer that affects certain types of white blood cells. Imatinib acts by specifically inhibiting a receptor tyrosine kinase enzyme that is characteristic of particular cancer cells, rather than non-specifically inhibiting and killing all rapidly dividing cells. By 2011, Gleevec® had been FDA approved to treat ten different cancers. Currently, scientists continue to study the drug’s effectiveness not only in various cancers, but also in other diseases, such as stroke (Su et al., 2008).

It has had a phenomenal success rate against CML. In one of the first clinical studies described in the medical literature, it was reported that "[c]omplete hematologic responses were observed in 53 of 54 patients with CML treated with daily dosage of 300 mg or more and typically occurred in the first four weeks of therapy” (Druker et al., 2001). In the case of CML, patients have too many immature white blood cells in their bone marrow and blood, a complete hematologic response occurs when the patient's white blood cell count returns to within normal range. More recently, Druker et al. found that, after 60 months of Gleevec® therapy, 98% of patients had shown a complete hematologic response. Also at 60 months, the estimated overall survival rate for patients was 89% with a relapse rate of only about 17% (Druker et al., 2006).

Arguably, Gleevec® has transformed CML treatment. In the past, the only options patients had were either bone marrow transplantation, which had serious side effects and was often fatal (and only about 20% to 25% of patients were eligible for the procedure because of age or other factors), or daily interferon infusions. The latter also had serious side effects and, moreover, was not a cure but merely a way to prolong survival. Thus, before Gleevec®, only 30% of patients with CML survived for even five years after being diagnosed (Pray 2008).

Gleevec® may be an exceptional case, and the same success may not be achieved with other cancers. Significantly, unlike most other cancers, which are caused by complex interacting factors and therefore have many potential therapeutic targets, CML is caused by a single aberrant protein related to a consistent chromosomal translocation. The Gleevec® story is a good example of how knowledge of the biological functioning of a cell can lead to life-saving medical treatment (Pray 2008).


9. Funding for Cancer R&D

Cancer research has a multi-billion Euro global network covering most domains of science and including all manner of research funders from industry to government and philanthropic funders.\textsuperscript{63} Europe and the USA account for the majority of global cancer funding with a combined spend of over €8 billion per annum, compared to circa €3 billion for the rest of the world. Despite different absolute spends Australia, Canada, and Japan have broadly similar per capita spending (this similarity remains regardless of comparative denominator (e.g. GDP) at €7.93, €8.27 and €7.88, respectively.\textsuperscript{63} In comparison, Europe as a whole only spends €5.79, however, when one views European cancer research spend as only those original EU15 Member States then this figure dramatically rises to €8.20. At €17.98 per capita, USA funding is one of the highest in the world along with the UK, which spends some €18.5 per capita (€13.18 of this comes directly from funding organizations and the remainder flows through infrastructure funding to the university and healthcare systems).\textsuperscript{63}

9.1 Europe

The next Framework Programme for Research and Innovation (2014 –2020) is Horizon2020. It is designed to address the major societal that need translational action, including “Health, demographic change, and well-being” theme. With a proposed budget of €80.8 billion over seven years, it will unite all EU funding in research and innovation in a single programme and support every stage of the innovation ecosystem “from research to retail”.

9.1.1 P 7: Final work programme: Cancer

See reference 64 and 65

The Seventh Framework Programme for Research and Technological Development (FP7, 2007–2013) has dedicated over €1.1 billion to cancer research, using a variety of funding mechanisms including collaborative research, frontier research, mobility programmes, public-private partnerships, and coordination of national research activities to strengthen the innovative translation of research discoveries to clinical application. With regard to cancers, research is supposed to focus on identification and validation of drug targets; prevention, early diagnosis, prognosis and treatment biomarkers; as well as on assessment of various preventive, diagnostic, prognostic, and therapeutic interventions. We note that the clinical trials to be supported will have to be registered in a publicly accessible clinical trials registry and their results published in peer-reviewed journals. Significantly, “patient advocacy groups which can contribute to the quality, feasibility and impact of clinical trials, may be involved where appropriate.” For this subject, the requested EU contribution per project shall not exceed €6 million.\textsuperscript{65}

The European Commission is also partnering with the European pharmaceutical industry to fund research via the Innovative Medicines Initiative (IMI), through which close to €80 million (of which €38 million is from FP7) have been devoted to cancer therapeutics research. For example, in the Sixth and Seventh Framework Programmes (FP6, FP7), 22 projects focused on child and adolescent cancers and were supported with a total budget of close to €150 million, €75 million of which was in FP7. Several projects focused on specific cancers,
for example Ewing’s sarcoma, leukaemia, and lymphoma. Others aimed to reduce the long-term side effects of cancer therapy in survivors. Many research groups focused on environmental factors in childhood that may lead to increased cancer risk. Others work on improving cancer therapies for children and on developing drugs for paediatric use. Appendix 6.5.1

The priority setting for the Health Work Programme (2013) –the last annual call for proposals of the Cooperation Programme in FP7– is intended to “respond to the major health-related socio-economic and societal challenges” in view of the Europe 2020 Strategy. Two topics focused on clinical trials in cancer research and one on cancer immune system calling for projects focusing on cell, antibody, or molecule-based immunotherapy and therapeutic cancer vaccines. In all three the requested EU contribution per project shall not exceed €6 million. Regarding the clinical trials topics, the first one called for "trials to combat or prevent metastases in patients with solid cancer" and the second one for "supportive and palliative care clinical trials and observational studies". We note that the clinical trials to be supported will have to be registered in a publicly accessible clinical trials registry and their results published in peer-reviewed journals. Significantly, “patient advocacy groups which can contribute to the quality, feasibility and impact of clinical trials, may be involved where appropriate”.

A third topic is supportive and palliative care clinical trials and observational studies. As above, the clinical trials to be supported need to be registered in a publicly accessible clinical trials and patient advocacy groups can contribute to the quality, feasibility and impact of clinical trials, “may be involved where appropriate.” The requested EU contribution per project is similar to the above.

Palliative and supportive care was proposed in order to complement a growing portfolio of projects focusing on quality-of-life research funded by the 7th Framework Programme of the EC, such as:

a) PanCareSurFup: PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies, a consortium of 16 European institutions, to carry out research studies into late effects of treatment for cancer, to establish guidelines for follow-up, and to disseminate the results and provide training and workshops for stakeholders. [http://www.pancaresurfup.eu/](http://www.pancaresurfup.eu/).

b) EURO IMPACT, a project developing an educational and research training framework, aimed at monitoring and improving the quality of palliative care. [http://www.euroimpact.eu/](http://www.euroimpact.eu/).

c) PRISMA: Reflecting the Positive diverseitities of European priorities for reSearch and Measurement in end of life cAre, a project that focused on mapping differences in end of life care and culture, comparing cancer end of life care research across, Europe and beyond, and developing measurement and quality indicators and online resources to support end-of-life care and research.

d) OPCARE9: Optimising clinical care in the last days of life, provided comprehensive 'state of the art' in the field of care in the last days of life, developed new research protocols a list of resources and quality indicators for measuring care in the last days of life [http://www.liv.ac.uk/opcare9/index.htm](http://www.liv.ac.uk/opcare9/index.htm).
Notwithstanding, funding for cancer research in Europe is split almost 50:50 between philanthropic and governmental sources. In Europe the majority of the spending is concentrated (>90%) in the original 15 Member States, a situation that remains unchanged since the original Report. Contributing some €10 million to European spending was also trans-European research funders such as the EORTC.  

According to the EC, annual total EU cancer research investments in 2012 were as follows: €2 billion in governments and charity; €1.4 billion in national health systems and universities; and €1.8 billion in industry. See Appendix 6.5.4.

Estimates of cancer research spend by the major pharmaceutical companies can underestimate total global spending by omitting small and medium enterprises (SMEs) and biotech firms and current spending on pivotal Phase III clinical trials. However, an estimated gross figures of just over €3 billion per year suggests that the private sector is responsible for around a quarter of global investment in cancer research.  

To put the industry expenditure into perspective, in 2004 global pharmaceutical research and development (R&D) expenditures reached €41 billion (about US$ 56 billion) with around 7% of this flowing into cancer research. Indeed Europe attracts some 45.9% of total pharmaceutical R&D expenditure (CMR International, 2006b).  

Despite an average annual expenditure of approximately €150 million since FP6, EU efforts represent only 3.5% of the total expenditure of cancer research in the EU’s 27 Member States, showing that the bulk of research in this field is funded at the national level. See Appendix 6.5.4. The European cancer research arena is characterized by a significant degree of fragmentation and diversity (e.g. multiplicity of support mechanisms, funding bodies, barriers between disciplines, suboptimal critical mass). The necessity to better coordinate cancer research throughout Europe, which requires a strong commitment from the scientific community, is now largely recognized.

In a study completed in 2006, the USA outspent Europe three to five times as a percentage of GDP or per capita. However, the regions have radically different systems and processes for disbursing funds. Europe (in particular the original EU15 Member States) channels a substantial amount of funding for cancer research through its university and/or healthcare systems. This accounts for between 21% and 44% of overall spending depending on the Member State. In comparison, public cancer research funding in the USA is almost entirely through federal and other philanthropic organizations. Indeed despite the majority of public funding in cancer research being concentrated in a few major funding organizations across Europe (80% funds come from just 18 funders) the overall complexity of investment streams, particularly through so called infrastructure funds into healthcare systems and universities makes the development of cancer funding policies difficult.

9.1.2 Horizon 2020: The importance of palliative care

Regarding Horizon 2020, exact details of cancer funding is still in process, and first calls are not yet published. For Horizon 2020 one important area is studies around palliative care. There are some examples related to palliative care research:

a. PanCareSureFup: PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies is a consortium of 16 European institutions, funded by the
Update on 2004 Background Paper, BP 6.5 Cancer

7th Framework Programme of the EC, to carry out research studies into late effects of treatment for cancer, to establish guidelines for follow-up, and to disseminate the results and provide training and workshops for stakeholders. [http://www.pancaresurfup.eu/](http://www.pancaresurfup.eu/)

b. IMPACT: EURO IMPACT is developing an educational and research training framework, aimed at monitoring and improving the quality of palliative care. [http://www.euro-impact.eu/](http://www.euro-impact.eu/)

c. PRISM: coordinating research on end-of life care

d. OPCARE: Optimising clinical care in the last days of life

 Estimates have been made of the financial resources being applied to paediatric oncology research worldwide in 2008. The estimate was about US$ 1.23 billion, of which an estimated 53% was from public or federal sources (US$ 656 million), 27% from private, non-profit sources (US$ 328 million) and 20% (US$ 245 million) from industry. The low level of funding in many countries coupled to the very small contribution by the private sector is a major concern.

9.2 The United States

One of the unique features of the U.S. National Cancer Act in 1971 was the creation of dedicated cancer research funding (National Cancer Institute) with bypass budget authority directly to the President without need for NIH or other authorisation. USA funding of cancer research has taken a radically different direction from Europe. The funding for cancer research has seen the budget allocation grow dramatically since 2000.

While the NCI has remained the core source of cancer research funding in the USA over the years many governmental and philanthropic funders have also joined. In comparison to Europe, where the contribution of governmental and philanthropic funding is almost equal, governmental funding in the USA (mostly through the NCI) accounts for over 90% of the total spending with a total funded portfolio of research of about $2.91 billion (about €2.21 billion) in fiscal year 2011. About 80% of the total NCI accounted-for research funding for 2011 is relegated to eleven cancers (see Figure 6.5.13).
Figure 6.5.13: Cumulative percentage of total NCI funding in fiscal year 2011

Source: NCI Funded Research Portfolio.
http://fundedresearch.cancer.gov/search/funded?action=full&fy=PUB2011&type=site

Using the NCI accounted-for research funding, we did a similar univariate scalar analysis as in the Figures above to “predict” the level of funding for various cancers if the funding was based on the mortality rate in the United States. Results are shown in Figure 6.5.14. Based on its large mortality, lung cancer seems under-represented in terms of funding and thus, clinical trials, and by extension, medicines in the pipeline.
In terms of per capita spend or as a proportion of GDP, the USA enjoys one of the highest levels of funding in the world, only bettered by the UK which has seen substantial levels of growth in funding (faster even than the USA). However, the gap between allocation and spending is growing representing a real downward pressure on available funds due to the increased cost per unit of research.\textsuperscript{69}

The impact of regulatory policy on research funding and productivity remains a critical issue for all countries. As Europe has recently discovered, changes to regulatory policy can have a dramatic effect on the cost of research.\textsuperscript{70} Over the last decade the increasing regulation across all domains (e.g. clinical trials, healthcare data, human tissue) has led to an increase in the unit cost of research.

### 10. Ways Forward from a Public Health Viewpoint with Regard to Public Funding

#### 10.1 Gaps Between Current Research and Potential Research Issues which Could Make a Difference.

The therapeutic pipeline is dynamic and significant private sector funding is being put into the cancer R&D system. There remain gaps between current and potential issues that could make a difference.
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- Basic knowledge of cancer etiology and potential links with other NCDs and or infectious diseases such as HIV-AIDs.

- Basic knowledge of cancer and resistance to therapy. There are still many unmet medical needs in cancer treatment and these should be well known to those with the relevant expertise. Single platform pathology processes for improved efficiency in diagnosis.

- Getting promising drug candidates for rare cancers “off of the shelf”
  - Notwithstanding the potential significance of pharmacogenomics, large pharmaceutical firms still face substantial pressures to produce medicines targeted at large patient populations. This business reality often deters investments in treatments for rare, life-threatening diseases. In addition, this business strategy often allows drug candidates to remain untested for these rare conditions.

- Point-of-care diagnostics
  Point-of-care testing allows patient diagnoses in the doctor’s office, an ambulance, or even at home or in the field. With the development of miniaturized devices and wireless communication, the way in which doctors care for patients will change dramatically and the role patients take in their own health care will increase. Low-cost diagnostic imaging devices can be used at the point-of-patient care for disadvantaged and under-served populations in the United States as well as in the developing world. The development of low-cost imaging devices could make affordable diagnostic imaging more widely available, particularly in remote or rural communities and small hospitals that do not have ready access to these technologies.

- Prevention and risk factors:
  - For example, *H. pylori* infection is a well-established risk factor for stomach cancer, and yet optimal *H. pylori* eradication and its impact on stomach cancer incidence remain to be defined. Although HBV is associated with a majority of liver cancer cases worldwide, there are 350 million chronic HBV carriers whom HBV vaccination cannot help and in many HBV-endemic areas, dietary staples are contaminated with aflatoxins, a potent human liver carcinogen.
  - Similarly, research into cancer risk in individuals living with HIV is needed, particularly in relation to their susceptibility to other cancer-associated chronic infections.
  - As breast cancer becomes the most common cancer in women and prostate cancer incidence likewise continues to increase in men, research into the most effective early detection approaches is vital, even in many low-income countries.
11. Conclusion: Cancer medicines for Europe and the World?

This Background paper ends with a question and a challenge. Since the 2004 Priority Medicines Report, there has been an unprecedented acceleration of research and development into cancer biology and genetics, cancer therapeutics, biomarkers, and diagnostics, some of the key elements being only briefly mentioned in this Background chapter. Substantial inequalities exist in cancer survival rates across countries (see Section 3.1.3). We can prevent new cancers by reducing risk factors, but strategies are needed to close the gap between developed and developing countries in cancer survival. 

In resource-constrained countries without specialized services, cancer could be partially prevented and treated using lessons learned from the public health battle against HIV/AIDS, such as using primary and secondary caregivers to screen and continue treatment, use of generic drugs, and application of regional and global mechanisms for financing and procurement. In those countries with national health insurance, cancer treatment can be included with an emphasis on a benefits package focusing on the least wealthy. Expensive immune and targeted therapies should not only be for those in upper income countries, although we should not be so naïve as to think that these can be made accessible without reducing costs, increasing access to health services, and strengthening health systems in low- and middle-income countries.

The United Nations took the issue of noncommunicable diseases (NCDs) to its high level meeting on 19 September 2011 because of the burden of the disease and high economic cost of NCDs. There was a consensus to continue on working for targets and indicators to fight against NCDs. The recent formal meeting of Member States during 5-7 November 2012 concluded the work on the comprehensive global monitoring framework, including indicators, and set voluntary global targets for the prevention and control of noncommunicable diseases. Nine voluntary global targets and 25 indicators were agreed to have a major progression by 2025 in the prevention and control of noncommunicable diseases. New opportunities are expected from this high level political agenda.

For the EC, in the period 2014 to 2020, one challenge will be to understand the inequalities between EU countries in levels of cancer control and care, including screening and follow-up for breast, cervical and colorectal cancer. Identification and promotion of good practice in prevention, diagnosis, treatment and care of all cancer types, including paediatric cancers, across the EU will be important. In addition, collaborations between EU countries can provide the “economies of scale” needed to manage this condition more effectively across all parts of the health care system.

References


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3 Sobin et al. TNM classification of malignant tumours, 7th edition 2009 John Wiley and Sons


13 Gatta G et al., Rare cancers are not so rare: The rare cancer burden in Europe, Eur J Cancer (2011), doi:10.1016/j.ejca.2011.08.008


BMJ Clinical Evidence, Lung Cancer, November 2010 at http://clinicalevidence.bmj.com/x/systematic-review/1504/overview.html


World Health Organization, Global Health Observatory at http://apps.who.int/gho/data/#).


Global Cancer Burden Infographics at http://www.worldcancerday.org/infographics
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59 Pharmaceutical Manufacturers Association at http:www.phrma.org

60 Pharmaceutical Manufacturers Association. Medicines in Development/Cancer 2012 PhRMA


62 U.S. Clinical Trials Database at http://www.clinicaltrials.gov


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72 WHO Formal meeting of Member States to conclude the work on the comprehensive global monitoring framework, including indicators, and a set of voluntary global targets for the prevention and control of noncommunicable diseases Geneva, 5–7 November 2012, A/NCD/2, 21 November 2012 at http://apps.who.int/gb/ncds/
Annex

Annex 6.5.1: Number of cancer medicines in each phase of R&D (United States) as a function of type of cancer

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>SUM</th>
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<tr>
<td>Leukemias</td>
<td>73</td>
<td>65</td>
<td>16</td>
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<tr>
<td>Breast</td>
<td>45</td>
<td>71</td>
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<td>Prostate</td>
<td>38</td>
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<td>Colorectal</td>
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<td>Melanoma</td>
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<td>Ovarian</td>
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<td>Pancreatic</td>
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<td>Kidney</td>
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<td>Liver</td>
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<td>Lymphomas</td>
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<td>4</td>
<td>0</td>
<td>40</td>
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<td>Small cell lung</td>
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<td>16</td>
<td>1</td>
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<tr>
<td>Bladder cancer</td>
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<td>13</td>
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<td>Gastric, stomach</td>
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<td>12</td>
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<td>Brain</td>
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<td>Fallopian tube</td>
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<td>Lung cancer</td>
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<td>Esophagus</td>
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<td>Adenocarcinoma</td>
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<td>Uterine</td>
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<tr>
<td>Vulvovaginal</td>
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<td>1</td>
<td>1</td>
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<tr>
<td><strong>Total</strong></td>
<td>364</td>
<td>454</td>
<td>113</td>
<td>931</td>
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Source: PhRMA
Update on 2004 Background Paper, BP 6.5 Cancer

![Graph showing cancer rates by phase and type](image-url)

- **Phase I**
- **Phase II**
- **Phase III**

Cancer types include:
- Leukemias
- Breast
- Prostate
- Colorectal
- Melanoma
- Ovarian
- Pancreatic
- Kidney
- Liver
- Lymphomas
- Small cell
- Bladder
- Gastro
- Brain
- Thyroid
- Fallopian
- Cervical
- Lung cancer
- Esophageal
- Adenocarcinoma
- CNS cancer
- Nasopharyngeal
- Orofacial
- Uterine
- Vulvovaginal
Appendices

Appendix 6.5.1  Childhood and adolescent cancer research: EU funding (2002-2009), (2009) Office for Official Publications of the European Communities
Appendix 6.5.2  HPV vaccines; Frequently Asked Questions June 2012. GAVI Alliance
Appendix 6.5.3  Cancer Medicine Prices in low- and middle-income countries. Management Science for Health.
Appendix 6.5.4  Power Point Slides from European Commission
Background Paper 6.6
Ischaemic and Haemorrhagic Stroke

By Rachel Wittenauer and Lily Smith

December 2012
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## Summary

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## 2. Burden of stroke

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## 3. Control strategy

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## 4. Major problem and challenges of stroke management: why does the disease burden persist?

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## 5. Stroke Research from 2004 Onwards

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## 6. What are the opportunities for research into new pharmaceutical interventions that might fill the current gap and make a substantial difference?

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**Abbreviations**

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<thead>
<tr>
<th>COPD: Chronic Obstructive Pulmonary Diseases</th>
<th>LRI: Low Respiratory Infections</th>
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<tr>
<td>CT: computerized tomography</td>
<td>MRI: magnetic resonance imaging</td>
</tr>
<tr>
<td>CVA: cerebrovascular accident</td>
<td>NIHSS: National Institutes of Health Stroke Scale</td>
</tr>
<tr>
<td>DALY: disability-adjusted life years</td>
<td>NINDS: National Institute of Neurologic Diseases Study</td>
</tr>
<tr>
<td>DWI: Diffusion-weighted imaging</td>
<td>ODD, other digestive diseases</td>
</tr>
<tr>
<td>EU: European Union</td>
<td>OID, other infectious diseases</td>
</tr>
<tr>
<td>EU10: European Union’s new accession countries.</td>
<td>OUI: other unintentional injuries</td>
</tr>
<tr>
<td>EU15: European Union with 15 countries</td>
<td>QALY: Quality-adjusted Life Years</td>
</tr>
<tr>
<td>EU25: European Union with 25 countries</td>
<td>rt-PA: recombinant tissue plasminogen activator</td>
</tr>
<tr>
<td>FDA: Food and Drug Administration</td>
<td>TBLC, trachea, bronchus, lung cancers</td>
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<tr>
<td>HL, hearing loss, adult onset</td>
<td>TIA: transient ischaemic attacks</td>
</tr>
<tr>
<td>IHD: Ischaemic Heart Disease</td>
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<td>LBW: low birth weight</td>
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Summary

Stroke is an abrupt onset of a focal neurological deficit secondary to a vascular event lasting more than 24 hours. An acute stroke refers to the first 24-hour-period of a stroke event. Stroke is classified as either ischaemic (caused by thrombosis or embolisms) or haemorrhagic (caused mainly by rupture of blood vessel or aneurysm).

The occlusion of the cerebral artery causes decreased blood flow and ischaemia. Depending on the severity of the ischemia, infarction (cellular death) will occur within minutes, causing irreversible damage even after blood flow is restored. This is called the “core” of the infarct. Surrounding the core is tissue that is affected but functionally that may recover if blood flow is restored. This is called the “ischaemic penumbra”. Most people will have such an ischaemic penumbra amendable to treatment within the first three hours of occlusion of the cerebral artery, but many patients may have it up to 12 hours. This is the so-called “therapeutic window”. Thus proper identification of treatable patients is crucial for the efficacy of the interventions.

Stroke is the second leading cause of death worldwide and in the European region. Ten per cent of the 55 million deaths that occur every year worldwide are due to stroke. The overall mortality from stroke has been declining both worldwide and in Europe. This is mainly due to improved access to appropriate health care, with the consequent rise in health care costs. In Europe, discharges following hospitalization for stroke doubled during the last 15 years of the twentieth century. The United Kingdom spends 6% of its national health budget on stroke care, twice as much spent on ischaemic heart disease (IHD).

The successful management of acute stroke is based on imaging followed by two main strategies: vascular recanalization and supportive care. Differential diagnosis with haemorrhagic stroke is important. Restoration or improvement of perfusion to the ischaemic area is a key therapeutic strategy. However, currently available options, aspirin (1% better than placebo) and recombinant tissue plasminogen activator (rt-PA) (10% better than placebo) are not very effective. Current stroke therapy, therefore, is mainly based on general care and rehabilitation.

In most patients who have had a haemorrhagic stroke, current treatment focuses on evacuation of the haematoma particularly in the cerebellum, and supratentorial larger than 3 cm, despite the fact that trials have failed to show any benefit of this practice. If the haemorrhage is due to rupture of an aneurysm or AVM early surgical or endovascular intervention are important to avoid re-bleeding.

Despite improvements in care, sequelae of stroke remain a major problem. Fifty to seventy per cent of those who survive an ischaemic stroke will recover functional independence three months after onset, but 20% will require institutional care. Stroke is the second leading cause of disability in Europe after ischaemic heart disease (IHD). Worldwide, stroke is the sixth leading cause of disability. It is also the second leading cause of mortality in Europe and worldwide.
The economic impact of stroke care goes beyond the costs of sophisticated acute care, costly secondary prevention (carotid endarterectomy) and its prolonged high dependent institutional chronic care as well as costs of rehabilitation. Neither mortality rate nor hospital discharges accurately reflect the level of disability, which is mainly borne by patients and their families.

There is little progress being made in research and development of drugs for treating acute stroke, particularly in the field of neuroprotection. Surprisingly low levels of resources have been devoted to research and development of drugs for treating stroke during the last 30 years (no more than 10% of those invested in IHD or cancer).

Major improvements are needed in the chain of care for identification of stroke by relatives (education); early treatment (possibly with aspirin); the prompt referral to an accident and emergency facility (mobile units); accurate diagnosis and fast appropriate treatment (protocols and specialized units); improving access to expanded and more efficacious therapeutic options; and prompt referral to rehabilitation services.

As “time is brain”, more efficacious treatments provided early in the chain of care are needed to minimise disability and avoid future suffering as well as reducing the economic costs in societies with higher ageing populations.

1. Introduction

1.1 Definition and classification

Stroke is defined as abrupt onset of a focal neurological deficit lasting more than 24 hours. It is also called cerebrovascular accident (CVA) or apoplexy. An acute stroke refers to the first 24-hour period of a stroke. Focal neurological deficit lasting less than 24 hours (usually 5–20 minutes) known as transient ischaemic attack (TIA) is relevant but beyond the scope of this discussion paper.

Stroke is classified on the basis of its aetiology as either ischaemic (87%) or haemorrhagic (13%). Ischaemic stroke is produced by occlusion of a cerebral artery [thrombotic or atherosclerotic (50%), embolic (25%) and microartery occlusion, “lacunar stroke”, (25%)]. Haemorrhagic stroke is caused mainly by spontaneous rupture of blood vessels or aneurysms or secondary to trauma. The International Classification of Diseases versions 9 and 10 have codified the different types as 430-438 and 160-169, respectively.

1.2 Ischaemic stroke

Neurological symptoms and signs of an ischaemic stroke usually appear suddenly, but less frequently, they occur in a progressive manner (stroke-in-progress). The typical presentation is the sudden onset of hemiparesis in an older person. Symptoms and signs vary depending on the location of the occlusion and the extent of the collateral flow. Atherosclerotic ischaemic stroke is more common in the elderly, and occurs without warning in more than 80% of cases. A TIA a few months before the stroke is considered an important warning
sign. The pathophysiology is similar to that of ischaemic heart disease; an atherosclerotic plaque in a cerebral artery ulcerates triggering the aggregation of platelets and coagulation of fibrin to produce the thrombus that occludes the artery. Fewer than 20% of cases do not evolve to ulceration, but progress to cause gradual obstruction of flow and may manifest as TIA. In hypertension-induced arteriosclerosis, small penetrating arteries of the deep white matter of the brain are affected producing small infarctions known as “lacunar infarcts”. In around 40% of elderly stroke patients no clear origin of the infarction can be found.

**Embolic ischaemic stroke** is more frequent in patients with atrial fibrillation (80%), myocardial infarction, prosthetic valves, rheumatic heart disease and larger artery atheroma (artery-artery embolus). Most emboli are of atherosclerotic origin, and may partially or temporally obstruct cerebral arteries causing TIA. Embolisms tend to be multifocal and may produce small haemorrhages around the obstruction.

The occlusion of a cerebral artery causes decreased blood flow and ischaemia. If it lasts only a few seconds or a minute, recovery is immediate and complete. Depending on the severity of the ischemia, infarction (cellular death) will occur within minutes, causing irreversible damage even after blood flow is restored. This is called the “core” of the infarct. Surrounding the core is tissue that is affected functionally due to diminished circulation but may recover if blood flow is restored. This is called the “ischaemic penumbra” of a stroke. Most people will have an ischaemic penumbra amenable to treatment for 3 hours, but many patients may have it up to 12 hours. This is known as the ‘therapeutic window’ available for thrombolysis. Thus proper identification of treatable patients is crucial for the efficacy of the interventions.

Due to changes in the vessels and parenchyma caused by ischaemia, the flow may not be restored even after the original cause of the obstruction has been removed (“no-reflow phenomenon”). Oedema is present in all necrotic tissue. In large areas of necrosis, massive oedema compresses adjacent tissue, which increases intracranial pressure and may cause herniation of the brain, leading to death within a few days in 80% of cases. Surgical decompression has been suggested for these cases. The extent of functional disability will depend on the extent and the localization of ischaemia and complications experienced by the patient.

Seizures at the time of stroke occur in 3–5% of infarctions, more often after embolism than thrombosis. The same proportion of patients will develop epilepsy from 6 to 18 months after a stroke. Idiopathic epilepsy in the elderly, therefore, may be the result of silent cortical infarction.

### 1.3 Haemorrhagic stroke

There are two types: one resulting from intracerebral haemorrhage secondary to hypertension, cerebral amyloid angiopathy, or degenerative arterial disease; and the other secondary to subarachnoid haemorrhages caused by rupture of an aneurysm. In the United States, 8–10 million people (3% prevalence) might have an aneurysm, and bleeding occurs in only 30 000 people per year. Other causes are uncommon, and sometimes, no source for the haemorrhage can be found. The main risk factors are advanced age, heavy alcohol consumption and hypertension. Cocaine abuse is an important cause of cerebral haemorrhage in young people.
Most intracerebral haemorrhagic strokes develop over 30–90 min. Symptoms will depend on the location and extent of the haemorrhage. Focal neurological symptoms, vomiting and drowsiness are common. Headache may be present, but stiff neck and seizures are uncommon. Large haemorrhages may cause stupor or coma. Most sub-arachnoid haemorrhages appear suddenly with intense headache, vomiting and neurological deficit and altered consciousness may occur in about 50% of patients. Occasionally, prodromal neurological symptoms, such as paralysis of a limb, difficulty in speaking, visual impairment or sudden unexplained headache, appear before a haemorrhage from an enlarging aneurysm causing pressure on the surrounding tissue or as a result of a leak of blood into the subarachnoid space (“warning leaks”).

Cerebral vasospasm is an early complication and re-bleeding or hydrocephalus may be complications of SAH in 30% of cases during the first month, resulting in an extra 60% mortality. Of those who survive, more than half will have significant disabilities. The annual risk of recurrence of bleeding of an aneurysm is 3%. Thus, early surgical or intravascular treatment of aneurysm in these patients improves their long term outcome. The effectiveness of evacuation of a supratentorial haematoma due to other causes has not been evaluated. However, surgical removal of a large cerebellar haematoma is the current practice.

**Acute Stroke Basics:**

A stroke results from sudden decrease of blood flow to the brain which causes rapid loss of function. Its symptoms, including hemiparesis, vomiting, drowsiness, and loss of consciousness, often go unrecognized as a stroke until after the acute treatment window has passed. Stroke causes a high burden of death and disability, both in Europe and around the world.

### 1.4 Investigation of a stroke

Outcome of investigations are crucial for effective management of acute stroke. Computerised tomography (CT) is the most immediately useful imaging method in identifying/differentiating cerebral haemorrhage from infarction. However, during the first few hours following ischaemic stroke, a CT may show only subtle changes or often nothing at all. A stroke assessment scale used in conjunction with a CT may help resolve uncertainties resulting from an inconclusive scan. On the other hand, magnetic resonance imaging (MRI) is the preferred method of investigation for ischaemic stroke and TIA. The disadvantages of MRI include its lack of wide spread availability and the time required to process the images, especially due to the fact that treatment within the presently available acute therapeutic window is critical to good patient outcomes.

MR or CT angiography demonstrates the cerebral vasculature and may add further information such as aneurisms, segmental narrowing or complete blockage of blood vessels. Doppler ultrasonography of carotid and vertebral vessels in the neck add further information – and is particularly useful in recommending patients for endarterectomy endovascular procedures or intravascular thrombolysis treatment. One analysis found that the immediate and long term success of thrombolysis is correlated with the site of occlusion as determined by Doppler ultrasonography.
None of these procedures is capable of accurately identifying the ‘ischaemic penumbra’ the most important area of brain that is amenable to treatment in a patient with acute stroke. The best method available for detecting this area is called the diffusion-perfusion mismatch. This technique involves comparing the discrepancy between the area of the brain with reduced perfusion (visualized with perfusion-weighted imaging) and the area with cellular swelling, the ischaemic core (visualized with diffusion weighted imaging). The ischaemic penumbra can also be seen up to 48 hours after acute stroke through the use of positron emission tomography (PET). Even though there are a few techniques available, future research in procedures that allow the identification of the penumbra are essential for improving stroke outcomes.²

1.5 Assessment of acute stroke

The evaluation and treatment of patients with acute ischaemic stroke should be performed without delay. The general and neurological history, together with brain imaging, provides the necessary information about the aetiology and potential contraindications to treatment with thrombolytic agents. Brain imaging is currently mandatory to guide acute interventions. The intervention protocols for haemorrhagic stroke are different from ischaemic stroke, and fatal complications may result from misdiagnosis. Other clinical and para-clinical tests required are not discussed here.⁶

The National Institutes of Health Stroke Scale (NIHSS) has come into widespread use in the United States for assessment of the severity of stroke and as an indicator of its prognosis (see Table 6.6.1). The initial NIHSS score provides important prognostic information. Approximately 60–70% of patients with an acute ischaemic stroke with a baseline NIHSS score under 10 will have a favourable outcome after one year as compared with only 4–16% of those with a score above 20.6 Two other scales are often used to measure long term disability following acute stroke. The Barthel Index measures patients’ performance in 10 daily activities and the possible scores range from 0-100. The Modified Rankin Scale scores patients on their independence and ranges from 0-5.¹⁴ The National Institutes of Health has also developed a “toolbox” (available at nihtoolbox.org) that is a multidimensional set of brief measures to assess cognitive, emotional, motor, and sensory function on a common scale. These results can then be used across diverse study designs and settings, and may provide value in measuring and understanding recovery from stroke.
Table 6.6.1: National Institutes of Health Stroke Scale (NIH-SS) (2012)

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Points available</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Level of consciousness - general</td>
<td>3</td>
</tr>
<tr>
<td>1b</td>
<td>Level of consciousness – questions</td>
<td>2</td>
</tr>
<tr>
<td>1c</td>
<td>Level of consciousness – commands</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Gaze</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Visual fields</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Facial palsy</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Motor – arms</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Motor – legs</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>Ataxia</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Sensory</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>Language (dysphasia)</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>Dysarthria</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>Inattention (neglect)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>42</td>
</tr>
</tbody>
</table>


Principal 2012 updates to the Introduction:
- Proportion of ischaemic to haemorrhagic stroke has increased slightly (Now 87% of strokes are ischaemic and 13% are haemorrhagic)
- Perfusion-diffusion mismatch, a new technique for identifying the ischaemic penumbra, has been identified and is now in use

2. **Burden of stroke**

2.1 **Epidemiology**

Stroke remains the second leading cause of death at the global level and in the European region. Of the 56 million deaths that occur every year worldwide, 10.8% are due to stroke (see Table 6.6.2). Eighty-five per cent of these stroke deaths among all ages occur in developing countries. Women have a higher lifetime risk of stroke than men: roughly one in five women (20% - 21%) and one in six men (14% - 17%) will suffer a stroke in their lifetime, according to a 2006 study.
Table 6.6.2: Ten Leading Causes of Death by Income Group (2008)

<table>
<thead>
<tr>
<th></th>
<th>Global</th>
<th>Low-income countries</th>
<th>Middle-income countries</th>
<th>High-income countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>Ischaemic heart disease (12.8%)</td>
<td>1) Lower respiratory infections (11.3%)</td>
<td>1) Ischaemic heart disease (13.7%)</td>
<td>1) Ischaemic heart disease (15.6%)</td>
</tr>
<tr>
<td>2) Stroke and other cerebrovascular disease (10.8%)</td>
<td>2) Diarrhoeal diseases (8.2%)</td>
<td>2) Stroke and other cerebrovascular disease (12.8%)</td>
<td>2) Stroke and other cerebrovascular disease (8.7%)</td>
<td></td>
</tr>
<tr>
<td>3)</td>
<td>Lower respiratory infections (6.1%)</td>
<td>3) HIV/AIDS (7.8%)</td>
<td>3) Chronic Obstructive pulmonary disease (7.2%)</td>
<td>3) Trachea, bronchus, lung cancers (5.9%)</td>
</tr>
<tr>
<td>4)</td>
<td>Chronic Obstructive pulmonary disease (5.8%)</td>
<td>4) Ischaemic heart disease (6.1%)</td>
<td>4) Lower respiratory infections (5.4%)</td>
<td>4) Alzheimer and other dementias (4.1%)</td>
</tr>
<tr>
<td>5)</td>
<td>Diarrhoeal diseases (4.3%)</td>
<td>5) Malaria (5.2%)</td>
<td>5) Diarrhoeal diseases (4.4%)</td>
<td>5) Lower respiratory infections (3.8%)</td>
</tr>
<tr>
<td>6)</td>
<td>HIV/AIDS (3.1%)</td>
<td>6) Stroke and other cerebrovascular disease (4.9%)</td>
<td>6) HIV/AIDS (2.7%)</td>
<td>6) Chronic Obstructive pulmonary disease (3.5%)</td>
</tr>
<tr>
<td>7)</td>
<td>Trachea, bronchus, lung cancers (2.4%)</td>
<td>7) Tuberculosis (4.3%)</td>
<td>7) Road traffic accidents (2.4%)</td>
<td>7) Colon and rectum cancers (3.3%)</td>
</tr>
<tr>
<td>8)</td>
<td>Tuberculosis (2.4%)</td>
<td>8) Prematurity and low birth weight (3.2%)</td>
<td>8) Tuberculosis (2.4%)</td>
<td>8) Diabetes mellitus (2.6%)</td>
</tr>
<tr>
<td>9)</td>
<td>Diabetes mellitus (2.2%)</td>
<td>9) Birth asphyxia and birth trauma (2.9%)</td>
<td>9) Diabetes mellitus (2.3%)</td>
<td>9) Hypertensive heart disease (2.3%)</td>
</tr>
<tr>
<td>10)</td>
<td>Road traffic accidents (2.1%)</td>
<td>10) Neonatal infections (2.6%)</td>
<td>10) Hypertensive heart disease (2.2%)</td>
<td>10) Breast cancer (1.9%)</td>
</tr>
</tbody>
</table>


Overall stroke mortality has been declining worldwide despite the increased percentage of people aged over 65 years (75% of stroke victims are above 65 years old). This is mainly due to decreased exposure to risk factors, mainly hypertension and smoking, and to improved access to better healthcare. Figure 6.6.3 illustrates the projected trends for stroke death through the year 2030.

The prevalence of stroke events is expected to increase significantly across the globe as the global population older than 65 years of age (the age segment which suffers the most strokes, see Table 6.6.4) continues to increase by approximately nine million people per year. In Europe, the proportion of the population over 65 years of age is expected to increase from 20% in 2000 to 35% in 2050. The number of stroke events in Europe is predicted to rise from 1.1 million in 2000 to 1.5 million per year by 2025, largely due to the ageing population.
Figure 6.6.3: projected trends for stroke deaths, by income group.

![Projected trends for stroke deaths by income group](image)


Table 6.6.4: Estimates of stroke incidence (a) per 100 000 men and (b) per 100 000 women at selected ages in the European Union. The number of individuals experiencing stroke increases substantially with age.

![Estimates of stroke incidence by country and age](image)

As the epidemiological and demographic transition extends through developing countries around the globe, stroke prevalence is increasing at an ever-growing rate and, in the period from 2000 to 2008, estimated stroke incidence in low- and middle-income countries surpassed stroke incidence in high-income countries for the first time, by 20%.

But mortality figures alone do not give an adequate description of the overall burden of stroke. Despite improvement in stroke care and survival, sequelae of stroke remain a major problem.

In 2005, the global prevalence of stroke survivors was estimated to be 62 million, with projections to reach 77 million by 2030. However, with the increasing prevalence of stroke survivors comes a consequent increase of people who suffer from stroke-related disabilities. Stroke is associated with 43.7 million lost DALYs (disability-adjusted life years) annually around the world (see Figure 6.6.5), which accounts for about 3.2% of all annually lost DALYs. Figure 6.6.6 illustrates the death and disease burden attributable to stroke.

**Figure 6.6.5: Global DALYs lost attributable to stroke:**

Figure 6.6.6: Burden of disease and death attributable to stroke in selected countries in the WHO European region:

Source: WHO 2009.

Eight to twelve per cent of ischaemic strokes and 37–38% of haemorrhagic strokes result in death within 30 days.\(^{24,25}\) Fifty to seventy per cent of patients who survive an ischaemic stroke will recover functional independence three months after onset, but 20% will require institutional care. Among patients above the age of 65 years, the severity of the attack and permanent disabilities are greater. It has been reported that six months after the attack, 50% of stroke patients had some hemiparesis, 30% were unable to walk without assistance, 26% were dependent on others for help with activities of daily living, 19% had aphasia, 35% had depressive symptoms and 26% were being cared for in a nursing home.\(^{26}\) Table 6.6.7 shows the disability component of diseases in terms of DALYs, ranking stroke second in Europe after IHD (as of 2004).

Due to ageing populations, especially in those countries currently undergoing rapid economic growth, projections to 2020 suggest that stroke will account for 6.3% of the total burden of illness.\(^{27}\) In addition, 2004 estimates predict that stroke will be among the five most important causes of disability in both developing and developed countries (Figure 6.6.8).\(^{28}\)

It is clear that the burden of stroke is on track to increase dramatically both in Europe and across the entire globe in the coming decades. Thus, without more effective strategies for the prevention, treatment, and rehabilitation of stroke, the cost of this disease will also increase dramatically.
Table 6.6.7: Leading Causes of Disability- Globally and in Europe (as per cent of total DALYs)

<table>
<thead>
<tr>
<th>Global</th>
<th>European Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Lower respiratory infections (6.2%)</td>
<td>1) Ischaemic heart disease (11.1%)</td>
</tr>
<tr>
<td>2) Diarrhoeal diseases (4.8%)</td>
<td>2) Stroke and other cerebrovascular disease (6.3%)</td>
</tr>
<tr>
<td>3) Unipolar depressive disorders (4.3%)</td>
<td>3) Unipolar depressive disorders (5.6%)</td>
</tr>
<tr>
<td>4) Ischaemic heart disease (4.1%)</td>
<td>4) Alcohol use disorders (3.3%)</td>
</tr>
<tr>
<td>5) HIV/AIDS (3.8%)</td>
<td>5) Hearing loss, adult onset (2.6%)</td>
</tr>
<tr>
<td>6) Stroke and other cerebrovascular disease (3.1%)</td>
<td>6) Road traffic accidents (2.4%)</td>
</tr>
<tr>
<td>7) Prematurity and low birth weight (2.9%)</td>
<td>7) Trachea, bronchus, and lung cancers (2.2%)</td>
</tr>
<tr>
<td>8) Birth asphyxia and birth trauma (2.7%)</td>
<td>8) Osteoarthritis (2.1%)</td>
</tr>
<tr>
<td>9) Road traffic accidents (2.7%)</td>
<td>9) Cirrhosis of the liver (2.0%)</td>
</tr>
<tr>
<td>10) Neonatal infections (2.7%)</td>
<td>10) Self-inflicted injuries (2.0%)</td>
</tr>
</tbody>
</table>


Figure 6.6.8: Leading causes of disability in 2004, and projections for 2030.

2.2 Economic impact

The economic impact of stroke goes beyond the cost of acute care to include sophisticated and costly secondary prevention such as carotid endarterectomy and its prolonged, highly dependent chronic care. The estimated mean lifetime cost per ischaemic stroke patient in the United States was US$ 140,048 in 1999. This includes inpatient care, rehabilitation and follow-up care necessary for lasting disabilities.29

In 2008, the estimated total direct and indirect cost for stroke in the U.S. was US$ 65.5 billion,30 which is higher than the 2004 estimation of US$ 53.6 billion.31 In the UK alone, the cost of stroke care is estimated to be around £9 billion each year (see table 6.6.8).32 This total is comprised of direct care costs (49%), informal care costs (27%), and indirect costs (24%).30 In 27 EU countries, total estimated cost for stroke is €27 billion: €18.5 billion (68.5%) for direct and €8.5 billion (31.5%) for indirect costs. A further sum of €11.1 billion is calculated for the value of informal care.33

Table 6.6.9: Costs of Stroke Care in the United Kingdom (as of 2009)

<table>
<thead>
<tr>
<th>Cost Item</th>
<th>Cost in £</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis costs</td>
<td>45.604 m</td>
<td>0.51</td>
</tr>
<tr>
<td>Inpatient care costs</td>
<td>865.862 m</td>
<td>9.64</td>
</tr>
<tr>
<td>Outpatient costs</td>
<td>109.679 m</td>
<td>1.22</td>
</tr>
<tr>
<td>Outpatient drug costs</td>
<td>505.588 m</td>
<td>5.63</td>
</tr>
<tr>
<td>Community care costs</td>
<td>2,857.113 m</td>
<td>31.82</td>
</tr>
<tr>
<td>Annual care cost total</td>
<td>4,383.858 m</td>
<td>48.82</td>
</tr>
<tr>
<td>Informal care costs total</td>
<td>2,420.921 m</td>
<td>26.96</td>
</tr>
<tr>
<td>Income lost due to mortality</td>
<td>592.733 m</td>
<td>6.6</td>
</tr>
<tr>
<td>Income lost due to morbidity</td>
<td>740.158 m</td>
<td>8.24</td>
</tr>
<tr>
<td>Productivity loss total</td>
<td>1,332.892 m</td>
<td>14.85</td>
</tr>
<tr>
<td>Benefit payments</td>
<td>841.254 m</td>
<td>9.37</td>
</tr>
<tr>
<td>Total</td>
<td>8,978.926 m</td>
<td></td>
</tr>
</tbody>
</table>


The total cost of stroke in the United States from 2005 to 2050, in 2005 US$, is projected to be $1.52 trillion for non-Hispanic whites, $313 billion for Hispanics, and $379 billion for blacks. The per capita cost of stroke estimates is highest in blacks ($25 782), followed by Hispanics ($17 201) and non-Hispanic whites ($15 597). Loss of earnings is expected to be the highest cost contributor in each race/ethnic group.25

In the European Union, hospital discharges for cerebrovascular diseases almost doubled during the last 15 years of the twentieth century. In the United States, the same pattern has been reported for the same period. Specialized stroke care has been shown to improve health and economic outcomes.34,35 Similar trends are observed for mortality and case fatality rate could be lowered by improved stroke services.
In the period between 1989 and 1999, the rate of hospitalization from acute stroke in the United States increased from 32.4 to 34.9 per 10,000. This rate subsequently fell to an average of 31.8 per 10,000 in 2009. Average length of hospital stay in the United States fell from 11.1 to 5.3 days between 1988 and 2009 (see Figure 6.6.10).

Figure 6.6.10: Hospitalization rates for stroke, by age: United States, 1987-2009

But, neither mortality rate nor discharge data from hospitals accurately reflect the level of disability, which is mainly borne by patients and their families. Stroke has been associated with greater use of informal care (family and friends). Health care costs are increasing despite the decrease in stroke incidence and mortality, and will continue to increase as our societies age.

These figures imply that the long-term chronic care that results from stroke is the most costly aspect of the disease, and treatments to reduce its large health and economic impacts are needed.

Priorities, therefore, should be placed on primary prevention of stroke, effective treatment of acute stroke, and effective treatment of recovery from stroke to minimise unfavourable sequelae and extend stroke management outside the hospital to improve accessibility and reduce hospital costs.
3. Control strategy

3.1 Stroke prevention

3.1.1 Risk factors

Stroke prevention is still very important. High blood pressure is one of the leading primary and secondary modifiable risk factors for stroke. While effective and widely available medicines exist for the treatment of hypertension, these are often not used.\(^{39}\) One study found that only 60% of patients used antihypertension medication as prescribed, due to a variety of factors such as misinformation about the condition and negative attitudes about medication.\(^{40}\) Lipid reduction with statins for patients with high cholesterol can reduce the risk of stroke—one meta-analysis found a relative risk reduction of 21%.\(^{41}\) Atherosclerosis may be surgically addressed with endarterectomy but the procedure is often impractical because of its costs and risks. Atrial fibrillation is a major cause of ischaemic stroke (one in six for those over 60) and can be managed with aspirin, warfarin, or a pacemaker. Risk of stroke in populations can be reduced by controlling other risk factors such as diabetes, smoking, and heavy alcohol use.\(^{42}\) The occurrence of fatal and nonfatal stroke also increases with decreasing socioeconomic status, even when all other factors are controlled (stroke incidence per 100 000 per year, European adjusted, 45-84 years): least disadvantaged, 200 (95% CI, 173 to 228); less disadvantaged, 251 (95% CI, 220 to 282); disadvantaged, 309 (95% CI, 274 to 343); most disadvantaged, 366 (95% CI, 329 to 403); 2 for ranks; \(p < 0.0001\), see Annex 1 for non-adjusted data). It has been suggested that prevention strategies to target specific geographical areas may be a cost effective intervention.\(^{43}\) Prevention is especially important in middle and low income countries where effective interventions such as stroke care units are either not feasible, unaffordable, or otherwise unavailable.\(^{44}\)

3.1.2 Secondary Prevention

A wide array of secondary prevention strategies now exist that reduce the rate of stroke reoccurrence.

Aspirin may be one of the most useful and cost effective methods of secondary stroke prevention. Long term aspirin monotherapy leads to an 18.1% risk reduction of recurrent stroke when compared to placebo (\(p = 0.013\)). Treatment with dipyridamole also shows a significant risk reduction (16.3%, \(p = 0.039\)). Furthermore, the greatest reduction in reoccurrence of stroke was seen with the combination treatment of aspirin plus extended-release dipyridamole, and it has been suggested that this should be the standard in secondary stroke prevention (37.0% risk reduction (\(p < 0.001\))).\(^{45}\) For patients who cannot use aspirin because of allergy or other side effects, clopidogrel had been shown to be equally as effective at reducing reoccurrence of ischaemic stroke and does not show any greater safety risks than aspirin.\(^{46}\) Aspirin plus clopidogrel combination treatment does not show greater benefits than either therapy alone and carries an increased risk of bleeding (absolute risk increase 1.3% [95% CI, 0.6 to 1.9]).\(^{47}\) One study found aspirin and aspirin plus dipyridamole to be of equal cost-effectiveness because while combination treatment improved outcomes but it also increased costs. Treatment with clopidogrel was found to be the least cost-effective of the three.\(^{48}\)
For patients with atrial fibrillation, warfarin can reduce the relative risk of recurrent stroke by about 70% (hazard ratio 0.34 [95% CI, 0.20 to 0.57]) but a large meta-analysis of trials showed no significant difference between the effects of warfarin and aspirin (OR 0.79 [95% CI, 0.61 to 1.02]). Furthermore, any possible added advantage of warfarin is offset by an increased risk of bleeding (0.3–0.6% per year).

Carotid endarterectomy is an effective secondary prevention strategy in patients who have at least 70% stenosis of the symptomatic carotid artery. The relative risk reduction of recurrent stroke is approximately 60% over three years (as shown in Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis, 1991). The current recommendation is for carotid endarterectomies to be performed within 12 weeks following acute stroke for maximum benefit.

Evidence suggests that treatment with blood pressure medications also serves as a secondary prevention. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) demonstrated a reduction in recurrent stroke of approximately 30% during five years. This reduction was observed independently of the patient’s baseline blood pressure.

The incidence of reoccurrence of stroke can also be reduced with the administration of statins. This benefit is not correlated with the baseline cholesterol concentration of the patient and may be due to alternative properties of statins, such as anti-inflammation or neuroprotection.

3.2 Acute Therapy

3.2.1 Acute ischaemic stroke

The successful management of acute ischaemic stroke is currently based on two vascular recanalization strategies: anti-platelet agents and thrombolysis.

Because most strokes are due to thromboembolic occlusion of an intracranial artery, restoration or improvement of perfusion to the ischaemic area is the key therapeutic strategy. The concept of an “ischaemic penumbra”, a potentially recoverable brain tissue, allows early intervention to improve the neurological symptoms, and decrease the functional disability after the attack.

There are many strategies suggested for treatment of acute stroke, but oral aspirin and intravenous rt-PA are the only two pharmaceuticals currently recommended for acute stroke treatment.

Anti-platelet Agents

The effectiveness of acute treatment of stroke with aspirin is still unclear. Two large studies have tested the effect of aspirin given once within 48 hours of stroke onset compared to a placebo. 300 mg of aspirin was associated with significantly fewer recurrent ischaemic strokes and did not increase the risk of haemorrhagic strokes, as reported by The International Stroke Trial. Chinese Acute Stroke Trial found that 160 mg of aspirin per day showed a similar decrease in incidence of ischaemic stroke in the aspirin group but was associated with an increase of haemorrhagic strokes. The combined results of the two trials
Update on 2004 Background Paper, BP 6.6 Stroke

showed an overall decreased risk of further stroke or death in the hospital in 9 per 1000 patients treated and showed no net increase in hazard with aspirin treatment. The combination of aspirin and thrombolytics may increase bleeding, and thus aspirin is currently recommended for those whose strokes are unable to be treated with thrombolysis. The advantages of acute aspirin treatment are its low cost, easy administration and low risk of toxic effects. However, it does carry some side-effects, such as abdominal pain, peptic ulcerations and allergy to aspirin, which may limit its wider use. Clopidogrel is an alternative when aspirin cannot be used. The rate of reoccurrence of stroke was 9.0% in patients who received aspirin plus extended-release dipyridamole and 8.8% in patients who received clopidogrel (hazard ratio 1.01 [95% CI, 0.92 to 1.11]). Anticoagulants, such as Warfarin, have not been shown to produce better outcomes than aspirin alone. No other antiplatelet agent has yet been reported as effective. The administration of acute aspirin can help salvage the ischaemic penumbra, but most of its potential benefits come from early secondary prevention.

Thrombolysis

In 1995, a clinical trial showed that the intravenous administration of rt-PA (0.9 mg/kg; maximum dose 90 mg) within three hours of onset of ischaemic stroke improved outcomes at three months when compared to a placebo (global odds ratio for a favourable outcome, 1.7 [95% CI, 1.2 to 2.6]) (see Figure 6.6.10). Largely due to the results of this trial, US Food and Drug Administration (FDA) approved rt-PA within the three hours after presentation of symptoms for the treatment of acute ischaemic stroke in 1996. Treatment with rt-PA is associated with potentially fatal intracranial haemorrhage in 6.3% of cases compared to 0.6% of cases treated with placebo. The safety and efficacy of rt-PA for the treatment of children has not been established. Common side-effects include bleeding from cuts, gums, wounds, injection sites, fever and low blood pressure. Because of potential fatal complications thrombolytic treatment should be carried out according to a strict pre-determined protocol. Rt-PA is only used in approximately 5% of patients due to factors such as lack of stroke experts and reimbursement issues.

To date, no other thrombolytic agent has been established as a safe and effective alternative to intravenous rt-PA. Currently available data do not support the clinical use of either streptokinase or ancred. The PROACT II study (1999) reported promising results in a trial testing treatment with prourokinase but the risk of intracranial haemorrhage during the first 24 hours following treatment was high (10% vs. 2% of control, p = 0.06). No recent clinical trials have been completed using prourokinase.
Figure 6.6.11: Improved patient outcomes after intravenous administration of rt-PA

As the ischaemic process progresses very fast, the time at which treatment starts has been shown to be critical if there are to be significant benefits. Treatment within the first three hours has been defined as the ‘therapeutic window’ for acute stroke, but evidence suggests that earlier treatment brings a better outcome (adjusted odds ratio for favourable three-month outcome: 0-90 min, 2.11 [95% CI 1.33 to 3.35]; 91-180 min, 1.69 [95% CI 1.09 to 2.62] (see figure 6.6.12). However, recent studies have shown that treatment up to four and a half hours after onset is still effective and does not carry an increased risk of haemorrhage.
Figure 6.6.12: Improved outcome with earlier treatment


As intracranial haemorrhage is difficult to treat it must be avoided at all costs. The National Institute of Neurologic Diseases Study (NINDS) of rt-PA showed the NIHSS score to be useful in identifying patients with higher haemorrhagic risk. Patients with a score of 20 or more on the NIHSS had a 17% chance of intracranial haemorrhage, whereas the risk of bleeding was only 3% among those with a score less than 10.67

The size of the infarct, based on computed tomography scan (CT scan), is also a predictor of haemorrhage and poor outcomes, but no study has yet determined whether treatment of severe cases with rt-PA might have higher risks than benefits. As a result, it has been suggested that the performance of these tests should not delay treatment with intravenous rt-PA. Other investigations, including imaging of cerebral vessels, carotid Doppler studies, cardiac echo can be delayed until after the thrombolytic treatment.67

3.2.2 Acute haemorrhagic stroke

Haemorrhagic stroke is the most difficult form of stroke to treat and few effective strategies exist to reduce disability and mortality. Mayer et al. reported promising results with the use of Recombinant Activated Factor VII, a drug that is FDA approved for the treatment of excessive bleeding in patients with haemophilia. Because Factor VII is not currently in use for the treatment of acute haemorrhagic stroke, it is discussed further in section 6.6.5
The assessment should be done in consultation with a neurosurgeon and the use of a CT scanner. The size and location of the haematoma determine the prognosis. Current treatment focuses on evacuation of the haematoma particularly in the cerebellum, and supratentorial region which is larger than 3 cm, despite the fact that trials have yet to show any benefit of this practice. Surgical evacuation of moderate-volume intracerebral haemorrhage was examined in the STICH trial, completed in 2007. The trial did not produce significant results—at 6 months, 26% of patients given the treatment had a favourable outcome compared with 24% of the patients given initial conservative treatment (OR 0.89 [95% CI 0.66 to 1.19], p = 0.414). However, a second study, STICH-2, is currently underway investigating the same issue.

Haemorrhagic stroke patients are at a risk for re-bleeding during the time in which surgery is delayed, antifibrinolytic agents which may reduce this risk are seen as an attractive option. A meta-analysis found that they are associated with a reduced incidence of aneurysmal re-rupture (OR 0.55 [95% CI 0.42 to 0.71]). However, treatment with antifibrinolytics did not improve poor patient outcome (death, vegetative state, or severe disability) (OR 1.12 [95% CI 0.88 to 1.43]) and was also associated with an increased risk of cerebral ischemia (OR 1.39 [95% CI 1.07 to 1.82]).

3.3 Supportive care

When cerebral infarction occurs, the immediate goal is to optimize cerebral perfusion of the ischaemic area, monitor potential stroke-related complications (cerebral oedema, seizures, haemorrhagic transformation, cardiovascular and pulmonary problems, fever and malignant hypertension) and to prevent the common complications of bedridden patients, such as malnutrition, infections, pressure sores, aspiration pneumonia, deep venous thrombosis and pulmonary embolism. Early mobilisation is very useful in preventing these complications. Early involvement of physical therapists may reduce the rate of long term stroke complications and may speed up the recovery process.

Good nutrition, support of paralyzed limbs, and general positioning of the patient may also minimize complications immediately following stroke. There are also on going trials evaluating the effectiveness of active cooling in the period following a stroke.

The provision of airway support and ventilatory assistance for patients with acute stroke who have depressed levels of consciousness or airway obstruction may be necessary. A further recommendation is to provide supplementary oxygen only to hypoxic patients. Fever is associated with poor outcomes and should be treated with antipyretics with no antiplatelet effect. There is general agreement to recommend control of hypoglycaemia or hyperglycaemia following stroke. A reasonable goal would be to lower markedly elevated glucose levels to <300 mg/dL (<16.63 mmol/L). Swallowing function should also be monitored and treated if necessary with dietary modifications or a nasogastric feeding tube. These strategies were found to be effective in a trial that implemented protocols for monitoring for hyperglycaemia, fever and swallowing dysfunction. These patients showed reduced death and dependency at 90 days following the incidence of a stroke.

As cardiovascular diseases (mainly myocardial infarction and arrhythmias) are risk factors and complications of an acute stroke, they should be carefully evaluated and treated using established protocols in stroke patients. Use of anticoagulants during the first 14 days should
be avoided. Controversy exists within the research community regarding whether or not hypertension should be actively treated during the acute phase of the stroke. Studies have been done confirming both arguments, thus more research is urgently needed in this area. Hypotension may also be a complication and should be carefully monitored.\textsuperscript{41}

Once the patient has been stabilized, patient and family education, screening and treatment of depression, and physical and functional rehabilitation should be started as soon as possible. Finally, the patient should have further evaluation to determine the cause of the stroke, and medical or surgical therapies should be administered to prevent recurrent ischaemic events.\textsuperscript{41}

In patients with malignant middle-cerebral-artery-territory infarction and space-occupying brain oedema, hemispheric decompression preformed within 48 hours of infarction has been shown to be beneficial. A combined analysis of three clinical trials found that 75\% of patients who received the surgery had an mRS\textless =4 at 12 months compared to 24\% of controls (pooled absolute risk reduction 51\% [95\% CI 34 to 69]). Though only a small group of patients will benefit from this surgery, it has been shown to be effective and should become part of protocol for patients who qualify for it.\textsuperscript{72}
### Table 6.6.13: Summary of stroke therapies that are proven or under investigation

#### Acute Stroke

<table>
<thead>
<tr>
<th>Study, year</th>
<th>RRR (95% CI)</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proven</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke unit</td>
<td>Langhorne and colleagues, 1993</td>
<td>6.5%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Thrombolysis (tPA)</td>
<td>NINDS, 1995</td>
<td>9.8%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>IST, 1997</td>
<td>2.6%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Decompressive surgery for IS</td>
<td>Vahedi and colleagues, 2007</td>
<td>48.8%</td>
<td>23.0%</td>
</tr>
<tr>
<td><strong>Under investigation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombinant factor VII</td>
<td>Mayer and colleagues, 2005</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Surgery for ICH</td>
<td>Mendelow and colleagues, 2005</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Extending time widow for thrombolysis</td>
<td>DIAS, 2005</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Sonothrombolysis</td>
<td>Alexandrov, 2004</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>MERCI, 2005</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Blood pressure lowering</td>
<td>ENOS, 2007</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Neuroprotection</td>
<td>SAINT, 2006</td>
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</tbody>
</table>

#### Secondary prevention

<table>
<thead>
<tr>
<th>Study, year</th>
<th>RRR (95% CI)</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proven</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Canadian Co-op Study Group, 1978</td>
<td>13.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Aspirin plus dipyridamole</td>
<td>Deiner, 1996</td>
<td>15.0%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Clopidrogel</td>
<td>CAPRIE, 1996</td>
<td>10.0%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>EAFIT, 1993</td>
<td>66.0%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>NASCET, 1991; ECST, 1991</td>
<td>44.0%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Blood pressure lowering</td>
<td>PROGRESS, 2001</td>
<td>28.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Cholesterol lowering</td>
<td>SPARCL, 2006</td>
<td>16.0%</td>
<td>2.2%</td>
</tr>
<tr>
<td><strong>Under investigation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angioplasty</td>
<td>Yadav and colleagues, 2004</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Thrombin inhibitors</td>
<td>SPORTIF, 2003</td>
<td>--</td>
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Note: NNT: number needed to treat to prevent one stroke patient dying or becoming dependent (acute stroke) or to prevent one fatal or non-fatal stroke (secondary prevention) per year. RRR: relative risk reduction. ARR: absolute risk reduction.
4. Major problem and challenges of stroke management: why does the disease burden persist?

The process of care begins with calling an ambulance or upon arriving in an accident and emergency facility. In one study in an urban area in the United States, only 17% of patients were admitted to hospital within the three-hour therapeutic window and in an international trial, only 4% of patients were admitted within three hours of symptoms onset. In a 2012 Japanese trial of 712 stroke patients, pre-hospital delays were significantly associated with decreased levels of consciousness at the time of patient admission to the hospital, measured by Glasgow Coma Scale score at admission. After adjusting for age and sex, a longer time between call and arrival at the hospital was associated with poorer GSC score (OR 1.020 [95% CI 1.002 to 1.038]). Though the results of the trial showed statistically significant outcomes, the improvement was not large and may be impractical to implement if the costs outweigh the patient benefits.

Lack of access to general health services might be an important factor in delayed treatment in developing countries. A 2012 study estimated the cost burden of post-stroke conditions in Nigeria, and on average the costs were N 95,000 (US$ 600) in a government hospital and N 767,900 (US$ 4860) in a private hospital. The researchers concluded that managing stroke care is too high of a cost burden to be afforded by an average Nigerian stroke sufferer. This, in turn, results in increased death and disability, and consequent burdens on both the patient and their caretakers.

In developed countries, a cause of delay in getting acute stroke care is the lag time between the stroke onset and when emergency services are actually called. A 2012 qualitative interview study in the United Kingdom revealed that the underlying reasons for this delay are quite complex. Factors influencing who called emergency services and when include: lack of knowledge of stroke symptoms, severity of the stroke symptoms, fear of hospitals and the consequences of stroke, and unwillingness to impose on medical staff, family, or friends. There remains a clear need for stroke-related education to ensure the general public understands when a stroke is occurring and the proper course of action to take when the situation arises.

Several educational studies using diverse formats, especially mass media, have been shown to increase public knowledge of stroke symptoms. Often these efforts focus on recognizing the symptoms of stroke and emphasizing the need to call emergency services. Some of these studies have demonstrated higher likelihood that patients or by-standers who have been exposed to these mass-media campaigns will call an emergency number, but many trials were brief and thus the large-scale and long-term benefits of such mass media campaigns are still uncertain. More research is needed in this area to increase the number of stroke victims who arrive at the hospital within the treatment window.

Once the patient is in contact with the health system a number of major barriers to treatment within the therapeutic window have been identified. Lack of specific protocols and training, delay in obtaining a diagnostic imaging test, delay in referring the patient to a specialized stroke unit and the low efficacy of available treatments (aspirin 1% and rt-PA 10% superior than placebo) are some of these factors in developed and developing countries. Lack of access to rt-PA might be an important factor in developing countries.
The majority of stroke research trials have not included patients with comorbidities, despite the fact that most stroke patients are over the age of 65 years, and often present comorbidities that add complexity to the management of the condition. Stroke is highly unstable during the acute phase and requires close monitoring and prompt attention to complications. Access to highly skilled professionals and the availability of costly resources have been shown to improve overall outcomes. The integration of rehabilitation services with acute hospital care has also been shown to be effective in improving health outcomes.\textsuperscript{79}

Though there have been intensive research efforts aimed at finding new acute stroke therapies, the vast majority of trials end in failure. The SAINT II (Stroke-Acute Ischaemic-NXY Treatment) and DIAS-2 (Desmoteplase in Acute Stroke) trials were designed on the basis of extensive promising preclinical data, as well as phase IIb and early phase III data. Yet, these two trials showed no efficacy. There have been multiple strategies proposed to address the continual lack of success in translating research from the bench to the bedside, as described in a 2008 review:

\begin{itemize}
  \item (1) vascular occlusion: current recanalization strategies have limited effectiveness and may have serious side effects;
  \item (2) complexity of stroke pathobiology: therapy must acknowledge the ‘Janus-faced’ nature of many stroke targets and must identify endogenous neuroprotective and repair mechanisms;
  \item (3) inflammation and brain-immune system interaction: inflammation contributes to lesion expansion, but is also instrumental in lesion containment and repair; stroke outcome is modulated by the interaction of the injured brain with the immune system;
  \item (4) regeneration: the potential of the brain for reorganization, plasticity and repair after injury is much greater than previously thought;
  \item (5) confounding factors, long-term outcome and predictive modeling
\end{itemize}

These five areas are linked on all levels and therefore need to be tackled by an integrative approach and innovative therapeutic strategies.\textsuperscript{80}

Thus, the primary challenges of stroke care that face the world are: the lack of timely and affordable care (especially care involving specialized stroke units), the low efficacy of available interventions, and the continual failure of translating therapies from the laboratory to the bedside.

An additional yet extremely important challenge is the insufficient funding for stroke-related research, especially when compared to the funding of other prevalent chronic diseases. A government review in the United Kingdom compared the amount of research funding to the impact of the disease on the population and the economy for four of the most prevalent chronic diseases: dementia, cancer, coronary heart disease (CHD) and stroke. The results are summarized below in Table 6.6.14.\textsuperscript{81}

This study demonstrates that funding for stroke research is quite disproportional to its relative burden. There is an evident mismatch between the funds allocated to research and development and the burden of stroke, whether measured in terms of mortality or disability. Lack of funding undermines the capacity to do valuable research to an extent that stroke scientists are no longer able to apply for further required funding. This disparity should be addressed to ensure advancements in stroke therapies are not smaller than the disease’s burden on society, both in terms of health and economics.
Update on 2004 Background Paper, BP 6.6 Stroke

Table 6.6.1: United Kingdom Research funding for four prominent chronic diseases

<table>
<thead>
<tr>
<th>Total Research Funding (£833 million = 100%)</th>
<th>Funding per 1000 DALYs</th>
<th>Funding per £1 million of health and social costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer (£590 million = 71%)</td>
<td>Cancer (£482)</td>
<td>Cancer (£129 269)</td>
</tr>
<tr>
<td>CHD (£169 million = 20%)</td>
<td>CHD (£266)</td>
<td>CHD (£73 153)</td>
</tr>
<tr>
<td>Dementia (£50 million = 6%)</td>
<td>Dementia (£166)</td>
<td>Stroke (£8745)</td>
</tr>
<tr>
<td>Stroke (£23 million = 4%)</td>
<td>Stroke (£71)</td>
<td>Dementia (£4882)</td>
</tr>
</tbody>
</table>


5. Stroke Research from 2004 Onwards

As was the status of stroke care in 2004, there have been no substantial breakthroughs in stroke therapy or management, though some promising research has been done. Investigation of neuroprotective therapies and methods of extending the treatment window still continues, and new directions of research have begun as well. These new areas of research include specialized stroke units, enhancing recovery, stem cell therapies, and methods to reduce haematoma growth.

5.1 Update on Neuroprotectives

There continues to be no substantial breakthrough in neuroprotective therapies for stroke, though some progress has been made since 2004. One 2005 study in particular demonstrated that edaravone, a free radical scavenger, significantly reduced the infarct volume (68.10 cm³ +/- 6.24%; p < 0.05) and provides a neuroprotective effect through the early free radicals scavenging pathway and a late anti-inflammatory effect (edaravone 05). This study suggests that edaravone may be important for expansion of the therapeutic time window in stroke patients but larger samples and higher quality trials are needed to confirm this trend.82

The 2006 Stroke-Acute Ischaemic-NXY Treatment (SAINT I) trial of about 1700 patients was one of the first successful translations of neuroprotectives into clinical practice,83 but the larger (about 3200 patients) and more comprehensive SAINT II study in 2007 showed no efficacy, suggesting the first study was a false positive [See Table 6.6.15].84 Though NXY was a failure in its primary outcome, it provides insight into the design faults of stroke trials, which could be the root cause of the repeated failure of neuroprotectives in clinical trials. There are multiple gaps in translating therapies from the lab to the bedside that need to be addressed, especially in the relevancy of animal trials, before neuroprotective research should be fully abandoned.
Table 6.6.15: Outcomes of SAINT I (2006) vs. SAINT II (2007) trials

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Odds Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAINT I i 1699 patients</td>
<td>1.20 (1.01-1.42)</td>
</tr>
<tr>
<td>SAINT II ii 3195 patients</td>
<td>0.94 (0.83-1.06)</td>
</tr>
</tbody>
</table>

*Primary Outcome defined as reduced disability at 90 days

There is a growing body of research on the effects of induced hypothermia immediately following acute ischaemic stroke. Promising results have been seen in animal studies but questions still remain about the safety and efficacy of the treatment. It is probable that hypothermia works through multiple sites of action, including reducing the size of the infarction, reducing intracerebral pressure, and reducing cerebral oedema formation. However, a 2011 clinical trial showed no difference in NIHSS scores at six months following acute stroke between patients given the hypothermia treatment and control subjects, though the trial had flaws including small sample size and single-blind study design. It is recommended that a larger, double blind study be conducted in the future to determine the efficacy of the treatment.

Consistent failures in trials for neuroprotective stroke therapies may indicate that the next logical step is to demonstrate proof-of-principle, perhaps with a preloaded dose of neuroprotectant in high-risk patients, which would provide reassurance that the strategy is effective in humans.

5.2 Extending the Treatment Window

As identified in the 2004 Stroke Background report, prolonging the treatment window for thrombolysis continues to be an important area of research for stroke therapy. Various approaches currently undergoing investigation include (1) standard tPA therapy with expanded entry criteria with therapeutic time windows of up to six hours; (2) imaging techniques to assess the presence of a penumbra with time windows of six hours or even nine hours; (3) combined approach with intravenous therapy followed by intra-arterial therapy; (4) combination therapies using, for example, glycoprotein (GP) IIb/IIIa antagonists with tPA, tested with time windows of up to 24 h (ReoPro Retavase Reperfusion of Stroke Safety Study—Imaging Evaluation [ROSIE]); and (5) use of alternative thrombolytic agents such as desmoteplase. Desmoteplase is the only thrombolytic agent in late-stage development for acute ischemic stroke that is now tested in patients with proven stroke pathology.

Ultrasound-enhanced thrombolysis is another promising therapy that may enhance thrombolysis. By mobilizing endogenous tPA, it increases the treatable surface area available
to exogenous tPA, as well as mechanically disrupting the clot. In a phase II trial, patients showed improved recanalization rates, with a nonsignificant trend toward an increased rate of recovery from stroke, as compared with placebo.\textsuperscript{56} A phase III trial is currently under way.\textsuperscript{56}

**5.3 Specialized Stroke Units**

Organized stroke unit care is provided in hospitals by doctors, nurses, and therapists who work as a coordinated team to provide specialized care to stroke patients. The results of a 2009 Cochrane systematic review indicate that patients receiving inpatient care in a stroke unit are more likely to survive, regain independence, and return home than those receiving less organized service. There are many forms of specialized stroke care that have evolved, including specialized wards and mobile stroke teams, but benefits were most apparent in units based in a dedicated ward.\textsuperscript{84} Compared with conventional-ward care, stroke-unit care was associated with a reduced probability of death or disability at the end of follow-up (OR 0.81 [95% CI 0.72 to 0.91]; \( p = 0.0001 \)) [see figure 6.6.16]. However, there is delay in implementing these specialized stroke units in Europe, and in North America there is still disagreement on the need to have such specialized teams.\textsuperscript{86} Further research may be necessary to identify which patients benefit from such units.

![Table 6.6.16: Health Outcomes of Stroke Unit vs. Control Care](image)

**Table 6.6.16: Health Outcomes of Stroke Unit vs. Control Care**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Stroke Unit (n=4936)</th>
<th>Control (n=6636)</th>
<th>Odds Ratio (95% CI)*</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital case fatality</td>
<td>542 (11%)</td>
<td>1034 (15%)</td>
<td>0.78 (0.64-0.95)</td>
<td>0.016</td>
</tr>
<tr>
<td>Long-term mortality</td>
<td>1363 (28%)</td>
<td>2382 (36%)</td>
<td>0.79 (0.68-0.91)</td>
<td>0.001</td>
</tr>
<tr>
<td>Death or disability</td>
<td>2611 (53%)</td>
<td>4112 (62%)</td>
<td>0.81 (0.72-0.91)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Not living at home</td>
<td>1743 (35%)</td>
<td>2829 (43%)</td>
<td>0.85 (0.74-0.97)</td>
<td>0.019</td>
</tr>
</tbody>
</table>


Note: *Adjusted by age, sex, time from stroke onset, intracranial haemorrhages, atrial fibrillation, and unconsciousness, and clustered at the hospital level.

**5.4 Enhancing Post-stroke Recovery**

The 2011 “Fluoxetine for motor recovery after acute ischaemic stroke (FLAME)” study demonstrated that the early prescription of fluoxetine with physiotherapy enhanced motor recovery after three months in ischaemic stroke patients with moderate to severe motor deficit. Table 6.6.17 below outlines the outcomes in fluoxetine and placebo patient groups. Fluoxetine is a well-tolerated drug that no longer has a patent, allowing the cost to be more affordable.
Update on 2004 Background Paper, BP 6.6 Stroke

Table 6.6.17: Fugl-Meyer motor scale (FMMS) scores.

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine (n=57)</th>
<th>Placebo (n=56)</th>
<th>Difference between groups (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Total Score</td>
<td>53.7</td>
<td>35.1</td>
<td>18.6 (9.2-27.9)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Mean Upper Limb Score</td>
<td>29.7</td>
<td>16.2</td>
<td>13.5 (6.2-20.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean Lower Limb Score</td>
<td>24</td>
<td>18.9</td>
<td>5.1 (2.1-8.1)</td>
<td>0.001</td>
</tr>
</tbody>
</table>


*note: Mean was adjusted for age, history of stroke, and FMMS score at inclusion*

5.5 Stem Cell Treatment for Ischaemic Stroke

Stem cells are an emerging therapeutic modality in treatment of stroke.\(^{91}\) This new arena is based on the relatively recent discovery that certain parts of the adult brain are capable of recovery. A 2006 study of patients with ischaemic stroke demonstrated the presence of a natural neurogenesis process in the ischaemic penumbra,\(^{92}\) but this endogenous regeneration is not effective enough to fully repair severe brain damage, such as that caused by a stroke. Targets for developing stem cell therapies include the promotion of these endogenous repair processes, as well as protecting at-risk tissue during the acute phase of the stroke, and direct replacement of already-damaged brain tissue.

Though the few existing experiments show promising results, there are many challenges that remain to be addressed in using stem cells for stroke therapy, including:

**Which type of stem cells should be used?**

There are multiple types of stem cells that can potentially be used in stroke therapy, and they all come from two main sources: embryonic stem cells (which are quite controversial) or adult stem cells (which are less controversial, but also have less differentiation potential). One of the more promising studies involved adult hematopoietic stem cells (HSCs), which have shown significant benefits in rodent stroke models, including evidence of functional improvement and reduced infarct volume. Furthermore, as HSCs are derived from bone marrow, peripheral blood, or umbilical cord blood, they are not associated with the bioethical controversy that surrounds embryonic or fetally derived stem cells.\(^{91}\) A further study investigating direct intracerebral implantation of HSCs one week after induced stroke in an animal model showed evidence of neurogenesis and angiogenesis, with differentiation of transplanted cells into cells expressing markers for neurons, glial cells, and vascular endothelial cells.\(^{93}\)

**What is the best mechanism of action?**

There are several potential paths of action that stem cells could take in order to treat stroke. Following an ischaemic stroke, neurons and glia die by a mixture of necrosis and apoptosis. Stem cell transplantation may elicit a neuroprotective response by rescuing the apoptic cells, particularly in the penumbral tissue, which in experimental models has led to improved neurological recovery.\(^{94}\) Another strategy under investigation is the use of stem cells to promote angiogenesis to aid in the regeneration of blood vessels and similar structures that are also damaged during acute stroke. A third potential mechanism of action is to promote
endogenous repair processes that occur naturally. When the patient has an ischaemic stroke, certain types of stem cells are mobilized from the bone marrow into the bloodstream. There is evidence that increased mobilization of these cells in stroke patients is correlated with increased neurological recovery. More research is needed to evaluate these various mechanisms.

Which patients will benefit from stem cell therapy?

The type and anatomical location of the stroke are important issues to consider when selecting the appropriate therapy for a patient. Additionally, demographic differences such as age and gender are likely to affect how patients respond to treatment. Most preclinical studies that have been conducted focus on young, healthy, male animals. The benefits that these studies demonstrate may not translate to elderly patients—the demographic in which the majority of strokes occur. The majority of preclinical studies have focused on ischaemic rather than haemorrhagic strokes, which make up one fifth of stroke cases. Finally, the current and completed studies do not include patients who suffer from comorbidities and other complications, an issue which must be addressed in future research efforts.

What is the optimum timing and method of delivery for treatment?

Preclinical trials have shown benefits in both acute and chronic stroke cases, thus future studies need to evaluate the optimal timing of treatments and their comparative effectiveness. The best method of delivery for stem cell treatments remains unclear. Positive results have been seen with intracerebral implantation (which is effective, but highly invasive) as well as intravenous and intra-arterial routes (which are less risky, but also less reliable because only a small proportion of injected cells reach the brain). Further studies are needed to compare these three methods, keeping in mind practicability and safety, and not solely the therapy’s effectiveness.

How can transplanted cells be tracked?

Tracking the stem cells once they are inside the patient’s body is essential to improving our understanding of cell migration and mechanisms of action. However, there is currently no ideal method of accomplishing this, so it is likely in the future that a combination of imaging and tracking methods will be used to give an overall assessment. More research is needed to determine the best process for tracking stem cell distribution.

Currently, the routine use of stem cells at the bedside for stroke patients is an exciting prospect, though realistically it remains a long way off. Stem cell transplantation in animal models of ischaemic stroke has shown encouraging results, but evidence in human patients is lacking and the current clinical trials are still in their infancy. There have been a number of recent phase I and II studies investigating ischaemic stroke therapy, but these trials have not yet addressed the best cell type, route of delivery, or timing of therapy. Large, well-designed trials are urgently needed in the arena of stem cell research.
5.6 Reducing Haematoma Growth

In stroke management, the development of a haematoma is a key indicator of a poor patient outcome. Consequently, there has been research investigating ways to reduce these haematoma, including two notable studies involving: (1) Recombinant Factor VII, and (2) early reduction of blood pressure.

5.6.1 Recombinant Factor VII (rFVIIa) Study

A 2005 study involving 399 patients investigated the potential stroke-related applications of recombinant factor VII (rFVIIa), which is usually given to patients to reduce haemorrhagic complications of major surgical procedures. Hematoma volume increased more in the placebo group than in the rFVIIa groups.

The mean increase was 29% in the placebo group, as compared with 16%, 14%, and 11% in the groups given 40 μg, 80 μg, and 160 μg of rFVIIa per kilogram, respectively (p = 0.01 for the comparison of the three rFVIIa groups with the placebo group). Growth in the volume of intracerebral haemorrhage was reduced by 3.3 ml, 4.5 ml, and 5.8 ml in the three treatment groups, as compared with that in the placebo group (p = 0.01). Sixty-nine percent of placebo-treated patients died or were severely disabled (as defined by a modified Rankin Scale score of four to six), as compared with 55%, 49%, and 54% of the patients who were given 40, 80, and 160 μg of rFVIIa, respectively (p = 0.004 for the comparison of the three rFVIIa groups with the placebo group). Mortality at 90 days was 29% for patients who received placebo, as compared with 18% in the three rFVIIa groups combined (p = 0.02).

But though treatment with rFVIIa within four hours after the onset of intracerebral haemorrhage limited the growth of the hematoma, reduced mortality, and improved functional outcomes at 90 days, there was a small increase in the frequency of thromboembolic adverse events. These events, mainly myocardial or cerebral infarction, occurred in 7% of rFVIIa-treated patients, as compared with 2% of those given placebo (p = 0.12). Furthermore, a follow up study completed by the same researchers in 2008 did not produce the same results in rFVIIa’s reduction of long term disability. They found that it was not associated with improved outcomes at 90 days. More research is needed to reduce the complications associated with this therapy, determine its efficacy, and to identify which patients would benefit from such therapy.

5.6.2 Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) Study

Early elevation of blood pressure (BP) is very common after intracerebral haemorrhage, and a number of observational studies have demonstrated strong associations between increasing levels of BP and poor patient outcomes. The 2010 INTERACT study aimed to examine the effects of BP-lowering treatment on haematoma and perihaematomatic oedema over 72 hours. The results of the study confirmed the reduction of haematoma growth in intracerebral haemorrhage over 72 hours, though there were no recognizable effects on perihaematomatic oedema. Because haematoma growth is a strong predictor of poor outcomes in intracerebral haemorrhage, these results reaffirm potential benefits of rapid physiological control of elevated BP and support the hypothesis that early intensive BP lowering may promote recovery from intracerebral haemorrhage. Further research is needed to fully translate these
practices to the bedside and confirm the improved patient outcomes of haematoma reduction.

6. **What are the opportunities for research into new pharmaceutical interventions that might fill the current gap and make a substantial difference?**

Opportunities for research can be divided into four categories:

a) reducing treatment delays;
b) identifying those patients who can benefit the most from a product;
c) prolonging the treatment window; and

d) therapies that work outside the treatment window.

6.1 **Strategies for reducing treatment delays**

Specialized stroke wards in hospitals have been shown to be very effective in reducing rates of death and disability in stroke patients. Though a 2007 study on the effectiveness of specialized stroke wards showed improved patient outcomes irrespective of the patient’s age, more research is needed in determining the effectiveness of these special units in terms of the type of stroke and the presence of comorbidities. Additionally, the benefits of mobile stroke units, especially in terms of cost-effectiveness, have yet to be proven but may have benefits for certain demographics of patients, such as those living far away from a well-equipped hospital. More research should be done in this area as well.

The use of rt-PA in mobile stroke units at the first contact with the patient and prompt referral to specialized centres, has been effective in improving health outcomes. As rt-PA is contraindicated in patients with haemorrhagic stroke or those likely to have it as a consequence of the treatment, research is required to develop and test diagnostic protocols to be used by the paramedics in these units. In order to avoid duplication of ambulance systems, the use of rt-PA by paramedics should be considered in normal ambulances rather than in mobile stroke units. The current major drawback is inaccessibility to CT scanning.

Another area of research is the development of safer drugs that could be used earlier in sequence with stronger intervention later in hospital. Aspirin is shown to be effective in improving health outcomes in acute stroke. It is safer for patients with haemorrhagic stroke and is readily available. Further research is required to evaluate the cost-effectiveness of using aspirin at the time of onset of symptoms at home, in the ambulance or on arrival at the hospital in relation to its interaction with rt-PA at different dosages; and the additional risk for patients with haemorrhagic stroke that may have been misdiagnosed as ischaemic stroke.

6.2 **Identifying the patients who can benefit the most from a specific product**

Drug efficacy may be lower and/or drugs may have a higher profile of side-effects for erroneous reasons, e.g. trials may have included patients who no longer have an ischaemic
penumbra, or who have experienced different physiopathological mechanism, or who were admitted using different concomitant treatment. Such patients should be identified and included in trials designed specifically for them.

Diagnosis using perfusion–diffusion MRI and CT may delineate the existence and extent of the ischaemic core, the extent and severity of perfusion impairments, occlusion of large vessels, and the ischaemic penumbra. It has also shown promising results in predicting health outcomes and identifying patients with treatable ischaemic penumbra beyond the standard three-hour therapeutic window. Several studies are currently evaluating some of these issues (the DWI Evaluation for Understanding Stroke Evolution (DEFUSE), the Echo Planar Imaging Thrombolytic Evaluation Trial (EPHITET), the Desmoteplase in Acute Stroke (DIAS) and the Stroke Evaluation for Late Endovascular Cerebral Thrombolysis). Further research is needed to evaluate feasibility of these techniques to be used clinically in resource-poor settings and also to be able to match specific treatments to specific patients using more advanced techniques.

In each therapy that is proven to be effective, research is necessary to determine which subset of patients will benefit most from the treatment, especially in minority subgroups such as women, disabled patients, and patients with comorbidities. This guidance will aid health professionals in determining the optimal course of treatment for their specific patients. Analyses of cost-effectiveness for each intervention will also be useful in reducing the economic burden of stroke.

6.3 Prolonging the treatment window

Therapies with neuroprotectives that are aimed at slowing down the cascade of events leading to cell death have been tested, but the results have been disappointing. These unfavourable results might have been the product of many methodological errors. If neuroprotectors are to be effective in slowing down cell death this may be very useful in prolonging the therapeutic window, and therefore the management of acute stroke. Some publications have suggested that it would be beneficial to begin the use of neuroprotector earlier in the chain of care, before treatment with fibrinolytic agents. More funding is urgently needed in this specific area of research.

Currently there are multiple ongoing trials for various therapies to expand the treatment window. Desmoteplase is the only thrombolytic agent in late-stage development for acute ischemic stroke that is now tested in patients with proven stroke pathology. Further research is needed in this area to translate these practices to the bedside.

Ultrasound-enhanced thrombolysis is another promising therapy that may enhance thrombolysis. A Phase III trial is currently under way, and its results will provide guidance on further approaches to apply this therapy to patients.

Treatments for late intervention

Many therapies that are not indicated in the early stages of care because of serious complications such as cerebral haemorrhage, but they may be useful at later stages when haemorrhages are less likely to occur. Some other therapies target mechanisms that appear several hours after the onset of the symptoms. Exploitation of such therapies will
significantly increase the number of patients that could be treated leading to major improvements in healthcare provision.

One of the fast-growing areas of research for stroke therapies outside (and in some cases, inside) the acute treatment window is applications of stem cells. Though no trials have been performed on patients to date, animal studies have been producing very promising results. Many questions remain to be answered, including which type of stem cells should be used, what the best mechanism of action is, which patients will benefit most, when the optimal timing to apply the stem cells is, and what the best way is to deliver and track the cells. More research and funding are urgently needed in this emerging area of research.

7. Where does Europe have an advantage?

The European Commission (EC) has a unique research advantage because it has the power to unite scientists, patients, policymakers, health care workers, and other actors across the continent towards a common goal. Through these partnerships, the EC can foster substantial advances in the arena of stroke-related research and management. Framework Programme 7 (FP7) works towards the creation of a European research area that contributes to the development of a knowledge-based economy and society in Europe via its goals of: supporting transnational cooperation across the EU, strengthening human potential in research and technology in Europe, and enhancing the excellence of European research institutions and universities. Several large-scale, EU-funded projects established under the Health theme (six-year budget of EUR 6100 million) of the FP7 are currently under way, and will provide further insight into the future of stroke care.98

The EUSTROKE initiative, with funding of nearly EUR 10 million, focuses on the "neurovascular unit" (NVU) - the complex system of neurons, microvessels, and supportive cells – as a target of ischaemic injury.99 This research will expand upon our understanding of this dynamic unit by looking beyond a single-cell approach towards a more integrated answer to ischaemic brain damage. The project will aim at developing new methods for targeting the NVU, in order to potentially evolve multi-targeted or combination therapeutic approaches. Past investigations into neuroprotectives focused more narrowly on neurons, and EUSTROKE researchers will expand this focus to include the entire neurovascular unit in hopes of increased translational success of these therapies.

Another major EC-funded program investigating new stroke therapies is ARISE (Affording Recovery In Stroke), which has a budget of over EUR 11 million. Its objective is to develop novel approaches to minimize the propagation of brain damage after stroke, and to repair damage if it cannot be prevented. Because of the substantial overlap between the ARISE and EUSTROKE programs, the two initiatives collaborate strongly and have joined to form the European Stroke Network (ESN, europeanstrokenetwork.eu), where researchers from all parties can share results, plan joint trials, and discuss challenges and opportunities, while being advised by a joint advisory board.99

One EU-funded study in particular that many experts are hopeful for is EUROHYP-1, a phase III clinical trial that will assess the benefits of therapeutic cooling in adult patients with
acute ischaemic stroke (including efficacy, safety, and economic impact of the therapy). In animal studies, cooling to 35°C reduced the size of the infarct by about one third, and cooling to 34°C reduced it by around 45%. Thus, this study aims to determine whether systemic cooling to a target temperature of 34 to 35°C started within 6 hours of symptom onset and maintained for 24 hours, improves functional outcome at three months in patients with acute ischaemic stroke. According to Dr. Malcolm Macleod, head of experimental neuroscience in the Centre for Clinical Brain Sciences at the University of Edinburgh, “A project of this scale would not be possible without a pan-European approach—no one country or smaller group of Member States has yet managed to organize a clinical trial of therapeutic cooling for stroke, despite widespread acknowledgement that this is an important and promising therapy.” Results of the EUROHYP-1 trial are not yet available.

Another long-awaited initiative being funded by the FP7 is investigation into a “polypill” designed to prevent heart attack and stroke. The project is titled UMPIRE (‘Use of a Multidrug Pill In Reducing cardiovascular Events), and is receiving EUR 3 million under the Health theme of the FP7. This low-cost one-a-day pill will contain multiple medicines: a low-dose aspirin, a statin to lower blood cholesterol, and two blood-pressure-lowering medicines. The concept behind the polypill is to make it easier for patients to take all of their needed medicines by combining them into one pill, rather than patients having to take multiple pills a day at different times, which often results in patients discontinuing the use of their medicines. UMPIRE researchers hope to investigate patient preferences regarding a polypill vs. multiple pills, as well as if the single-pill strategy actually reduces blood pressure and lowers cholesterol. The European results will eventually combine with trials carried out in Australia, Brazil, Canada, China, India, New Zealand, and South Africa. Ultimately, the final data will represent 7,000 patients across ten countries. The polypill’s low cost makes it an attractive candidate for use in low- and middle-income countries, where people often do not have frequent access to affordable health services. Its health and economic value in high-income countries will be evaluated in the UMPIRE study as well. Encouraging preliminary results were presented at the American Heart Association conference in 2012. (See Chapter 6.3).

The disease burden of stroke in Europe has not largely changed between 2004 and 2012. This means that, in addition to medicines, other stroke-care issues such as health systems are important to include when assessing the value of current stroke prevention and treatment methods. The EUROHOPE (European Health Outcomes, Performance, and Efficiency) project, with a budget of 3.99 million, will evaluate the performance of health care systems across EU Member States. Researchers will measure performance, quality, use of resources, and health care costs for five key public health issues, one of which is stroke care, which still suffers from gaps in timely access and access to effective thrombolytic treatments. They will also investigate the relationships between patient outcomes and costs of various treatments across European countries and regions, and assess potential causes behind any differences. The study will begin by investigating seven Member States (Finland, Hungary, Italy, the Netherlands, Norway, Sweden, and the United Kingdom), and expanding from there.

Horizon 2020, the programme to follow FP7, will take place from 2014 to 2020 and will be the financial instrument implementing the Innovation Union, a flagship initiative that is aimed at securing Europe’s global competitiveness. It will combine funding currently provided through the Framework Programmes for Research and Technical Development (FP), Competitiveness and Innovation Framework Programme (CIP), and the European Institute
Update on 2004 Background Paper, BP 6.6 Stroke

of Innovation and Technology (EIT), and will have a total budget of approximately EUR 80 billion over six years.\textsuperscript{104}

Expanding upon the research that the EUROHOPE study will provide about health systems across Europe, Horizon 2020 is placing an emphasis on personalized health care.\textsuperscript{105} Much remains to be understood and resolved about personalized health care, including its costs, patient benefits, necessary regulatory processes, and whether it is a realistic possibility in the current health budget framework, given the high costs of screening, diagnosis, and treatment (see Chapter 8.4). Additionally, patients with comorbidities, as is often the case with stroke, present challenges. Large-scale research studies are necessary to ensure that patients receive the treatment they will benefit the most from, and the European Commission has the power to initiate such influential trials.

Future research funded by the European Commission should be on carefully chosen topics that can make important contributions to improving care for stroke, but which private sector actors, such as pharmaceutical companies, will not explore themselves. An example of such research is the aforementioned EUROHYP-1 study, which does not necessarily involve a profitable medical device or pharmaceutical that would be developed by a private company. Future areas for public sector research to explore include (a) comparative effectiveness research and (b) development of clear and safe guidelines along the entire chain of stroke care.

The European Union has the advantage of containing a large number of highly skilled professionals in many sectors throughout its diverse Member States. Thus, they are uniquely positioned to implement large-scale projects by coordinating funds and fostering partnerships to increase efficiency and reliability of research that will get necessary stroke treatments developed and implemented. Applications of these studies could potentially have positive impacts on reducing the burden of stroke throughout not only Europe, but the entire world.

8. Conclusions

Ischaemic and haemorrhagic stroke are the second leading cause of death and disability worldwide. Acute stroke accounts for 3.2\% of total DALYs globally, the estimated cost of lifetime care for a stroke survivor in the US is \$140,048. The mortality, economic costs, disability, and associated with acute stroke are only expected to rise as the world’s population ages.

The natural progression of stroke allows for many possible points of intervention. During ischaemic stroke, the occlusion of blood flow produces irreversible cellular death within a few minutes. Surrounding the ischaemic core is the tissue that is affected by ischaemia, but still functional and recoverable. Any therapeutic measures should be directed in stopping the progression of the ischaemia and achieving functional recovery of tissue as soon as possible. Time is a major factor in treatment of acute stroke due to the nature of the disease.
The management of patients with acute stroke requires multiple interventions, an accurate initial diagnosis, close monitoring of potential complications and skilled highly trained professionals. The evidence suggests that mortality can be reduced further and neurological disability can be avoided or improved with the appropriate treatment of acute stroke.

Major improvements in stroke care have been made since 2004. Many patients around the world are now treated in specialized stroke units which increase patient survival and improve long term positive outcomes. Increasing access to stroke units around the world should be a top priority and is an opportunity to improve stroke outcomes for many. Several recent studies indicate that the therapeutic window for thrombolysis treatment can safely be extended from three hours to four and a half hours. Recent advancements in secondary prevention, such as long term treatment with aspirin or statins, reduce stroke reoccurrence. Lastly, improvements in post stroke supportive care speed recovery and increase patients’ quality of life.

There is a still long way to go. Major improvements are needed in the chain of care, in the identification of an attack by relatives (education), early treatment (aspirin?), the prompt referral to an accident and emergency facility (mobile units), accurate diagnosis and fast and appropriate treatment (protocols and specialized units), improving access to efficacious therapeutic options, and prompt referral to rehabilitation services.

The results of trials of therapies currently in the pipeline have been disappointing, especially in the field of neuroprotectors. Promising advancements have been made in the field of hypothermic treatments and stem cell applications, though they are not yet ready for implementation in the health system. More research is necessary in these areas, especially for patients with comorbidities.

The decrease in mortality is due to the provision of complex and costly general care and not as a result of salvaging the ischaemic brain by specific stroke therapy. Most patients sadly have significant disability when they are discharged from the hospital where the society is expected to support. More efficacious treatments provided earlier in the chain of care are needed to avoid future suffering and the economic cost of increasing disability in rapidly ageing societies.

Principal messages from the 2012 update:

- Stroke research remains severely underfunded despite its high burden in both Europe and the world.
- A breakthrough therapy has yet to be approved and there are still no highly effective acute therapies available.
- Promising research is being done in the areas of hypothermia, stem cell therapies, and a polypill for secondary prevention of stroke.
- More clinical trials that focus on patients with comorbidities and the elderly are needed.
- Due to lack of advancement in acute pharmaceutical treatments for stroke, there should be an emphasis on prevention and improving health approaches such as specialized stroke units.
References


Update on 2004 Background Paper, BP 6.6 Stroke


Update on 2004 Background Paper, BP 6.6 Stroke

57 Berge E, Sandercocck P. Anticoagulants versus antiplatelet agents for acute ischaemic stroke. [see comment]. [Review] [33 refs]. Cochrane Database of Systematic Reviews. 2002;CD003242.
Update on 2004 Background Paper, BP 6.6 Stroke


Intracerebral peripheral blood stem cell (CD34+) implantation induces neuroplasticity by enhancing beta1 integrin-mediated angiogenesis in chronic stroke rats. J Neurosci. 2006;26:3444–3453

Intravenous bone marrow stromal cell therapy reduces apoptosis and promotes endogenous cell proliferation after stroke in female rat. J Neurosci Res. 2003;73:778–786


Annex

Annex 6.6.1: Demographic Data on Stroke Patients and Base Population for Each Area of Socioeconomic Disadvantage

<table>
<thead>
<tr>
<th>Area of Socioeconomic Disadvantage</th>
<th>Strokes n</th>
<th>First-Ever No. (%)</th>
<th>Male (%)*</th>
<th>Mean Age* (years)</th>
<th>Current Smoker n (%)**</th>
<th>Hypertension n (%)***</th>
<th>Population Base &gt;65 Years</th>
<th>%</th>
<th>% Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least disadvantaged</td>
<td>346</td>
<td>253 (73.1)</td>
<td>39.1</td>
<td>77.9</td>
<td>18 (7.1)</td>
<td>118 (47)</td>
<td>17.2</td>
<td>38.5</td>
<td></td>
</tr>
<tr>
<td>Less disadvantaged</td>
<td>381</td>
<td>260 (70.6)</td>
<td>39.4</td>
<td>77.2</td>
<td>18 (6.7)</td>
<td>148 (55)</td>
<td>16.0</td>
<td>37.6</td>
<td></td>
</tr>
<tr>
<td>Disadvantaged</td>
<td>321</td>
<td>228 (71.0)</td>
<td>47.4</td>
<td>71.8</td>
<td>50 (21.9)</td>
<td>125 (55)</td>
<td>12.9</td>
<td>43.3</td>
<td></td>
</tr>
<tr>
<td>Most disadvantaged</td>
<td>373</td>
<td>285 (76.4)</td>
<td>49.5</td>
<td>71.5</td>
<td>59 (20.7)</td>
<td>167 (59)</td>
<td>13.5</td>
<td>42.5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1421</td>
<td>1035 (72.8)</td>
<td>43.9</td>
<td>74.6</td>
<td>145 (14.0)</td>
<td>559 (54)</td>
<td>14.9</td>
<td>40.2</td>
<td></td>
</tr>
</tbody>
</table>

*Mean and proportion of first-ever strokes only; †missing values in smoking status are 59 (23%) in the least disadvantaged, 42 (16%) in the less disadvantaged, 20 (3%) in the disadvantaged, and 23 (8%) in the most disadvantaged; ‡there are 10 missing values in hypertensive status (<1.0%).

Background Paper 6.7
Human Immunodeficiency Virus (HIV)/
Acquired Immune Deficiency Syndromes (AIDS)

By Warren Kaplan, Ph.D., JD, MPH

15 February 2013
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What is new since 2004?

**Treatment as prevention.**

There is increasingly strong scientific evidence for use of antiretrovirals (ARV) in the prevention of HIV transmission. HIV transmission only occurs from people with HIV, and the greatest risk factor for HIV transmission is the viral load and lowering the viral load reduces the risk of transmission. ARV therapy dramatically lowers viral load and numerous observational studies have demonstrated its potential for prevention of HIV transmission.\(^1\)

The so-called HPTN 052 Trial clearly demonstrated the effectiveness of treatment as prevention. The early initiation of antiretroviral therapy reduced rates of sexual transmission of HIV-1 and clinical events, indicating both personal and public health benefits from such therapy.\(^4\)

Prevention of maternal-to-child transmission (PMTCT) offers further proof of concept that ARV therapy essentially interrupts HIV transmission. In the USA and Europe, perinatal AIDS cases have been virtually eliminated most likely due to the implementation of guidelines for the universal counseling, voluntary HIV testing and ARVs for pregnant women and newborn infants.\(^5\) In 2008, the majority of the 430 000 new paediatric HIV infections were in sub-Saharan Africa, where there is recent evidence that ARVs can be used to decrease transmission to 1%.\(^1\)

Improvement in 2\(^{nd}\) and 3\(^{rd}\) line therapeutics (e.g. approval of integrase inhibitors, CCR5 inhibitors new Protease inhibitors and NNRTs). See Section 3.2, below

**The rise and fall of treatment sparing/episodic regimens.**

The inherent risks and problems associated with lifelong antiretroviral therapy have led to studies of treatment-sparing strategies that might provide the benefits of antiretroviral therapy while minimizing the risk of adverse events and other risks associated with long-term use. The SMART trial showed that episodic antiretroviral therapy guided by the CD4+ count significantly increased the risk of opportunistic disease or death from any cause, as compared with continuous antiretroviral therapy, largely as a consequence of lowering the CD4+ cell count and increasing the viral load. Episodic antiretroviral therapy does not reduce the risk of adverse events that have been associated with antiretroviral therapy.\(^6\)

**Treating patients earlier as illustrated in various guidelines, to counter the effects of non AIDS-related morbidities.**

Key guidelines are now recommending treatment for all adults with HIV infection; the strength of the recommendation and the quality of the evidence increase with decreasing CD4+ cell count and the presence of certain concurrent conditions.\(^7\)

In brief, recommended initial regimens include two nucleoside reverse transcriptase inhibitors (tenofovir/emtricitabine or abacavir/ lamivudine) plus a non-nucleoside reverse transcriptase inhibitor (efavirenz), a ritonavir-boosted protease inhibitor (atazanavir or darunavir), or an integrase strand transfer inhibitor (raltegravir).\(^8\) Alternatives in each class
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are recommended for patients with or at risk of certain concurrent conditions. CD4+ cell count and HIV-1 RNA level should be monitored, as should engagement in care, ART adherence, HIV drug resistance, and quality-of-care indicators.\(^8\) Confirmed treatment failure should be addressed promptly and multiple factors considered.

**Pre-exposure prophylaxis (PrEP):**

Taking a daily pill to reduce HIV risk is a potential breakthrough pharmaceutical prevention strategy. Daily use of some antiretrovirals (Truvada®; Gilead) has shown up to 73% effective in preventing HIV/AIDS transmission among men who have sex with men (MSM).\(^9\)

**Vaginal microbicides:**

There have been setbacks in the development of a gel containing tenofovir– a microbicide that can be used vaginally or anally to prevent HIV transmission. The CAPRISA study, unveiled to much fanfare in 2010, found such a gel partially prevented infection in women.\(^10\) But this year, another study was partly cancelled after researchers discovered that one of the gels it was testing failed to prevent infection.\(^9\) Scientists are unsure why the latest trial was unsuccessful.

Several microbicide candidates are under study. Following several failures in Phase II/III trials (PRO 2000, BufferGel and VivaGel), new candidates using active ingredients from ARVs have shown promising results in Phase II trials. These include dapivirine gel, a long acting dapivirine-based microbicide ring, and CAPRISA 004 tenofovir-gel, which is currently being fast-tracked by the FDA pending results of confirmatory trials.\(^11\)

**Global Progress**

The most recent study in 2012 by the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that new HIV infections and AIDS-related deaths have fallen to the lowest levels since the peak of the epidemic. See Appendix 6.7.1 and Appendix 6.7.2.

Briefly, in the last ten years the landscape of national HIV epidemics has changed for the better in most countries, especially in sub-Saharan Africa. There were 700 000 fewer new HIV infections across the world in 2011 than in 2001. Latest data show that a 50% reduction in the rate of new HIV infections (HIV incidence) has been achieved in 25 low- and middle-income countries between 2001 and 2011.

However, in the Middle East and North Africa, the number of people newly infected with HIV increased by 35% between 2001 and 2011, and the rate of new HIV infections continues to rise in Eastern Europe and Central Asia.

The commercial market for antiviral therapeutics will ensure that there will be no shortage of private research funding for the immediate future. Opportunities exist for public funding of research. Both private and public funders, however, should consider the following:

- Although the clinical efficacy with the existing antivirals has improved dramatically, additional forms of therapy and treatment strategies are needed.
- Antiviral therapy alone will not end the epidemic and a comprehensive public health approach remains essential.
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- Because the HIV genome mutates very rapidly, during the course of an infection, the development of resistance to antivirals is common. There is a continuing need for the development of new antiviral agents.
1. Introduction

AIDS is the deadliest epidemic of our time. The infective agent, human immunodeficiency virus (HIV), has already infected more than 60 million people around the world. AIDS is the leading cause of infectious disease mortality, surpassing tuberculosis and malaria. In 2008, about 68% of people living with HIV were in sub-Saharan Africa with around 35% in eight countries alone. In 2005 and 2009, the G8 met in Scotland and Italy and committed to achieving universal access to HIV prevention, care and treatment by 2010. However, universal access remains a dream for millions of people and faces serious technical, economic and political challenges on a number of fronts. See Appendices 6.7.1-4.

2. What are the Epidemiological Trends for Europe and the World?

2.1 Western and Central Europe

At the end of 2010 it was estimated that around 840,000 people were living with HIV in Western and Central Europe. See also Appendix 6.7.5.

The HIV epidemic is fairly stable as a whole, with the transmission rate having changed little since 2004. See Appendix 6.7.1. Although the total number of people living with HIV and AIDS in the European region is relatively small when compared to areas such as Asia and sub-Saharan Africa, HIV and AIDS in Western and Central Europe is still considered to be a major public health issue. See Appendix 6.7.5: WHO (2010) 'European Action Plan for HIV/AIDS 2012-2015’ and Appendix 6.7.6: WHO Europe (2009, December) ‘HIV/AIDS surveillance in Europe 2008’.

More encouragingly, the total deaths due to AIDS in this region have decreased since the introduction of combination antiretroviral treatment in the mid-1990s (See also Figure 6.7.2). Most Western and Central European countries benefit from wealthy economies, stable infrastructures and developed healthcare systems, and so the majority of people needing antiretroviral treatment are receiving it. Many people now consider HIV as a chronic disease. Generally HIV and AIDS have affected Western Europe more than Central Europe. See Figure 6.7.1. At an estimated 0.6%, Portugal has the highest HIV prevalence, followed by Switzerland, Spain and France. See also Appendix 6.7.1. In 2010 the UK reported the highest number of new HIV diagnoses, where incidence had increased by more than 50% between 2000 and 2009. (See Appendix 6.7.6).

HIV prevalence in Central Europe has remained at a relatively low level (see Figure 6.7.1). Croatia, Slovakia and Slovenia all have HIV prevalence figures under 0.1% (see also Appendix 6.7.1 and Appendix 6.7.6). Generally in the region key populations at higher risk include injecting drug users (IDUs) and their sexual partners, men who have sex with men (MSM), transgender people, prisoners, sex workers and migrants (see Appendix 6.7.5). In Western Europe the epidemic is homogenized, with heterosexual transmission accounting for 40% of diagnoses, many of which are among people who became infected in regions where there is a generalized epidemic.
In both Western and Central Europe injecting drug use (IDU) accounted for 4% of new HIV diagnoses in 2010. There has been a steady decline in new HIV infections among injecting drug users in Western and Central Europe since the beginning of the century, which could be explained by the increasing availability of harm reduction measures, such as needle exchanges. IDU is still an important factor in several countries, and there have been some large increases in particular localized areas (see Appendix 6.7.7). Poland has reached an HIV prevalence of 18% in some areas among IDUs, and in Greece and Romania there have been significant increases in cases of HIV among this group. 

Figure 6.7.1 below shows the estimated adult HIV prevalence in 2009.

Figure 6.7.1: Estimated adult HIV prevalence in 2009

With the roll-out of anti-retrovirals (ARVs) there was a general expectation that the widespread availability of antiretroviral therapy would act as an incentive for individuals to get tested for HIV. Once diagnosed, the drugs will help them stay healthy for a longer period of time. However, in Western and Central Europe, rates of late diagnosis have either remained at high levels or have increased. Unfortunately, definitions of “diagnosing late” vary from less than 50 to less than 200 CD4+ T cells/microliter. Even now, many people are unaware that they are living with HIV. Opportunities to diagnose HIV infections are often missed, particularly in healthcare settings, and testing among injecting drug users is
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particularly low. Late diagnosis of HIV has serious implications for both the individual and public health. Even considering that treatment reduces transmission rates, if a person is diagnosed at a late stage they are more likely to develop an AIDS-related illness, are less likely to respond to antiretroviral treatment and are at an increased risk of mortality. As people are more likely to take precautions to prevent transmission if they know they are infected with the virus, late or no diagnosis can increase the risk that HIV will be transmitted, which has wider public health implications.

In sum, reasons why people in Western and Central Europe still die from AIDS include:

- **A high number of late diagnoses.**
  Early diagnosis of HIV infection is essential to ensuring that patients are referred promptly for evaluation, provided treatment (if indicated), and linked into counseling and related support services to help them reduce their risk for transmitting HIV to others. Diagnosing persons during acute infection is particularly important. It is during this phase that HIV-infected persons are most infectious, but test negative for HIV antibodies and therefore unknowingly continue to engage in those high-risk behaviors associated with HIV transmission. A key point for emphasis therefore is the need to diagnose all persons with HIV. There is a critical need to encourage wider uptake of voluntary testing for HIV to ensure earlier access to counselling and treatment (as needed). It would appear that testing uptake increases with ‘opt-out’ policies – whereby a test is performed unless the patient asks not to have one.

- **Access to treatment and care for migrants may be limited.**
  There is some evidence that in some European countries, migrants from countries with generalized HIV epidemics are disproportionately affected by HIV and do not access testing or treatment services as readily as other populations.

- **Drug resistance.**

- **Ageing and disease progression.**
  The prevalence of human immunodeficiency virus (HIV) in the over-50 age group is increasing as a consequence of younger adults ageing with HIV, in addition to new diagnoses in later life. Older adults are vulnerable to late or missed diagnosis and poorer treatment outcomes, due to the misconception that they are not at risk. As the HIV population ages, the emergence of disease and treatment complications such as cardiovascular disease, osteoporosis and dementia are evident. Renal function declines with age and HIV infection, affecting drug clearance – the risk of drug toxicities and mortality associated with cardiovascular events. Management of older adults with HIV and multiple comorbidities presents challenges to infectious diseases physicians and geriatricians alike. Inclusion of older adults in future HIV clinical trials will help design healthcare models to provide for this growing population.

### 2.2 Eastern Europe

Driving the epidemics in Eastern Europe is unprotected sex (including between men) and sharing contaminated drug-injecting equipment. See also Appendix 6.7.1. The HIV incidence among people who inject drugs in St Petersburg, Russian Federation, for example, was 8.1 per 100 person-years in 2009, almost twice the rate five years earlier. Appendix 6.7.1. By some estimates, there could be as many as 3 million injecting drug users in the Russian Federation alone, more than 600 000 in Ukraine and up to 200 000 in Kazakhstan. In Estonia and Latvia, it has been estimated that up to 1% of the adult population injects illicit drugs,
while, in Kyrgyzstan, that figure could approach 2%. Most of these drug users are male and many are very young. In St Petersburg, studies found that 30% of males were under 19 years of age, while in Ukraine 20% were still in their teens. The situation regarding HIV in IDUs in Eastern Europe is worrying. Data on reported HIV cases in IDUs suggest increasing incidence of HIV infection among people who inject drugs. In 2007, IDUs accounted for 57% of newly diagnosed HIV infections reported in this region.

The prevalence of HIV infection among adults in 2009 was 1% [0.9–1.2%] in the Russian Federation and 1.1% [1.0–1.3%] in Ukraine. See Appendix 6.7.1. Together, those countries account for almost 90% of the people newly reported to be diagnosed with HIV infection in this region and are home to twice as many people living with HIV as all of Western and Central Europe combined. See Appendix 6.7.1. Unlike most other regions, the number of people dying from AIDS-related causes continues to rise in Eastern Europe and Central Asia. The HIV epidemic claimed an estimated 83 000 [69 000–100 000] lives from AIDS-related causes in 2010, which is 11 times more than the estimated 7800 [6000–11 000] in 2001. See Appendix 6.7.1.

Since the mid-1990s, there has been a significant decline in AIDS-related mortality in Western and Central Europe (“EU27” and “EU15”). Most people living with HIV in these regions have access to combination therapy. As Figure 6.7.2 illustrates, the rate of HIV/AIDS deaths (per 100 000) has dramatically dropped in the EU27 and EU 15 due to the widespread availability of antiretroviral treatment beginning in the mid-late 1990s. In the EU12, HIV/AIDS is driven primarily by injecting drug use and the mortality changes are due to programmes that reach injecting drug users, including those in prisons and those who belong to marginalized minorities. See Appendix 6.7.1.

Figure 6.7.2: Standardized death rates (per 100 000 persons) of HIV/AIDS among country-components of the European Union
2.2 The World (including Europe)

The most recent 2012 UNAIDS report, Together We Will End AIDS (Appendix 6.7.1) shows a more than 50% reduction in the rate of new HIV infections has been achieved across 25 low- and middle-income countries most affected by HIV. In some of the countries which have the highest HIV prevalence in the world, rates of new HIV infections have been cut dramatically since 2001 due to increased access to medicines and improved healthcare delivery; by 73% in Malawi, 71% in Botswana, 68% in Namibia, 58% in Zambia, 50% in Zimbabwe and 41% in South Africa and Swaziland.

Sub-Saharan Africa increased the number of people on antiretroviral treatment by 59% in the last two years alone. The available evidence in the Middle East and North Africa points to ongoing increases in the number of people acquiring HIV infection. In this region in 2011, an estimated 36 000 [26 000–56 000] adults acquired HIV infection, 29% more than in 2001.
More specifically, the number of people dying annually from AIDS-related causes worldwide decreased from a peak of 2.3 million [2.1 million–2.5 million] in 2005 to an estimated 1.7 million [1.6 million–2.0 million] in 2011. This is most evident in sub-Saharan Africa, where an estimated 550 000 (31%) fewer people died from AIDS-related causes in 2011 than in 2005, when the number of AIDS-related deaths peaked. AIDS-related deaths in the Middle East and North Africa increased from 14 000 [8600–28 000] in 2001 to 25 000 [17 000–35 000] in 2011. See Appendix 6.7.1.

In Latin America, wide access to antiretroviral therapy has helped reduce the annual number of people dying from AIDS-related causes to 57 000 [35 000–86 000] in 2011, down from 63 000 [35 000–105 000] 10 years earlier. In the Caribbean, an estimated 10 000 [8000–12 000] people died from AIDS-related causes in 2011, about half as many as in 2001.

In Western and Central Europe and North America, the extensive availability of antiretroviral therapy, especially in the countries with the largest epidemics, has significantly reduced AIDS-related mortality. The combined number of people dying from AIDS-related causes in these regions has varied little during the past decade and totalled an estimated 29 000 [26 000–36 000] in 2011. However, the report shows that HIV continues to have a disproportionate impact on sex workers, men who have sex with men and people who inject drugs. HIV prevention and treatment programmes are largely failing to reach these key populations.

The number of people dying from AIDS-related causes has remained stable in Asia (about 330 000 [260 000–420 000] persons in 2011), the largest number of deaths outside of sub-Saharan Africa. In Eastern Europe and Central Asia, AIDS-related deaths continue to rise. In 2011, an estimated 90 000 [74 000–110 000] people died of AIDS-related causes, six times more than the estimated 15 000 [11 000–26 000] in 2001. In the Russian Federation alone, the number of people reported newly diagnosed increased from 39 207 in 2005 to 62 581 in 2010. Since 2005, newly reported HIV cases have also been increasing in the smaller epidemics in Central Asia (Kyrgyzstan, Tajikistan and Uzbekistan). The use of contaminated injecting equipment remains the main route of transmission in this region.

HIV-related tuberculosis (TB) remains a serious challenge as TB remains the leading cause of death among people living with HIV. More than 80% of the people living with HIV and TB are in sub-Saharan Africa. Appendix 6.7.1.

Table 6.7.1 is taken from Appendix 6.7.9 (2011 UNAIDS report) and while slightly different than the numbers cited above (Appendix 6.7.1) they do show the order of magnitude changes in these metrics over time.
Table 6.7.1: Various measures of HIV/AIDS burden of disease since 2001

<table>
<thead>
<tr>
<th></th>
<th>2001</th>
<th>2005</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>People living with HIV</td>
<td>28.6 million</td>
<td>31.0 million</td>
<td>32.3 million</td>
<td>32.9 million</td>
<td>34 million</td>
</tr>
<tr>
<td></td>
<td>[26.7-30.9 million]</td>
<td>[29.2-32.7 million]</td>
<td>[30.4-33.8 million]</td>
<td>[31.0-34.4 million]</td>
<td>[31.6-35.2 million]</td>
</tr>
<tr>
<td>New HIV infections</td>
<td>3.15 million</td>
<td>2.81 million</td>
<td>2.74 million</td>
<td>2.72 million</td>
<td>2.67 million</td>
</tr>
<tr>
<td></td>
<td>[2.96-3.33 million]</td>
<td>[2.63-2.97 million]</td>
<td>[2.52-2.93 million]</td>
<td>[2.48-2.93 million]</td>
<td>[2.46-2.90 million]</td>
</tr>
<tr>
<td>AIDS-related deaths</td>
<td>1.85 million</td>
<td>2.22 million</td>
<td>2.04 million</td>
<td>1.89 million</td>
<td>1.76 million</td>
</tr>
<tr>
<td></td>
<td>[1.67-2.16 million]</td>
<td>[2.07-2.48 million]</td>
<td>[1.87-2.21 million]</td>
<td>[1.72-2.05 million]</td>
<td>[1.59-1.91 million]</td>
</tr>
<tr>
<td>New infections in children</td>
<td>550 000 [490 000-620 000]</td>
<td>540 000 [480 000-600 000]</td>
<td>460 000 [400 000-510 000]</td>
<td>430 000 [370 000-490 000]</td>
<td>390 000 [340 000-450 000]</td>
</tr>
</tbody>
</table>

Source: Appendix 6.7.9; 2011 UNAIDS report

3. What is the Control Strategy? Is There an Effective Package of Control Methods Assembled into a “Control Strategy” for Most Epidemiological Settings?

3.1 Is there a pharmaceutical ‘gap’?

Yes, there is a gap because there is no cure for HIV. Further, the presence of continued resistance demands more therapeutic options going forward and this constitutes a “gap” as well. Notwithstanding the many treatments that are clinically efficacious, operationally effective and prolong life. (See Section 3.2), prevention of resistance is a priority that requires unrelenting patient education regarding the risks of resistance and the use of improved drug regimens that ensure optimal tolerance, adherence, and potency. Third, although the HIV intra-cell life cycle is well known, there need to be more therapeutics that attack all aspects of its life cycle.

3.2 Treatment options and targets

3.2.1 Viral life cycle

Whereas the HIV-1 life cycle presents many potential opportunities for therapeutic intervention, only a few have been exploited. The replication scheme of HIV-1, shown in Figure 6.7.6 (see page 42) (taken from Moore and Stevenson, 2000), marked with the steps blocked by approved inhibitors as of 2012 (numbers in panel 2A). A timing of the retroviral lifecycle is described in panel B based on the specific time window of inhibition by a specific drug class. In panel 2C, the inhibitors in development (normal text) or FDA approved (italic/bold text) are listed by inhibition of a specific retroviral replication event.

Attempts to block HIV-1 infection attack many steps in the viral life cycle of HIV-1. These steps include virus–cell attachment, virus entry and virus uncoating. The reverse transcription of viral cDNA, nuclear import and integration into the host cell’s genome are
also potential sites of inhibition. One antagonist of viral entry (e.g. fusion inhibitors) has been approved by the FDA (Table 6.7.2) and others are now in, or approaching, human clinical trials. Fusion inhibitors are directed against both the viral glycoproteins that interact with receptors and co-receptors on the host cell membrane. The co-receptors CCR5 is also now a target for an approved medicine.

The design of post-entry inhibitors remains problematic; the more advanced inhibitors include agonists of the integrase enzyme, which mediates viral cDNA integration into the host cell’s genome. Design of new viral-entry inhibitors also considers the escape pathways adopted by the evolving HIV-1 virus in response to inhibition of its normal entry route. The most successful therapeutic approach will likely be a ‘cocktail’ of inhibitors, which block infection at several points, including the potential escape pathways.

Specifically, the first step in the HIV-1 replication cycle, viral entry is the target for several classes of antiretroviral agents: attachment inhibitors, chemokine receptor antagonists, and fusion inhibitors. The HIV-1 envelope gp120/gp41 has affinity for the CD4 receptor and directs HIV-1 to CD4+ immune cells. Interaction of the gp120 subunit of the HIV-1 envelope with CD4 is followed by binding to an additional co-receptor, either the CC chemokine receptor CCR5 or the CXC chemokine receptor CXCR4. These sequential receptor-binding events trigger conformational changes in the HIV-1 envelope, exposing a hydrophobic domain on gp41 that mediates fusion with the cellular membrane. The entire entry process is completed within 1 h of virus contact with the cell (Fig. 2B). Gp120 and CD4 are targets for attachment inhibitors BMS-626529 which binds to the HIV-1 gp-120 envelope protein and prevents it from attachment to CD4 receptors and TNX-355, each of which have shown some clinical promise. TNX-355 (Ibalizumab) is a humanized anti-CD4 monoclonal antibody that binds to CD4 and inhibits HIV-1 envelope docking, but does not inhibit CD4 function in immunological context. It has not yet been evaluated by the U.S. Food and Drug Administration (FDA). Gp41 and the co-receptor CCR5 are the targets for the two approved entry agents: the peptide-based fusion inhibitor, fuzeon, and the small-molecule CCR5 chemokine receptor antagonist, maraviroc. See Section below.

In constructing an antiretroviral therapy (ART) regimen for a patient the treating clinician now has nearly 30 separate medicines in different classes as well as a variety of fixed dose combination pills to choose from – a remarkable diversification in just 25 years since the introduction of AZT for the treatment of HIV. See Table 6.7.2. For the first time in over a decade a new class drug – the integrase inhibitor raltegravir – has now been added to the preferred choices for first line ART to be used in combination TDF/FTC. The preferred nucleoside/nucleotide “backbone” for NNRTI, boosted PI regimens and raltegravir has been narrowed to a single choice – that of TDF/FTC because of toxicity concerns associated with the other choices. In particular thymidine analogs – zidovudine (AZT) and stavudine (D4T) are no longer part of the preferred list because of the increased risk of lipatrophy and other metabolic complications associated with long-term use. Dideoxyinosine (ddI) specifically in combination with tenofovir as a nucleoside backbone is generally not recommended due to toxicity considerations. See also Table 6.7.3.

Table 6.7.2 is a list of all approved anti-HIV medicines in the USA. Some, but by no means all of these, include both adult and paediatric dosages. See AIDSinfo Drug Database http://aidsinfo.nih.gov/drugs/search/searchterm/0/1/
Table 6.7.2: List of all approved anti-HIV medicines in the USA

<table>
<thead>
<tr>
<th>Medicine</th>
</tr>
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<tbody>
<tr>
<td>Abacavir</td>
</tr>
<tr>
<td>Abacavir / Lamivudine</td>
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<tr>
<td>Abacavir / Lamivudine / Zidovudine</td>
</tr>
<tr>
<td>Acyclovir</td>
</tr>
<tr>
<td>Atazanavir</td>
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<tr>
<td>Darunavir</td>
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<tr>
<td>Delavirdine</td>
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<tr>
<td>Didanosine</td>
</tr>
<tr>
<td>Efavirenz</td>
</tr>
<tr>
<td>Efavirenz / Emtricitabine / Tenofovir Disoproxil Fumarate</td>
</tr>
<tr>
<td>Elvitegravir / Cobicistat / Emtricitabine / Tenofovir Disoproxil Fumarate</td>
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<td>Emtricitabine</td>
</tr>
<tr>
<td>Emtricitabine / Rilpivirine / Tenofovir Disoproxil Fumarate</td>
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<tr>
<td>Emtricitabine / Tenofovir Disoproxil Fumarate</td>
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<tr>
<td>Enfuvirtide</td>
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<td>Fosamprenavir</td>
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<td>Indinavir</td>
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<td>Lamivudine</td>
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<td>Lamivudine / Zidovudine</td>
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<td>Lopinavir / Ritonavir</td>
</tr>
<tr>
<td>Maraviroc</td>
</tr>
<tr>
<td>Nelfinavir</td>
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<tr>
<td>Nevirapine</td>
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<td>Raltegravir</td>
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<td>Saquinavir</td>
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<td>Stavudine</td>
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<tr>
<td>Tenofovir Disoproxil Fumarate</td>
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<tr>
<td>Tipranavir</td>
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<td>Zidovudine</td>
</tr>
</tbody>
</table>


3.3 Treatment strategies

3.3.1 SMART trial and progeny

The inherent risks and problems associated with lifelong antiretroviral therapy have led to the study of treatment-sparing strategies that might provide the benefits of antiretroviral therapy while minimizing the risk of adverse events and other risks associated with long-term use.

The SMART trial compared a control strategy, consistent with the 2003 guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents, in which available antiretroviral regimens were used in an uninterrupted manner with the goal of maximal and
continuous suppression of HIV replication. The experimental drug conservation strategy entailed the episodic use of antiretroviral therapy according to CD4+ count thresholds: the use of antiretroviral therapy was deferred until the CD4+ count decreased to less than 250 cells per cubic millimeter, at which time antiretroviral therapy was to be initiated (or reinitiated) and continued until the CD4+ count increased to more than 350 cells per cubic millimeter. Total enrollment was 5472 persons in 33 countries and 318 sites. See http://pag.aids2012.org/session.aspx?s=124#2.

The experimental protocol also permitted antiretroviral therapy to be initiated (or reinitiated) if symptoms of disease from HIV infection (e.g. oral thrush) developed or the percentage of CD4+ lymphocytes (CD4+ percentage) was less than 15%. On confirmation that the CD4+ count was more than 350 cells per cubic millimeter, antiretroviral therapy was to be stopped and then resumed when the CD4+ count was less than 250 cells per cubic millimeter. During periods of antiretroviral therapy, the goal was to achieve maximal viral suppression. The CD4+ count thresholds for stopping and starting antiretroviral therapy were chosen on the basis of reported associations between CD4+ counts and the risks of opportunistic diseases and death.

Trial enrollment was stopped because those patients receiving episodic therapy had twice the risk of disease progression (the development of clinical AIDS or death), the major outcome of the study. That is, episodic antiretroviral therapy guided by the CD4+ count significantly increased the risk of opportunistic disease or death from any cause, as compared with continuous antiretroviral therapy, largely as a consequence of lowering the CD4+ cell count and increasing the viral load. Episodic antiretroviral therapy did not reduce the risk of adverse events that have been associated with antiretroviral therapy.

Results of SMART established a new research agenda. The HIV treatment agenda includes research aimed at understanding the effects of untreated HIV on serious non-AIDS (SNA) diseases; studies of novel inflammatory and coagulation markers as predictors of SNA conditions; studies of new treatments for people with HIV to reduce inflammation and eliminate possible causes of inflammation; comparisons with non-HIV populations to understand the effects of HIV and HIV treatments on accelerated aging; genetic studies of SNA risk and of elevated biomarker levels; and a large clinical trial on when to start ART (the START trial). Overall, SMART provides an appreciation of the role of non-AIDS related mortality and morbidity in patients with HIV.

The START Trial:
See START trial (Strategic Timing of Antiretroviral Treatment) (http://www.niaid.nih.gov/volunteer/hivandinfectious/hivstudies/Pages/STARTStudy.aspx) (http://clinicaltrials.gov/ct2/show/NCT00867048)

The consensus is that continued substantial viral transmission remains the key stumbling block in overcoming the HIV pandemic and that initiation of ART makes persons less infectious. Generally, therapy is of net health benefit to HIV+ persons with HIV-related symptoms or with CD4<350 cells/µL.

The 2010 WHO Guidelines (http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf) assert that all adolescents and adults including pregnant women with HIV infection...
and CD4 counts of ≤350 cells/mm³, should start ART, regardless of the presence or absence of clinical symptoms. The controversy is whether anti-retroviral therapy is of net health benefit to the asymptomatic HIV-positive person if started at a CD4 count >350 cells/µL (i.e. early ART).

As of January 2013, the START study is still recruiting but its objectives are to find out if the chance of developing a serious non-AIDS illness or of getting AIDS is less if patients start taking HIV medicines at a time when their CD4+ T cell count is still fairly high, instead of waiting until the CD4+ count is at the level where the evidence is good for starting treatment (< 350 cells/µL). The primary outcome is a composite endpoint: AIDS, serious non-AIDS diagnoses, and all-cause mortality.

The experimental arm is early ART in which patients are to be initiated on ARTs immediately following randomization using any licensed antiretroviral medication, in accordance with national treatment guidelines. The active comparator arm is the deferred ART protocol in which ART is held off until the CD4+ count declines to <350 cells/µL or AIDS develops.

### 3.3.2 Paediatric HIV: treatments, guidelines and dosage forms

There is still a major gap between children and adults in coverage of antiretroviral therapy. Globally, about 562 000 children received antiretroviral therapy in 2011 (up from 456 000 in 2010), but coverage was only 28% [25–32%]: higher than the 22% [20–25%] in 2010 but much lower than the 57% [53–60%] coverage of antiretroviral therapy among adults. Even though antiretroviral therapy services still reach only a small fraction of eligible children, substantially fewer children are dying from AIDS-related causes: 230 000 [200 000–270 000] in 2011 versus 320 000 [290 000–370 000] in 2005. See Appendix 6.7.1.

In part, this is due to the fact that the cumulative number of new HIV infections averted among children more than doubled between 2009 and 2011 in low- and middle-income countries, as services to eliminate new HIV infections among children were expanded (see Appendix 6.7.1). Almost 600 000 new HIV infections among children have been averted since 1995 due to the availability of antiretroviral prophylaxis both for pregnant women living with HIV and for their infants. Most of the children involved live in sub-Saharan Africa.

Globally, the majority of children with HIV are infected at the time of birth or shortly thereafter when they have limited immune function and an immature central nervous system. Infancy and early childhood is therefore a period of extreme vulnerability, and HIV infection in these first days or weeks of life can lead to rapid disease progression that can be sudden and deadly. To illustrate this, two-thirds of the deaths among infants enrolled in the deferred treatment arm of the South African Children With HIV Early Antiretroviral Therapy (CHER) study occurred before the age of 26 weeks. 32

Many of these children died suddenly of common childhood illnesses with what was considered, at the time, a “normal” or “safe” CD4 cell count. Contrast this with the natural history of HIV in adults, who can survive for many years without symptoms and in whom CD4 cell counts are highly predictive of disease progression. In recognition of the aggressiveness of HIV infection in infants and young children, national and international guidelines have now moved to recommend universal treatment of all children with
confirmed HIV infection younger than the age of 12 months regardless of clinical stage or CD4 cell count. See for example, reference 33.

It is essential to identify and treat HIV-infected children in infancy before the virus causes irreparable harm. Unfortunately, the diagnosis of HIV infection in young infants remains a challenge. The passive transfer of maternal antibodies confounds the diagnosis in children less than 18 months of age when they are most vulnerable. While expansion of early infant diagnosis programs utilizing dried blood spot systems has allowed for the identification of HIV-infected infants even in remote settings, this requires the participation of antenatal and obstetrical services to first identify HIV-positive mothers and the subsequent follow-up of infants to test them at the appropriate time.

In settings such as sub-Saharan Africa where the prevalence of HIV is high, significant resources are needed to ensure universal antenatal HIV testing, training all healthcare workers in the management of HIV diagnosis and treatment, and integrating HIV care and treatment into the overall healthcare system. Routine testing at entry points to care such as immunization clinics or inpatient wards is very effective in identifying HIV-exposed and HIV-infected children in countries such as South Africa and Zambia. 36, 37

The development of paediatric dosage forms has lagged behind the corresponding development for adults. A list of approved paediatric HIV medicines in the USA can be found at: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm118951.htm and the most recent dosing chart from the CDC is at http://www.cdc.gov/globalaids/resources/pmtct-care/pmtct-pediatric-dosing-guide.html. See also Appendix 6.7.10.


The Paediatric European Network for the Treatment of AIDS (PENTA: http://www.pentatrials.org/) was established in 1991 as a collaboration between paediatric HIV centres in Europe. Trials are principally funded by the European Commission, by governmental bodies in a number of European countries and by support from the pharmaceutical industry. PENTA has guidelines of their own (as of 2009) intended for treating children with HIV in Europe, available on their website. http://www.pentatrials.org/HIV_759.pdf.

It is worth noting that PENTA wrote a letter to the WHO (See at http://www.pentatrials.org/PENTA%20letter%20re%20WHO%20jul%202010.pdf) asserting that the 2010 WHO guidance for children between age 1 and 5 are based on programmatic considerations, in particular as there is generally an inability to closely monitor a child clinically and by repeat CD4 count measurement if they are not started on antiretroviral therapy. PENTA noted that this kind of monitoring is available routinely in Europe and that “the evidence basis for these [WHO] recommendations is weak or very weak”.

6.9-18
3.3.3 Pre-exposure prophylaxis

This is an HIV prevention method in which people who do not have HIV, take a daily pill to reduce their risk of becoming infected. When used consistently, PrEP has been shown to be effective in men who have sex with men (MSM) and heterosexually-active men and women. In November 2010, the National Institutes of Health (NIH) announced the results of the iPrEx clinical trial, a large, multicountry research study examining PrEP among men having sex with men (MSM). Among MSM with detectable levels of the medication in their blood, the risk of HIV acquisition was reduced by more than 90%.

In July 2011, the TDF2 study conducted in partnership with the Botswana Ministry of Health, found that once-daily TDF/FTC reduced the risk of acquiring HIV infection by 62% overall in the study population of uninfected heterosexually-active men and women. Blood level data showed that participants who became infected had far less drug in their blood, compared with matched participants who remained uninfected suggesting that medication adherence is associated with the efficacy of PrEP in preventing HIV infection.

The Partners PrEP study (by the CDC) found that two separate antiretroviral regimens – TDF/FTC in combination and tenofovir alone – when provided to uninfected persons whose partners have HIV infection (serodiscordant couples) significantly reduced HIV acquisition (by 75% and 67%, respectively).

A CDC study is also underway to evaluate whether PrEP is safe and effective in reducing the risk of HIV infection through injection drug use (Bangkok Tenofovir Study), but those results are not yet available.

Based on studies to date, in July 2012 the U.S. Food and Drug Administration approved the combination medication tenofovir disoproxil fumarate plus emtricitabine (TDF/FTC) for use as PrEP among sexually active adults at risk for HIV infection.

3.3.4 Microbicides: CAPRISA and Progeny

Over the past 15 years, six microbicides have been tested in 11 clinical trials, with none showing protection. In 2010, a microbicide gel containing Gilead’s HIV drug tenofovir used by women before and after sex was shown to reduce their risk of HIV infection by nearly 40%. The Centre for the AIDS Programme of Research in South Africa (CAPRISA) trial curbed the risk of infection by the human immunodeficiency virus (HIV) by 54% among those women who used it most consistently. The net impact seen in the CAPRISA study reflects the combined effect of many variables, only one of them being the action of tenofovir, which penetrates into the vaginal tissue, protecting the cells that HIV targets for infection. Other variables include the prevalence of HIV infection in the male population; the number of sexual partners a woman had; the amount of AIDS virus (‘viral load’) in an infected man’s semen; concurrent use of condoms; and, most important, the consistency with which a woman used the gel. The trial was not designed to have enough statistical power to win regulatory approval for the gel. A larger trial of about 5,000 women, using the same gel but with a different dosing regimen, is under way in Africa. Results are not expected until 2013.

Another more recent study had less substantial impacts. This study was the VOICE study – Vaginal and Oral Interventions to Control the Epidemic in sub-Saharan Africa and was
designed to evaluate the safety and effectiveness of applying vaginal gel (tenofovir gel) daily or taking tenofovir once a day. It was announced in late 2011 that the oral tenofovir and tenofovir gel arms of VOICE were dropped following interim reviews of data that determined neither product was effective in the women assigned to those study groups. See http://www.mtnstopshiv.org/node/3909.

4. What is Known of the Affordability, Feasibility, and Sustainability of the Control Strategy?

4.1 Economic Burden

The global HIV/AIDS epidemic, through its devastating scale and impact, constitutes a global emergency and undermines social and economic development throughout the world and affects all levels of society. It is no longer a health crisis but has been transformed into a development crisis. The HIV/AIDS epidemic has erased decades of progress in combating mortality and has seriously compromised the living conditions of current and future generations. It is difficult to estimate a global or even regional economic burden, given the difficulties in finding data and in aggregating disparate metrics and methods. Nonetheless, work by various authors has shown that, at the level of the firm, the cost of HIV/AIDS to businesses can be significant. For instance, a survey in 2004 in six formal sector enterprises in South Africa and Botswana provided detailed human resource, financial, and medical data. At that time, HIV prevalence in the workforces studied ranged from 7.9 to 25.0%. HIV/AIDS among employees added 0.4–5.9% to the companies’ annual salary and wage bills. The present value of an incident HIV infection ranged from 0.5 to 3.6 times the annual salary of the affected worker. Costs varied widely across firms and among job levels within firms. Key reasons for the differences included HIV prevalence, levels and stability of employee benefits, and the contractual status of unskilled workers. AIDS caused labor costs for businesses in southern Africa to rise.

4.2 Affordability

Over the past decade activist pressure, the emergence of competition from generic manufacturers, and direct negotiation with pharmaceutical companies have all contributed to a dramatic drop in the price of certain ARVs to treat HIV and AIDS in developing countries.

The availability of low cost antiretroviral drugs has been instrumental in treatment scale-up for resource-poor settings hard hit by the AIDS epidemic. Around 6.64 million people in low- and middle-income countries are currently receiving ARVs to treat HIV/AIDS. This would simply not have been possible without the reduction in the price of ARVs.

Despite significant advances, a number of problems related to the price of HIV drugs remain. Not all drugs to treat HIV and AIDS are available at a suitably low price for poor countries, meaning that many of the newer, more effective drugs are only available in the West.
Generic antiretrovirals are now widely used to treat HIV/AIDS in the developing world. They have been integrated into many treatment programmes including PEPFAR - the U.S. President's Emergency Plan for AIDS Relief. PEPFAR, the single greatest supporter of treatment provision for HIV and AIDS in the developing world, began to distribute generic drugs through its programmes in 2004-5. Generics now account for 98% of the drugs procured and supplied through PEPFAR's Supply Chain Management System (SCMS), which provides antiretroviral drugs to sixteen PEPFAR supported countries. From 2005-2008, generic ARVs allowed PEPFAR to significantly scale up its procurement of ARV drugs, without a commensurate increase in its spending on ARVs. Over this period, the increase in the proportion spent on generics by PEPFAR went from 9.2% to 76.4% and resulted in more than $300 million in cost savings.

4.3 Sustainability

For the moment, most people who need antiretrovirals in low- and middle-income countries are on first-line therapy. However, as treatment becomes more widespread, people stay on treatment for longer and resistance increases, the high price of second-line drugs is becoming a major issue. Addressing this issue will become increasingly important to ensure the most cost-effective use of available resources and the sustainability of treatment programmes. The current international financial crisis represents a major impediment to sustainable funding and the necessary increased numbers of patients on treatment.

We are already witnessing decreased funding and slow dispersal of funds across Africa, leading to decreased treatment targets and the withdrawal of care for some patients. PEPFAR has issued a system-wide recommendation to decrease scale-up and focus on sustained technical assistance. Wealthy countries are not meeting their repeatedly pledged targets, resulting in decreased support to the Global Fund and other unilateral and multilateral contributions.

5. Why Does the Disease Burden Persist?

In brief, HIV and AIDS persist in large part because there is no cure. Of course, risky behavior, governmental neglect and denial, growth of antiviral resistance and complex structural/societal factors all contribute as well. These structural factors that influence HIV transmission are deep seated within society. In the medium or long term, they can be addressed through sustained, pro-poor economic growth; poverty-reduction policies and programmes; control of injectable drug trafficking; effective judicial reforms to reduce overcrowding in prisons; improvement of employment opportunities for young adults; curtailment of human trafficking; and improvement of the public health infrastructure to support testing, counseling, tuberculosis control, and other population-based approaches to HIV/AIDS and tuberculosis. See Appendix 6.7.1.

With regard to therapeutic interventions, a safe, effective and affordable vaccine is the best hope to bring the AIDS epidemic under control. There is widespread belief among scientists that development of such a vaccine is possible. Yet, thirty years into the epidemic, the AIDS vaccine research effort faces extraordinary hurdles. See Section 6.4 below.
6. **What Can Be Learned from Past/Current Research into Pharmaceutical Interventions for this Condition?**

6.1 **Introduction**

Multiple ART drug combinations continue to successfully reduce viral load and restore immune responses in many HIV-infected individuals. However, these regimens also can result in serious toxicities and side effects, single- and multiple drug-resistance, and other complications that make them unacceptable for some individuals.

We might expect that such side effects and complications will increase as HIV-infected individuals continue to survive longer on various drug regimens and we might expect therefore more deaths occurring from liver failure, kidney disease, and cardiovascular complications in this patient population. The SMART clinical trial was one of the largest HIV/AIDS treatment trials ever conducted at that point in time. Non-AIDs related morbidity was significant in the treatment arm with CD4+ cell-guided episodic (i.e. “conserved”) treatment as there was an increase in major complications such as cardiovascular, kidney and liver diseases. These complications have been associated with ART, and it was hoped that they would be seen less frequently in those patients receiving less drug. As this does not seem to be the case with episodic/conserved therapy, and it appears that continuous antiretroviral therapy is superior to episodic therapy, it will be important to identify mortality and morbidity from all causes, not just attributed to HIV, during what appears to be the current treatment norm of continuous therapy.

Better antiretroviral drugs and treatment regimens are needed with less toxicity, increased activity in viral and cellular reservoirs, reduced ability to develop drug resistance, improved pharmacodynamics and pharmacokinetics, easier compliance, and lower cost.

The following brief summary was extracted from the BMJ Clinical Evidence series:

Infection with HIV usually leads to 8–10 years of asymptomatic infection before immune function deteriorates and AIDS develops. Without treatment, about 50% of infected people will die of AIDS over 10 years. Triple antiretroviral treatments are now standard for people with HIV infection. At this point in time, the issue with respect to pharmaceutical interventions is NOT whether treatments are effective, because they are. The issue is which treatments are most effective and which new treatments need to be researched because of the development of resistance.

6.2 **Antiretroviral Drug Resistance**

Drug-resistant HIV-1 is a cause of growing clinical and public-health concern. As the inevitable consequence of the incomplete suppression of HIV-1 replication by antiretroviral drugs, resistance is a permanent threat for patients who are undergoing antiretroviral treatment, and transmission of resistant viruses is becoming an important concern.

Once established, resistance evolves, diversifies, and may become irreversible. Nonetheless, new drugs are becoming available that appear to retain substantial antiviral activity against HIV-1 strains that are resistant to multiple drugs. These are either drugs from existing classes...
that have increased potency and improved pharmacokinetic properties or drugs from new classes that are not susceptible to cross-resistance.

Although preliminary data indicate that viral resistance to these new drugs can also develop the lessons learned about the development of viral resistance to the currently available antiretroviral drugs may prove helpful in devising treatment strategies with optimized antiviral potency that can minimize the development of resistance to these new agents.47

Resistance to one drug commonly confers cross-resistance to other drugs within the same therapeutic class, which suggests that sequencing strategies based on resistance should not be used. Cross-resistance is particularly common within the non-nucleoside reverse transcription inhibitor (NNRTI) class. A single mutation commonly precludes the use of all other NNRTIs,48, 49

The transmission of HIV drug resistance among people recently infected with HIV increased from about 1% in 2005 to about 3% in 2010. See Appendix 6.7.9. Among people initiating treatment in low- and middle-income countries, about 5% had drug resistance in recent surveys, with resistance increasing somewhat with the scale-up of treatment programme coverage.

6.3 Adverse Events

With improving efficacy and patient life span, attention to adverse events (AEs) experienced with each regimen and the resulting quality of life has become a major determinant in selecting a regimen for the individual patient. Recommendations for treatment regimens are currently based on large randomized controlled trials (RCTs). These trials also serve as an important platform for assessing antiretroviral drug-related AEs. Although not all AEs appear during the limited follow-up period of RCTs, some rare AEs are revealed only after longer exposure of larger populations.50

Hypersensitivity to drugs in HIV-1-infected patients is about 100 times more common than in the general population.51 A syndrome (or syndromes) of lipodystrophy affecting HIV-1-infected patients was first described only 30 years ago. The main clinical features are peripheral fat loss in the face, limbs, and buttocks and central fat accumulation within the abdomen, breasts, and over the spine. Metabolic features significantly associated with lipodystrophy include elevated blood lipids, insulin resistance and type 2 diabetes mellitus.

Table 6.7.3. lists the most common AEs from current anti-retroviral treatments, adapted from Hawkings, 2010 52 and from product labels.

Treatment for some of the most common side effects such as hypersensitivity reactions (HSR), lipodystrophy and DSPN (distal sensory polyneuropathy) remains inadequate and research must continue to find solutions. Possibly, pharmacogenomics might offer further promise of fine tuning HAART and tailoring therapy for each individual patient based on their genetic susceptibility to different ARVs. 53
### Table 6.7.3 Adverse effects associated with different classes of antiretrovirals.

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td>Zidovudine</td>
<td>Anemia, nausea, rash, myopathy, dyslipidemia</td>
</tr>
<tr>
<td></td>
<td>Stavudine didanosine</td>
<td>Nausea, lipoatrophy, DSPN, dyslipidemia, pancreatitis, lactic acidosis, hepatic steatosis, heart disease (?) DSPN</td>
</tr>
<tr>
<td></td>
<td>Abacavir</td>
<td>HSR, hepatotoxicity, heart disease (?)</td>
</tr>
<tr>
<td></td>
<td>Tenofovir</td>
<td>Renal insufficiency, bone loss</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td>Efavirenz</td>
<td>CNS adverse effects, rash, hepatotoxicity, lipoatrophy (?), teratogenicity, hypertriglyceridemia</td>
</tr>
<tr>
<td></td>
<td>Nevirapine</td>
<td>Rash, HSR, hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Etravirine</td>
<td>Rash, hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine</td>
<td>Depressive disorder, insomnia, headache, nausea, vomiting</td>
</tr>
<tr>
<td><strong>&quot;QUAD&quot;</strong></td>
<td>elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate</td>
<td>&quot;Black box&quot; warning: boxed warning for risk of potentially fatal lactic acid buildup in the blood</td>
</tr>
<tr>
<td><strong>Protease Inhibitors</strong></td>
<td>All PIs</td>
<td>Nausea, diarrhea, rash, dyslipidemia, insulin resistance, hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Atazanavir</td>
<td>Jaundice, scleral icterus, nephrolithiasis</td>
</tr>
<tr>
<td></td>
<td>Indinavir</td>
<td>Jaundice, scleral icterus, nephrolithiasis</td>
</tr>
<tr>
<td></td>
<td>Darunavir</td>
<td>Rash, poor liver function</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir</td>
<td>Diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td></td>
<td>Nelfinavir</td>
<td>Diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td></td>
<td>Lopinavir/ritonavir</td>
<td>Diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td></td>
<td>Tipranavir</td>
<td>Diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td><strong>Entry inhibitors</strong></td>
<td>Enfuvirtide</td>
<td>Injection site reactions, pneumonia, HSR</td>
</tr>
<tr>
<td><strong>Chemokine coreceptor antagonists</strong></td>
<td>Maraviroc</td>
<td>Cough, fever, respiratory tract infections, rash, hypotension (postural) hepatotoxicity, HSR</td>
</tr>
<tr>
<td></td>
<td>Raltegravir</td>
<td>Headache, insomnia, dizziness, fatigue</td>
</tr>
<tr>
<td></td>
<td>Elvitegravir/cobicistat</td>
<td>Insomnia, abnormal dreams, rash</td>
</tr>
</tbody>
</table>

Sources: Hawkins T. 2010 Understanding and managing the adverse effects of antiretroviral therapy. Antiviral Research 85 (1) 201–209 / Product labels
6.4 HIV Vaccines

Is prevention of infection achievable or even feasible by the use of HIV vaccines? In general, early work suggested that scientists would not expect that a previous infection or vaccination would provide absolute protective immunity against reinfection by HIV. 54 55

Sterilizing immunity—the absence of any infection of a host cell by the agent—has rarely been seen with any vaccine. Early evidence from the poliomyelitis, measles, rubella, mumps, and influenza virus vaccine trials indicated that neither killed nor live-attenuated (nonpathogenic) viruses have prevented infection of immunized hosts by wild-type virus. 56 57 58 59 60

The AIDS vaccine development effort has already been facing various challenges. The fundamental biological challenge resides at the level of understanding the basic biology of HIV-1 infection and an effective antiviral immune response. 61

By contrast with other viruses for which there is a vaccine, the HIV infected cell can be the source of transmission and must be recognized by the immune system. Hopefully, a vaccine will stimulate the immune system sufficiently to maintain control of this virus, as is seen in the few HIV-infected individuals living for more than 20 years without symptoms and treatment. 62 In some of these patients, the virus could eventually emerge to cause disease, but only late in life when the immune system ages. Thus, in principle pathogenesis but not infection could be prevented or at least delayed a long time by vaccine.

6.4.1 The RV144 Trial

Major HIV vaccine efficacy trials conducted by VaxGen Inc (AIDSVAX 003 and AIDSVAX 004) and the NIH-supported HIV Vaccine Trials Network (HVTN 502 and HVTN 503) failed to demonstrate efficacy. However, a recent trial conducted in Thailand (RV144 trial) demonstrated a low level of efficacy, resulting in some renewed optimism. 63

The vaccine regimen tested in Thailand consisted of priming with a genetically engineered viral vector carrying three synthetic HIV genes. The priming was followed by booster inoculations with two recombinant envelope proteins from HIV, clade B and E. The results showed no efficacy in a Phase III trial in Thai injecting drug users. Although the trial had been criticized scientifically, RV144 showed that, by modified intent-to-treat analysis, 3.5 years after initial vaccination, the vaccine regimen was 31.2 % efficacious in preventing HIV infection. There was no effect on early post-infection HIV-1 RNA viral load or CD4+ T-cell count. 46

This is very modest efficacy but it is the first evidence that a safe and effective preventive HIV vaccine is possible. In September 2011, additional follow-up analysis of the RV144 Thai vaccine trial revealed a significant discovery. Aiming to better understand how RV144 protected against HIV infection, the study team found two important molecular clues—two antibodies correlated with the risk of HIV infections. The highly-anticipated post hoc analysis of RV144 and an array of new insights into the mechanics of broadly neutralizing antibodies against HIV have brought the vaccine field closer than ever before to finding a strategy for an effective HIV vaccine. 64
Additionally, the Pox-Protein Public Private Partnership (P5) is working to develop a regimen that will be tested in follow-on trials to RV144. See Appendix 6.7.11.

6.4.2 Selected Obstacles to HIV-Vaccine Development and Their Implications

Current AIDS vaccine candidates are unable to induce broadly neutralizing antibodies (bNAb) against primary HIV isolates or only to a very limited and narrow extent presenting a major stumbling block in the development of an effective HIV vaccine. The immune response elicited by a successful vaccine possibly will require both antibodies and T cells that recognize, neutralize and/or inactivate diverse strains of HIV and that reach the site of infection before the infection becomes irreversibly established.\textsuperscript{65,66,67}

- Extensive viral subtype and sequence diversity limits the efficacy of current vaccine approaches to specific subtypes.
- There is a narrow window of opportunity for the immune system to clear initial infection before early establishment of latent viral reservoirs.
- The immune correlates of protection remain unknown.
- Viral escape from humoral and cellular immune responses may limit sustained efficacy.
- Conserved antibody targets on the outer envelope protein are hidden.
- There is a lack of a predictive animal model.
- Still limited interest of the pharmaceutical industry.

7. What is the Current “Pipeline” of Products that Are to Be Used for this Particular Condition?

Tracking pharmaceutical pipelines over time reveals various therapeutic candidates appearing and disappearing, only to be replaced by other hoped-for products. Thus, snapshots of HIV pipelines need to be viewed as a ‘work in progress’. Table 6.7.4 is adapted from information provided by the Pharmaceutical Manufacturers of America,\textsuperscript{68} but it is not intended to be a fully comprehensive view of the United States pipeline. We attempted to place each intervention into its appropriate therapeutic class (e.g. protease inhibitor, NNRTI, and so on) although this is not always possible.
Table 6.7.4: The current development pipeline of HIV medicines in US

<table>
<thead>
<tr>
<th>Integration</th>
<th>Transcription</th>
<th>Virus Assembly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elvitegravir</td>
<td>ALX40-4C</td>
<td>bevirimat</td>
</tr>
<tr>
<td>GSK1349572 MK-2048</td>
<td>CGP64222</td>
<td>vivecon</td>
</tr>
<tr>
<td></td>
<td>L50 RNAi DRB</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD4 binding</th>
<th>CCR5 binding</th>
<th>Fusion</th>
<th>Reverse transcription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-542</td>
<td>PSC-RANTES</td>
<td>T-1249</td>
<td>NNRTI</td>
</tr>
<tr>
<td>BMS-378806</td>
<td>AOP-RANTES</td>
<td>5-helix</td>
<td>atevirdine</td>
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<tr>
<td>TNX-355</td>
<td>NNY-RANTES</td>
<td></td>
<td>NRTI</td>
</tr>
<tr>
<td></td>
<td>TAK-779</td>
<td></td>
<td>amdoxovir</td>
</tr>
<tr>
<td></td>
<td>vicriviroc</td>
<td></td>
<td>apricitabine</td>
</tr>
<tr>
<td></td>
<td>aplaviroc</td>
<td></td>
<td>celevudine</td>
</tr>
<tr>
<td></td>
<td>Pro-140</td>
<td></td>
<td>elvucitabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>entecavir</td>
</tr>
</tbody>
</table>


We analyzed the United States clinical trials database ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) to develop another estimate of the pipeline activity - the clinical trial sponsoring organizations.

Figure 6.7.3 (See Annex 6.7.2) summarizes the information as of the original Report (late 2003) and as of late 2012 shown as side-by-side comparisons on the bar graph (2003 data on the left/2012 data immediately adjacent). The number in parenthesis on the X-axis is the proportion of total HIV interventional clinical trials in the database on that date relegated to that sponsor. i

The greatest total number of clinical trials related to HIV (primarily early stage Phase I and Phase II trials) is being sponsored by the National Institutes of Health. Significantly, the fraction of total HIV trials conducted by the NIH has decreased from 54% to 37%, since the original Report as the difference is being taken up by universities and non-governmental organizations. The proportion of total HIV trials sponsored by the industry has changed little since 2003, although the total numbers of trials have increased across the board since 2003.

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i The search term “HIV” included HIV therapeutics, vaccines HIV diagnostics, drug to drug comparisons, opportunistic infections, side effects (cardiac effects, lipodystrophy and the like).
As for HIV vaccine trials, as of 16 Nov 2012, the results are presented below in Table 6.7.5.

**Table 6.7.5: HIV vaccine trials**

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>190</td>
<td>104</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Other Federal Government</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>All industry</td>
<td>85</td>
<td>49</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>University/Other Organizations</td>
<td>53</td>
<td>35</td>
<td>11</td>
<td>17</td>
</tr>
</tbody>
</table>

Source: United States clinical trials database ([www.clinicaltrials.gov](http://www.clinicaltrials.gov))
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There appears to be far less information about European HIV clinical trials that is available. We searched the same www.clinicaltrials.gov database but restricted the search to the UK, France and Germany for all interventional HIV trials. As of 16 November 2012, there are 437 European (UK + France + Germany) studies allocated as follows: 84 Phase I, 149 Phase II, 150 Phase III and 67 Phase IV.

8. What is the Current Status of Institutions and Human Resources Available to Address the Disease?

8.1 Introduction

Given the number of institutions and human resources involved in the HIV pipeline, we can state with some confidence that the private research and development (R&D) sector in the United States and Europe is already heavily investing in addressing this disease. The United States has by far the greatest financial and human resource contribution in this regard (see Section 7). We note, however, that there appears to be no paucity of private funding with regard to HIV R&D, the clinical trial analysis shows the United States government (NIH) supporting the majority of clinical trials.

8.2 Public Funding for HIV/AIDS in the European Union

Overall, from 2007 to 2010, the EU invested an average of nearly €250 million a year in R&D to develop new tools to prevent, diagnose and treat HIV & AIDS, TB and malaria. See Appendix 6.7.12. About €80 million a year was directed to HIV/AIDS during this time and this number is dominated by the United States investment in R&D for HIV/AIDS.

8.2.1 Framework 7

Research on HIV/AIDS is a top priority for the European Commission. Projects financed under Framework Programme 6 (FP6) are progressing through the development of new vaccines, microbicides, drugs and therapeutic options. Two “networks of excellence” have been created, one for HIV prevention, and the other one for HIV treatment, with the participation of most of the top European HIV researchers and clinicians. Moreover, in order to allow further development of successful products, the European and Developing Countries Clinical Trials Partnership (EDCTP: http://www.edctp.org/), has the ability to finance capacity building and clinical trials in sub-Saharan Africa.

In FP7, the first four proposal calls (2007-2010) were for €83 million, yielding over 15 projects. HIV/AIDS prevention funding over this time period was about €43.5 million directed to new HIV vaccines inducing broadly-reactive neutralizing antibodies, discovery and/or development of new and promising anti-HIV microbicides, transcutaneous and mucosal HIV vaccine based on novel delivery strategy (See below: CUT’HIVAC). An additional € 34.5 million was allocated for therapeutics, paediatric formulations of ARVs. http://ec.europa.eu/health/sti_prevention/docs/ev_20100505_co04_en.pdf
Within the area of HIV FP7 has funded one very large project to foster utilization of clinical care data to improve pharmacotherapy: EuroCoord – Coordinating the A-Z of HIV. It is expected that funding this or similar initiatives will continue in Horizon 2020. See http://www.eurocoord.net/.

Examples of other FP7 projects extending over the next several years are the following:

- **HIVERA**: Harmonizing, Integrating and Vitalizing European Research on HIV/AIDS (2010-2014). **This is a coordination/networking activity (Total cost: €2 434 320. EU contribution: €2 million)** proposed as a dedicated ERA-NET paving the way for the coordination and cooperation of national programmes, starting first in 8 countries (BE, DE, EE, FR, IT, PT, RO, TR), but flexible enough to integrate new Member States by the end of the Grant duration. Duplicating existing European activities will be avoided by actively linking up HIVERA with ongoing existing networks and the EDCTP, and by concentrating pilot joint calls on emerging issues in HIV/AIDS.

- **COBRA**: Co-morbidity in relation to Aids (2013-2017). This is a focused research project (Total cost: €7 800 378. EU contribution: €5 998 758) designed to understand age-associated comorbidities (diabetes, cardiovascular conditions, osteoporosis) that occur in persons on long-term ARVs, the object of which is to conduct longitudinal HIV cohort studies in Amsterdam and London to find a robust estimate of the effect of treated HIV infection on the prevalence, incidence and age of onset of these co-morbidities.

**Diagnostics are also being tested.**

- **PREVENTIT**: Point-of-Care Device for Syphilis and HIV in Pregnant Women and New Born (2012). This is a focused research project (Total cost: €2 870 242. EU contribution: €2 097 373) designed to develop, validate and start manufacturing of a multi-analyte device for the diagnosis of congenital syphilis and HIV co-infections.

- **HIVBIOCHIP**: Point-of-care Biochip for HIV Monitoring in the Developing World (2012-2017). This is a starting grant (Total cost: €1 986 000. EU contribution: €1 986 000) to develop a portable, inexpensive imaging system for counting the absolute number of CD4 cells from whole blood.

Biomarkers are not being tested at the moment but they might be important to judge the efficacy of vaccines. Adherence is currently not a priority area within HIV. There are only some projects around adherence that are supported involving mHealth. They are funded by the public health program of FP7. There is relatively little research on development of diagnostics. Several of the projects are on capacity building in research and clinical care. (Personal communication, Dr. Alessandra Martini, European Commission Directorate-General for Research and Innovation Scientific Officer, Infectious Diseases)

Vaccines are a priority, albeit in combination with other interventions. There are currently some candidates which are promising and are currently tested in phase I clinical trials (CUTHIVAC is one important example of a study that is funded by FP7 on vaccine development http://cordis.europa.eu/search/index.cfm?fuseaction=proj.document&PJ_LANG=EN&PJ_RC N=11121837&pid=0&q=7B76A86D11A45DCA1AE16FD9356572C2&type=adv).
FP7: CUT’HIVAC: Cutaneous and mucosal HIV vaccination: 2010 to 2014

This is a large-scale integrated project with 15 partners. Clinical trials will be implemented with combined vaccination by transcutaneous, intradermal routes and/or mucosal administration of HIV-envelop protein-based vaccine. The total cost is over €15 million and the EU contributes nearly €12 million. See http://cordis.europa.eu/projects/index.cfm?fuseaction=app.details&TXT=HIV&FRM=1&STP=10&SIC=&PGA=&CCY=&PCY=&SRC=&LN=en&REF=93671

8.3 Public Funding for HIV/AIDS in the United States

President Obama’s Fiscal Year (FY) 2013 federal budget request (including NIH and many other HIV related activities, not all R&D), released on February 13 2012, includes an estimated Domestic HIV/AIDS funding at US$22.25 billion. The FY 2013 request represents a 3% increase (US$766 million) over FY 2012 levels.

Federal funding for HIV/AIDS, however, represents a small fraction (<1%) of the overall federal budget of the United States. The FY 2013 budget request for HIV/AIDS includes US$6.2 billion for the global epidemic, 3% less than FY 2012. Of this amount, US$4.5 billion is for the following: bilateral activities centrally operated at the Office of the Global AIDS Coordinator and in countries and regions (approximately US$4.1 billion); international research (US$389 million); and multilateral contributions to UNAIDS (US$45 million), the International AIDS Vaccine Initiative (US$28.7 million), and Microbicides (US$45 million). The request also includes US$1.65 billion for the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund), a 27% increase over FY 2012 funding levels. See http://kaiserfamilyfoundation.files.wordpress.com/2013/01/7029-08.pdf.

8.4 Private Sector R&D Funding

8.3.1 Product Development Partnerships for HIV

Product Development Partnerships (PDPs) are playing an increasingly important role in the development of new medicines for neglected diseases of the developing world.69

The International AIDS Vaccine Initiative (IAVI) in 2007 provided US$81,297,482 for HIV/AIDS vaccine development. The International Partnership for Microbicides (IPM) provided US$46,311,916, the Program for Appropriate Technology in Health (PATH) provided US$745,000 (out of a total funding stream of US$38,024,679) for various “unspecified” HIV projects, and the World Health Organization: Special Programme for Research and Training in Tropical Diseases (WHO/TDR) provided US$3,228,410 (out of a total of US$32,675,307) for HIV/AIDS diagnostics.52 See also Appendix 6.7.11.

8.4 Paediatric fixed dose combinations

In July 2012, the Drugs for Neglected Diseases Initiative (DNDi), a not-for-profit research and development (R&D) organization, announced a new collaboration with Indian drug manufacturer Cipla to develop and produce an improved first-line antiretroviral (ARV) combination therapy specifically adapted to meet the treatment needs of infants and toddlers living with HIV/AIDS.70
Fixed-dose combination dissolvable ‘baby pills’ (for example Triomune® Baby and Junior produced by Cipla in 2007) are used throughout most of Africa, but they are not optimal for the youngest children who have very high levels of virus in their blood and have already been exposed to some of these drugs from their mother. An important alternative drug (Kaletra®: lopinavir-ritonavir protease inhibitor) has been used mainly in South Africa, but has problems, including poor taste, impractical multiple liquid preparations that are cumbersome to transport, requirements for refrigeration, high cost, difficulties for caregivers to administer, and negative interactions with tuberculosis (TB) drugs. The goal of the collaboration between DNDi and Cipla is to develop a 4-in-1 ARV combination product for HIV-infected children under the age of three years, including those who have been exposed to drugs while in the womb, and also those who are coinfected with TB.

Historically, major pharmaceutical companies have invested little in R&D specifically aimed at addressing the needs of young children with HIV/AIDS largely because of the absence of a viable market. This is because the virtual elimination of mother-to-child transmission of HIV in high-income countries means that nearly all HIV-positive children live in low- and middle-income countries, with over 90% in sub-Saharan Africa.

Cipla will work with DNDi and other partners to test new combinations of HIV treatment for infants and young children, such as a fixed-dose combination of lopinavir/ritonavir (LPV/r) 40-/10-mg sprinkle formulation (‘Lopimune Sprinkles’), combined with one of two other powerful ARV drug combinations, abacavir/lamivudine (ABC/3TC) or zidovudine/lamivudine (AZT/3TC). Cipla will work to produce an appropriate 4-in-1 combination sachet product, in which the four ARV drugs will be in taste-masked, granular form, for easy mixing into food or liquids such as water, juice, or breast milk, with the aim of registering the drug by 2015.

In early December 2012, UNITAID in Geneva committed up to US$ 120 million for specific projects, among them a grant of up to US$ 17.3 million to DNDi to make child-adapted paediatric HIV treatments available. In addition to these principle grants, the UNITAID Executive Board approved four “market entry” grants to help manufacturers of “point-of-care” HIV diagnostic machines in the final stages of development. UNITAID also provided up to US$ 8 million to continue a project which ensures that procurement of paediatric HIV medicines will continue into 2013 and 2014.

8.5 HIV Vaccine R&D

Since 2001, global preventive HIV vaccine R&D investment has an average yearly investment of US$ 824 million (a major portion of which is provided by the entities shown in the Figures above). The 2011 total investment represents an overall 12% drop since the height of vaccine funding in 2007. See Appendix 6.7.13 at: http://www.hivresourcetracking.org/sites/default/files/HIV%20Vaccine%202011%20Funding%201-pager.pdf.

United States government agencies alone accounted for 74% (US$ 623 million) of all HIV vaccine R&D funding, again reflected as the National Institutes of Health (NIH) in Figure 6.7.5, below. Investment by European governments was US$ 48.5 million in 2011, a decrease of over US$ 12 million (21%) from the previous year and a 40% decrease from their US$ 82 million peak in 2006. Philanthropic investments in HIV vaccine R&D increased in 2011 by US$ 10 million (10%), as new philanthropic groups entered the funding space and as others,
such as the United Kingdom’s (UK) Wellcome Trust and the Spanish Fundació la Caixa, increased their funding. See Appendix 6.7.13.

The year 2011 saw lower United States public-sector investment in HIV vaccines and the end of the United States stimulus funding to the NIH, along with decreased European investment overall. Yet, philanthropic investment increased in 2011, offsetting cuts to public-sector funding. Investment overall decreased by 2%, an effective flat lining of funding. In an age of economic challenges, continued investment without significant cuts can be considered a sign that the top funders understand the importance of continuing to invest in HIV prevention R&D, but this sustained funding will need to be supplemented as new strategies are explored and promising candidates move toward more expensive late-stage vaccine trials. See Appendix 6.7.13.

8.6 Overall HIV Funding: Response of donors/governmental funders to the HIV epidemic post 2003

In 2003, the United States government announced the United States President’s Emergency Plan for AIDS Relief (PEPFAR). At US$ 15 billion over five years, it was the largest single funding commitment for a disease in history. PEPFAR was reauthorized in 2008 for up to US$ 48 billion to combat AIDS, TB and malaria from 2009 to 2013. Additional innovations in global health funding followed. By 2006, Brazil, Chile, France, Norway and the United Kingdom had agreed to create UNITAID, an international drug purchase facility financed through a modest levy on airline tickets.

Due probably to the global economic situation, in recent years domestic and international HIV-specific funding has decreased from US$ 15.9 billion in 2009 to US$ 15 billion in 2010. International assistance declined from US$ 8.7 billion in 2009 to US$ 7.6 billion in 2010.71

However, global spending on HIV has increased, totaled about US$ 16.8 billion in 2011, up from the 2010 estimate. See Appendix 6.7.1. Domestic public spending continues to increase, with some low- and middle-income countries now funding their own response, however, HIV programmes in low-income countries still rely on external aid to a much greater extent than the health sector overall.

8.6.1 Medicines and basic research for LMIC research: Top 12 Funders (G-Finder)

Funding targeted to specifically to developing-country presentations has recently been analyzed (G-FINDER 2012 Report at http://www.policycures.org/downloads/GF2012_Report.pdf).

For basic research, this was defined as research into mechanisms related to preventative vaccines and microbicides (e.g. immunological responses to potential antigens, mechanisms of mucosal transmission) but excluding general research that could also be applied to commercial products.

Research into HIV drugs also included only developing-country-specific applications, such as label extensions to paediatric patient groups, fixed dose combinations, and slow release formulations. These restrictions were important to prevent developing-country-specific
funding being swamped by the high level of public and private investment into HIV R&D targeted at Western needs.

Overall, as in previous years, the three ‘top tier’ diseases – HIV/AIDS, malaria and tuberculosis (TB) – again received approximately one-third to one-fifth of total global neglected disease R&D funding each, with HIV/AIDS receiving about one-third of the total for 2011. Nonetheless, this share continued to decline, with cuts for HIV/AIDS (down US$ 41.1m (-4.0%) from 2010 to about US$ 1 billion).

As defined, this HIV/AIDS R&D funding was highly concentrated with 12 groups providing 93.6% of funding. See Figure 6.7.4 and 6.7.5 extracted from the G-FINDER database (See Annex 6.7.3). Decreases in HIV funding in 2011 were widespread, with ten of the top 12 funders reducing funding from 2010. Although the U.S. National Institutes of Health remained by far the largest funder, contributing 61.4% (US$ 631.4 million) of the global total, it also registered the biggest drop in funding in 2011 (down US$ 26 million, -3.9%). Of the top 12 funders, only the U.S. Department of Defense (DOD) and the Wellcome Trust increased funding.

In 2011, the public and philanthropic sectors collectively provided 97.8% of HIV/AIDS R&D funding, with the public sector providing 84.6% (US$ 870.5 million) of total funding and the philanthropic sector providing 13.1% (US$ 135.2 million). Public funding accounts for the majority of HIV/AIDS R&D funding, therefore public sector budget cuts following the global financial crisis have had a large impact.
Figure 6.7.4: Top 12 HIV/AIDS R&D Funders (% of the top 12 annual funding)


Note: Figures are adjusted for inflation and reported as 2007 US dollars
9. Ways Forward from a Public Health Viewpoint with Regard to Public Funding

9.1 Gaps Between Current Research and Potential Research Issues which Could Make a Difference

There are some problems with current HIV therapeutics. Among these are emergence of drug resistant HIV variants, adverse effects, metabolic abnormalities and toxicities, poor adherence to complex, multi-drug regimens, and primary infection with drug-resistant and multi-resistant HIV variants. Thus, notwithstanding the large pipeline and private sector investments, therapeutics discovery and development remains a critical activity:
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- new delivery or formulation methods to enhance the clinical potential of anti-HIV drugs (FDA-approved or those undergoing clinical testing) in infected adults and children;
- validating new viral and cellular targets for HIV inhibition and for developing new drugs (or developing new agents against existing targets).
- Continued development of HIV vaccines and microbicides

9.2 What is the Comparative Advantage of the EU with Regard to Public Funding of Pharmaceutical R&D?

The European Union cannot match the private or public funding levels of the United States with regard to HIV research and development (See Figures 6.7.4 and 6.7.5). However, based upon what we understand to be the epidemiology of HIV/AIDS in expanded Europe and the rest of the world, and the current states of private and public sector institutions in this regard, we believe the European Union can, from a public health viewpoint, fill gaps in the following areas:

- Target affected populations, especially women, injecting drug users (IDUs), children, adolescents, older adults, and across racial/ethnic groups. Conduct studies that permit evaluation of potential differences in response to therapy due to gender and/or racial or ethnic differences. We believe the opportunities clearly exist to conduct clinical studies into specialized populations in Africa, possibly with EDCTP involvement.
- Promote innovative mechanisms of funding to attract additional investigators to undertake multidisciplinary research on microbicides discovery and development.
- Expand capacity (infrastructure and human resources) and strengthen coordination to conduct Phase II/III microbicides and fixed dose combination clinical trials.

10. Conclusion

Globally the number of people newly infected with HIV is decreasing. First-line treatments are effective and fairly inexpensive, second line treatments are effective but expensive. At this point, access to treatment and prevention efforts must continue. We are not yet close to an effective vaccine.

In Eastern Europe the number of infected people continues to rise. The annual incidence (rate of newly diagnosed HIV cases) was stable in central and western Europe between 2004 and 2009, whereas it increased by two-thirds in eastern Europe and Central Asia. In the European region, the HIV epidemic continues to spread and treatment is not keeping pace with new infections.

There is sufficient scientific evidence, as well as an extensive pool of normative guidance, on all aspects of HIV prevention, treatment and care. Aligning national legislation and policies with internationally recognized standards and ensuring their effective implementation will contribute to a successful response to the HIV epidemic.
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References


12. United States Department of Health and Human Services, NIH Discal Year 2005 Budget Request Jack Whitescarver, Ph.D. Director, Office of AIDS Research April 1, 2004


14. ECDC / European Monitoring Centre for Drugs and Addiction (2011)

15. HIV and AIDS in Western and Central Europe, at http://www.avert.org/aids-europe.htm


19. HIV and AIDS in Western and Central Europe. Available at http://www.avert.org/aids-europe.htm


Centre for the AIDS Programme of Research in South Africa, CAPRISA at http://www.caprisa.org/SitePages/Home.aspx


PEPFAR(2011, April) Statement of Ambassador Eric Goosby, MD, US Global AIDS Coordinator, US Department of State, Before the US Senate Committee on Foreign Relations, Subcommittee on African Affairs


64 Investing to End the Epidemic: A New Era for HIV Research & Development. The HIV Vaccines and Microbicides Resource Tracking Working Group at www.hivresourcetracking.org


Figure 6.7.6: HIV-1 life cycle and potential opportunities for therapeutic intervention

### Annex 6.7.1: Standardized death rates (per 100,000 people) for HIV/AIDS among country-components of the European Union

<table>
<thead>
<tr>
<th>Year</th>
<th>EU</th>
<th>0000 SDR, All causes, per 100000</th>
<th>0060 SDR, Infectious and parasitic diseases, per 100000</th>
<th>% infec/parasitic of all causes</th>
<th>0120 SDR, Intestinal infectious diseases, per 100000</th>
<th>0180 SDR, Tuberculosis, per 100000</th>
<th>0300 SDR, AIDS/HIV (as recorded by routine mortality statistics system), per 100000</th>
<th>% AIDS/HIV of infectious/parasitic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>EU</td>
<td>811.75</td>
<td>6.82</td>
<td>0.84%</td>
<td>0.36</td>
<td>2.14</td>
<td>4.19</td>
<td>11.63888889</td>
</tr>
<tr>
<td>1996</td>
<td>EU</td>
<td>799.6</td>
<td>7.75</td>
<td>0.97%</td>
<td>0.37</td>
<td>2.02</td>
<td>3.7</td>
<td>10</td>
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<tr>
<td>1997</td>
<td>EU</td>
<td>781.07</td>
<td>8.12</td>
<td>1.04%</td>
<td>0.35</td>
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<td>1.98</td>
<td>5.657142857</td>
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<td>1998</td>
<td>EU</td>
<td>773.68</td>
<td>7.99</td>
<td>1.03%</td>
<td>0.4</td>
<td>1.87</td>
<td>1.4</td>
<td>3.5</td>
</tr>
<tr>
<td>1999</td>
<td>EU</td>
<td>760.48</td>
<td>8.12</td>
<td>1.07%</td>
<td>0.38</td>
<td>1.72</td>
<td>1.31</td>
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<tr>
<td>2000</td>
<td>EU</td>
<td>733.95</td>
<td>8.54</td>
<td>1.16%</td>
<td>0.45</td>
<td>1.6</td>
<td>1.26</td>
<td>2.8</td>
</tr>
<tr>
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<td>EU</td>
<td>716.87</td>
<td>8.11</td>
<td>1.13%</td>
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<td>1.57</td>
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<td>2002</td>
<td>EU</td>
<td>712.51</td>
<td>8.44</td>
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<td>0.49</td>
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<td>2003</td>
<td>EU</td>
<td>714.23</td>
<td>9.13</td>
<td>1.28%</td>
<td>0.55</td>
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<td>1.22</td>
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<td>2004</td>
<td>EU</td>
<td>678.9</td>
<td>8.65</td>
<td>1.27%</td>
<td>0.59</td>
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<td>EU</td>
<td>669.7</td>
<td>8.81</td>
<td>1.32%</td>
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<td>1.18</td>
<td>1.08</td>
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<tr>
<td>2006</td>
<td>EU</td>
<td>643.49</td>
<td>8.73</td>
<td>1.36%</td>
<td>0.88</td>
<td>1.1</td>
<td>1.01</td>
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<td>2007</td>
<td>EU</td>
<td>632.92</td>
<td>9.01</td>
<td>1.42%</td>
<td>1.04</td>
<td>1.04</td>
<td>0.99</td>
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<td>2008</td>
<td>EU</td>
<td>622.03</td>
<td>9.01</td>
<td>1.45%</td>
<td>0.97</td>
<td>0.99</td>
<td>0.92</td>
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<tr>
<td>2009</td>
<td>EU</td>
<td>611.06</td>
<td>8.86</td>
<td>1.45%</td>
<td>0.91</td>
<td>0.92</td>
<td>0.83</td>
<td>0.912087912</td>
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<tr>
<td>2010</td>
<td>EU</td>
<td>602.73</td>
<td>8.6</td>
<td>1.43%</td>
<td>0.89</td>
<td>0.84</td>
<td>0.82</td>
<td>0.921348315</td>
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<td>Year</td>
<td>EU members before May 2004</td>
<td>0000 SDR, All causes, per 100000</td>
<td>0060 SDR, Infectious and parasitic diseases, per 100000</td>
<td>% infec/parasitic of all causes</td>
<td>0120 SDR, Intestinal infectious diseases, per 100000</td>
<td>0180 SDR, Tuberculosis, per 100000</td>
<td>0300 SDR, AIDS/HIV (as recorded by routine mortality statistics system), per 100000</td>
<td>% AIDS/HIV of infectious/parasitic</td>
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<tr>
<td>1995</td>
<td>EU members before May 2004</td>
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<td>6.25</td>
<td>0.87%</td>
<td>0.34</td>
<td>1.09</td>
<td>5.26</td>
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<td>EU members before May 2004</td>
<td>709.55</td>
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## Update on 2004 Background Paper, BP 6.7 HIV/AIDS

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<th>0000 SDR, All causes, per 100000</th>
<th>0060 SDR, Infectious and parasitic diseases, per 100000</th>
<th>% infec/parasitic of all causes</th>
<th>0120 SDR, Infectious diseases, per 100000</th>
<th>0180 SDR, Tuberculosis, per 100000</th>
<th>0300 SDR, AIDS/HIV (as recorded by routine mortality statistics system), per 100000</th>
<th>% AIDS/HIV of infectious/parasitic</th>
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<td>1995</td>
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<td>0.21</td>
<td>3.15</td>
<td>0.39</td>
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<td>0.23</td>
<td>3.09</td>
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<td>2.78</td>
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<tr>
<td>2010</td>
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<td>840.22</td>
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<td>0.35</td>
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<td>0.39</td>
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EU: the 27 Member States of the European Union;
*EU members before May 2004: the 15 Member States of the European Union prior to 1 May 2004;
*EU members since 2004 or 2007: the 12 new Member States of the European Union from 1 May 2004 or 1 January 2007;
## Annex 6.7.2: Number of Clinical Trials, including those no longer recruiting

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<td>343</td>
<td>288</td>
<td>130</td>
<td>26</td>
<td>788</td>
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<tr>
<td>Other Federal Government (.76%)</td>
<td>6</td>
<td>3</td>
<td>2</td>
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<tr>
<td>All industry (40%)</td>
<td>200</td>
<td>226</td>
<td>133</td>
<td>29</td>
<td>588</td>
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<tr>
<td>University/Other Organizations (4.7%)</td>
<td>23</td>
<td>23</td>
<td>15</td>
<td>7</td>
<td>68</td>
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<td><strong>2012</strong></td>
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<td>NIH (37%)</td>
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<td>604</td>
<td>221</td>
<td>67</td>
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<tr>
<td>Other Federal Government (2%)</td>
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<td>26</td>
<td>15</td>
<td>98</td>
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<td>All industry (39%)</td>
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<td>505</td>
<td>356</td>
<td>223</td>
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<tr>
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<td>261</td>
<td>160</td>
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Note: Searched under sponsor "HIV infections." There are some overlaps (unknown) in sponsor
Annex 6.7.3: Top 12 HIV/AIDS R&D funders for Low and Middle Income Countries

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<td>688 900 175</td>
<td>60.51%</td>
<td>657 340 665</td>
<td>61.26%</td>
<td>631 394 882</td>
<td>61.38%</td>
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<td>Gates Foundation</td>
<td>91 975 642</td>
<td>8.49%</td>
<td>160 531 263</td>
<td>13.78%</td>
<td>119 431 387</td>
<td>10.49%</td>
<td>118 655 020</td>
<td>11.06%</td>
<td>110 940 741</td>
<td>10.78%</td>
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<td>USAID</td>
<td>67 457 000</td>
<td>6.23%</td>
<td>67 813 102</td>
<td>5.82%</td>
<td>68 169 518</td>
<td>5.99%</td>
<td>68 385 015</td>
<td>6.37%</td>
<td>65 005 117</td>
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<td>US DOD</td>
<td>27 800 000</td>
<td>2.57%</td>
<td>24 448 940</td>
<td>2.10%</td>
<td>34 236 010</td>
<td>3.01%</td>
<td>31 671 138</td>
<td>2.95%</td>
<td>42 188 575</td>
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<td>Aggregate industry</td>
<td>19 635 626</td>
<td>1.81%</td>
<td>47 449 865</td>
<td>4.07%</td>
<td>35 342 218</td>
<td>3.10%</td>
<td>30 103 341</td>
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<td>22 969 327</td>
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<td>UK MRC</td>
<td>31 151 182</td>
<td>2.88%</td>
<td>28 718 490</td>
<td>2.47%</td>
<td>38 305 345</td>
<td>3.36%</td>
<td>21 050 427</td>
<td>1.96%</td>
<td>16 638 498</td>
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<td>European Commission</td>
<td>24 794 890</td>
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<td>26 305 301</td>
<td>2.26%</td>
<td>27 100 813</td>
<td>2.38%</td>
<td>19 073 421</td>
<td>1.78%</td>
<td>18 564 822</td>
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<td>Russian MHSD</td>
<td>16 666 666</td>
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<td>16 055 877</td>
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<td>0.00%</td>
<td>0.00%</td>
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<td>0.00%</td>
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<tr>
<td>French ANRS</td>
<td>10 511 570</td>
<td>0.97%</td>
<td>14 700 289</td>
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<td>11 919 251</td>
<td>1.05%</td>
<td>11 141 961</td>
<td>1.04%</td>
<td>9 490 184</td>
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<td>13 101 548</td>
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<td>11 635 919</td>
<td>1.00%</td>
<td>11 737 927</td>
<td>1.03%</td>
<td>11 940 880</td>
<td>1.11%</td>
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<td>Wellcome Trust</td>
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<td>9 296 776</td>
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<td>16 813 469</td>
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<td>Inserm</td>
<td>342 620</td>
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<td>1 180 483</td>
<td>0.10%</td>
<td>12 497 386</td>
<td>1.10%</td>
<td>13 931 413</td>
<td>1.30%</td>
<td>13 841 576</td>
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<td>Disease Total</td>
<td>1 083 018 193</td>
<td>1.00%</td>
<td>1 164 882 551</td>
<td>1.00%</td>
<td>1 138 511 159</td>
<td>1.00%</td>
<td>1 073 033 520</td>
<td>1.00%</td>
<td>1 028 723 121</td>
<td>1.00%</td>
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Appendices

Appendix 6.7.1 Together we will end AIDS, (2012). UNAIDS
Appendix 6.7.7 2011 Annual report on the state of the drugs problem in Europe. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)
Appendix 6.7.8 Joint EMCDDA and ECDC rapid risk assessment; HIV in injecting drug users in the EU/EEA, following a reported increase of cases in Greece and Romania, (2012). The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)
Appendix 6.7.13 Funding for HIV Vaccine R&D in 2011. HIV Vaccines and Microbicides Resource Tracking Working Group
Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper
Written by Dr Mary Moran

Background Paper 6.8
Tuberculosis

By Laurien Rook, MSc
01 March 2013
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<tr>
<th>Terms and acronyms</th>
<th>Definitions</th>
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<td>Acquired Immunodeficiency Syndrome</td>
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<tr>
<td>ARVs</td>
<td>Antiretroviral drugs</td>
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<tr>
<td>BCG</td>
<td>Bacille-Calmette-Guérin vaccin</td>
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<tr>
<td>Bill &amp; Melinda Gates</td>
<td>Philanthropic organization with a large global health program.</td>
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<td>Foundation</td>
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<td>BMBF</td>
<td>German Federal Ministry of Education and Research</td>
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<td>Case notification rate</td>
<td>Notified TB cases for each given year per 100,000 population</td>
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<td>CDC</td>
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<td>CPTR</td>
<td>Critical Path to TB Drug Regimens</td>
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<td>CRO</td>
<td>Contract Research Organization</td>
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<td>Directly Observed Treatment, Short-course</td>
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<td>DST</td>
<td>Drug sensitivity testing</td>
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<td>EDCTP</td>
<td>European and Developing Countries Clinical Trials Partnership</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>FDC</td>
<td>Fixed Dose Combination</td>
</tr>
<tr>
<td>FIND</td>
<td>Foundation for Innovative New Diagnostics</td>
</tr>
<tr>
<td>FP6</td>
<td>European Commission’s Sixth Framework Programme</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>Institut Pasteur</td>
<td>Private non-profit foundation with a focus on infectious disease. It provides education, supports biology research and provides public health services through its medical centre.</td>
</tr>
<tr>
<td>IUATLD</td>
<td>International Union against Tuberculosis and Lung Disease. Non-governmental organization.</td>
</tr>
<tr>
<td>Janssen</td>
<td>Johnson &amp; Johnson, a multinational pharmaceutical company.</td>
</tr>
<tr>
<td>LED</td>
<td>Light emitting diode</td>
</tr>
<tr>
<td>LMIC</td>
<td>Low and Middle Income Countries</td>
</tr>
<tr>
<td>LTBI</td>
<td>Latent Tuberculosis Infection</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>Multi Drug Resistant Tuberculosis. Resistant to at least isoniazid and rifampicin.</td>
</tr>
<tr>
<td>NDWG</td>
<td>Stop TB Partnership’s New Diagnostics Working Group</td>
</tr>
<tr>
<td>NGO</td>
<td>Non-governmental Organization</td>
</tr>
<tr>
<td>NIAID</td>
<td>United States National Institute of Allergy and Infectious Diseases. Part of the NIH.</td>
</tr>
<tr>
<td>NIH</td>
<td>United States National Institutes of Health</td>
</tr>
<tr>
<td>PDP</td>
<td>Product Development Partnership. A form of Public Private Partnerships (PPPs) focused on development of a specific (group of) product(s).</td>
</tr>
</tbody>
</table>
**Update on 2004 Background Paper, BP 6.8 Tuberculosis**

<table>
<thead>
<tr>
<th>Terms and acronyms</th>
<th>Definitions</th>
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<tbody>
<tr>
<td>PPP</td>
<td>Public Private Partnership. A long-term collaboration between the public-sector and one or more private sector companies.</td>
</tr>
<tr>
<td>SMEs</td>
<td>Small and Medium Enterprises</td>
</tr>
<tr>
<td>SSI</td>
<td>Statens Serum Institute. A public enterprise under the Danish government</td>
</tr>
<tr>
<td>STAG-TB</td>
<td>WHO Strategic and Technical Advisory Group for Tuberculosis</td>
</tr>
<tr>
<td>STBVAC</td>
<td>Stop TB Partnership’s Working Group on New TB Vaccines</td>
</tr>
<tr>
<td>Stop TB Partnership</td>
<td>Network of international organizations, countries, financial donors from the public and private sectors, governmental or non-governmental organizations and other entities, housed within WHO. It contains seven Working Groups that all focus on different aspects of tuberculosis.</td>
</tr>
<tr>
<td>TAACF</td>
<td>Tuberculosis Antimicrobial Acquisition and Coordinating Facility</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TBDA</td>
<td>TB Drug Accelerator. A partnership between several large pharmaceutical companies and research institutes.</td>
</tr>
<tr>
<td>TBTC</td>
<td>United States Centers for Disease Control and Prevention’s TB Trials Consortium</td>
</tr>
<tr>
<td>TBVI</td>
<td>Tuberculosis Vaccine Initiative. Public Private Partnership aimed at development of new TB vaccines.</td>
</tr>
<tr>
<td>TDR</td>
<td>Special Programme for Research and Training in Tropical Diseases. Based at WHO.</td>
</tr>
<tr>
<td>UK DFID</td>
<td>UK Department for International Development</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
</tr>
<tr>
<td>Wellcome Trust</td>
<td>Philanthropic organization that supports outstanding researchers, accelerating the application of research, and exploring medicine in historical and cultural contexts.</td>
</tr>
<tr>
<td>WGND</td>
<td>Stop TB Partnership’s Working Group on New TB Drugs</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>Extensive Drug Resistant Tuberculosis. Defined as MDR-TB plus resistance to a fluoroquinolone and at least one second-line injectable agent (amikacin, kanamycin and/or capreomycin)</td>
</tr>
<tr>
<td>Xpert MTB/RIF</td>
<td>GeneXpert <em>Mycobacterium tuberculosis</em>/rifampicin: automated, cartridge-based nucleic amplification assay for the simultaneous detection of TB and rifampicin resistance directly from sputum.</td>
</tr>
</tbody>
</table>
Executive Summary

The 2004 Priority Medicines Report stated that “Tuberculosis (TB) is a major and growing threat to public health for Europe and the world, with new epidemiological challenges.” Global trends since then show that tuberculosis (TB) incidence, prevalence, and mortality rates are gradually declining. However, the increase in multi-drug resistant (MDR)- and extensive drug resistant (XDR)-TB cases is worrisome. Tuberculosis remains a disease of poverty with a high burden of disease in the low and middle-income countries (LMICs) and in countries with high HIV incidence. Within the European Union (EU)/European Economic Area (EEA) the incidence rates of drug-sensitive and drug-resistant TB are declining in most countries.

Overall, the existing TB tools are not sufficient to eradicate tuberculosis. A substantial number of new diagnostics tools, including the Xpert MTB/RIF assay, have been endorsed by the WHO-STAG, but none of these tests are suitable for use in a point-of-care setting in the LMICs. The current treatment regimens are lengthy, have a high pill burden, require commitment from the patient, and can have severe side effects. There is currently only one vaccine available for prevention of TB, however, its protective effects are highly variable. New TB tools are needed and must be suitable for all forms of TB in people of all ages, including the HIV-positive population and children. These tools must deliver quick results and be suitable for use in the LMICs.

Since the 2004 report one novel pharmaceutical (bedaquiline) has obtained market authorization by the United States regulatory authority (FDA). Bedaquiline is also under evaluation by the EU regulatory authority (EMA). A second novel pharmaceutical (delamanid) has applied for market authorization with the EMA. There are several compounds in phase II, but the early clinical pipeline is empty. In contrast, the field of diagnostics has seen many changes since 2004. The Xpert MTB/RIF assay rollout has changed the face of TB diagnosis in several countries, most importantly South Africa. The diagnostics pipeline is relatively full and looks promising. Another promising research area is the development of vaccines. The current pipeline shows there are 16 vaccines in clinical trials. Vaccines for prevention of TB are only in phase II of development. In general product development partnerships (PDPs) and public-private partnerships (PPPs) have played a crucial role in the development of these promising pipelines of new TB tools.

The global funding available for tuberculosis research has increased annually from 2007-2010. In 2010, the annual global funding available for tuberculosis was US$575.4 billion. The majority of 2010 funding was supplied by the pharmaceutical industry, the US National Institute of Health (NIH) and the Bill & Melinda Gates Foundation, who together accounted for 92.4% of global TB research and development (R&D) funding. In 2010, the EC funded US$22,180,461 for TB R&D, this equals 3.9% of funding globally. The European Commission (EC) (Framework Programmes six and seven and European and Developing Countries Clinical Trials Partnership (EDCTP) have been crucial in the support provided to PPPs and PDPs.

Considerable progress has occurred since 2004 in the development of new treatments, diagnostics, and vaccines, often with EC support. Continued and increased support from the EC is required and needs to be a long-term commitment.
What is new since 2004:

- The new Global Plan To Stop TB was launched;
- One new pharmaceutical (bedaquiline) was approved by the FDA for use in MDR-TB;
- Two new pharmaceuticals (bedaquiline and delamanid) are in under evaluation by stringent market authorities;
- Several new diagnostic tools were endorsed by the WHO/STAG;
- The Xpert MTB/RIF assay is being enrolled globally and changing the diagnosis of TB;
- Global funding for TB research has increased annually;
- The global incidence of TB is declining.
1. **Introduction**

In 2004 a report *Priority Medicines for Europe and the World* was written by Warren Kaplan and Richard Laing and published by the World Health Organization (WHO). A chapter (6.8) and background paper on tuberculosis were written for this publication. This background paper is an update of the 2004 paper published at [http://archives.who.int/prioritymeds/report/background/tuberculosis.doc](http://archives.who.int/prioritymeds/report/background/tuberculosis.doc). This background document will provide an update of developments in the field of tuberculosis tools, in particular those developments involving basic research, diagnostics, treatments, and vaccines. Issues such as incentive systems for pharmaceutical innovation and regulatory practices are beyond the scope of this background chapter and will be discussed in chapter eight of the 2013 Priority Medicines report.

Tuberculosis (TB) is an infectious disease, caused by *Mycobacterium tuberculosis*. It primarily presents as pulmonary TB, but can affect other sites (extrapulmonary TB). Tuberculosis typically progresses slowly from the latent stage (infection without active disease, LTBI) to active TB, except in HIV co-infected patients where progression can be rapid and fatal. Only a small proportion of people infected with *M. tuberculosis* will go on to develop active TB from LTBI.\(^1\)

### 1.1 TB burden of disease

#### 1.1.1 Global burden of disease

Since 2005, the worldwide incidence rate has dropped slowly. In 2011, an estimated 8.7 million cases occurred globally including 1.1 million cases among the HIV-infected population. The global incidence rate is 125 cases per 100 000 population. The 22 high-burden countries account for 82% of the global TB burden.\(^1\) These countries are all low-and-middle-income countries (LMIC) and the incidence rates in 14 of these countries are declining, six countries have stable rates and two countries have an increasing TB incidence rate. The number of TB deaths was approximately 1.4 million in 2011. Globally the treatment success rate has reached 85% in 2009.\(^1\) Global trends in the incidence, prevalence and mortality rates are depicted in Figure 6.8.1.

Since the 2004 Priority Medicines report the world has seen an increase in the incidence of *M. tuberculosis* resistant to first-line drugs (Multi-Drug Resistant TB; MDR-TB) and the emergence of Extensively-Drug Resistant TB (XDR-TB) in 2006. Since 2006, several countries (e.g. Italy, Iran and India), reported TB strains with severe patterns of drug resistance. The term “Totally-Drug Resistant TB” is used for these TB strains, but has not been accepted by the WHO for several reasons.\(^2\) The treatment of MDR-TB is difficult and expensive, taking a long time (18-30 months) with a relatively low success rate. Most MDR-TB treatments are with medicines that are not generally used due to low effectiveness, substantial side effects and high costs.\(^3\) Global trends in MDR-TB rates are unclear due to the lack of data in several countries. Combined data showed that on average multidrug resistance occurs in 3.4% and 19.8% of new and previously treated TB cases respectively.\(^4\) Countries with a high burden of MDR-TB cases in Europe include Estonia, Lithuania, Moldova and Belarus. Data on XDR-TB are much scarcer, but globally approximately 9.4% of all MDR-TB cases were extensively drug resistant with high burdens in Estonia, Latvia, South Africa and Tajikistan.\(^4\) In the EU/EEA the percentage of drug resistance (both MDR- and XDR-TB) varies from 0% to 24.2%.
At least one-third of the world’s HIV-positive population is infected with TB. Co-infected TB/HIV patients are 21-34 times more likely to develop active TB than those living solely with LTBI. Tuberculosis is the leading cause of death among HIV-positive people. In 2010, 350,000 people died due to HIV-associated TB. For HIV-positive TB patients, it is crucial to detect MDR as soon as possible due to their high risk of mortality. Mortality rates can exceed 90% in patients co-infected with XDR-TB and HIV.

Figure 6.8.1: Global trends in TB. 1990-2011

Source: Global Tuberculosis Report (2012) WHO.
Note: Estimated rates of TB incidence per 100,000 population (green), 1990-2011 prevalence (blue) and mortality (orange, excluding HIV-positive people) rates with 2015 predictions. The red line represents the estimated incidence rate of HIV-positive TB. The dashed lines represent the Stop TB Partnership’s 2015 targets. Shaded areas represent uncertainty bands.

1.1.2 EU/EEA burden of disease

In the EU/EEA region, the overall case notification rate in 2010 was 14.6 per 100,000 population with a total of 73,996 TB cases reported. The case notification rate decreased by an average 8% from 2009 and the EU/EEA region maintains this downward trend. Over the years 2006-2010 the mean five-year decline in case notification rate was -4.4%. The trends in TB-notification rates are shown in Figure 6.8.2. The five European high-burden countries are Bulgaria, Estonia, Latvia, Lithuania, and Romania. These high-burden countries have seen steep declines in case notification rates. Increases on 2009 figures were seen in Belgium, Cyprus, Hungary, and Iceland. Only Cyprus and Sweden showed increasing five-year trends from 2006-2010 though the absolute numbers were low. The individual countries case notification rates for 2010 can be found in annex 6.8.1A.
Multi-drug resistance among new TB cases and previously treated TB cases were found to be 4.6% and 17.6% respectively in the EU/EEA region in 2010. The notification rate for MDR-TB remained stable from 2006-2010 at around 0.3 per 100 000 population. In 2010, 13.2% of reported MDR-TB cases were also resistant to second-line drugs (XDR-TB). The prevalence of MDR-TB and XDR-TB was highest in the Baltic countries. Trends in MDR-TB notification rates are depicted in Figure 6.8.3. The individual countries MDR-TB and XDR-TB percentages for 2010 can be found in annex 6.8.1B.

Note: Notification rates are given as TB cases per 100 000 population. Number of low-incidence countries: 23. Number of high-incidence countries: six.
1.2 TB Control Strategy

The 2004 Background paper, page 6-9, elaborated on Directly Observed Treatment, Short-Course (DOTS) a globally used TB control strategy and its limitations. In 2006, the WHO and Stop TB Partnership developed a new six point Stop TB Strategy. It’s goal is to reduce the global burden of disease by 2015 and eliminate TB as a public health problem by 2050. The six components of the Stop TB strategy:

- Pursue high-quality DOTS expansion and enhancement;
- Address TB-HIV, MDR-TB and the need of poor and vulnerable populations;
- Contribute to health system strengthening based on primary health care;
- Engage all care providers;
- Empower people with TB and communities through partnership;
- Enable and promote research.7

In 2006, the Stop TB Partnership published the Global Plan to Stop TB 2006-2015, a roadmap for scaling up prevention and treatment, for research and development, and for financing. The R&D component of this plan indicates what needs to be done to develop new tools that are required to eventually eliminate TB.8

Current TB tools

The tools available for the control of TB are diagnostics, pharmaceuticals, and vaccines. For the sake of this background paper, tools such as capacity building and operational research will not be discussed.

1.2.1 Diagnostics

Rapid, accurate diagnosis of tuberculosis (TB) is critical for timely initiation of treatment, and ultimately, control of the disease. The most commonly used diagnostic test for pulmonary TB, sputum smear microscopy, is over a 100 years old and is relatively insensitive, though very specific. The current gold standard is microbiological culture. However this is time- and labour-intensive and requires an extensive laboratory infrastructure that is not readily available in many of the countries with a high burden of disease. Results of drug-sensitivity testing (DST) can take weeks. Ideally a diagnostic test for TB would be low in cost, simple, rapid, suitable for use at the point-of-care (e.g. health clinics), and would provide drug susceptibility results.1,9 The WHO Strategic and Technical Advisory Group for Tuberculosis (STAG-TB) has successively endorsed since 2007 the following tests for diagnosis of active TB:

- Liquid culture including first/second line DST (2007);
- Rapid speciation from culture (2007);
- Molecular line probe assay (2008);
- Light emitting diode (LED) fluorescence microscopy (2009);
- Noncommercial culture methods and rapid DST (2010)
  - Microscopically Observed Drugs Susceptibility
  - Nitrate Reductase Assay
  - Colorimetric Redox Indicator
- Xpert MTB/RIF assay (2010).1,9
These tests are beginning to be implemented in LMICs and the Xpert MTB/RIF in particular has the potential to transform the diagnosis of TB and drug-resistant TB. The Xpert MTB/RIF assay is available for several countries at discounted prices.

There are several other diagnostic tools available, but these are currently not recommended by the WHO for the detection of active TB:

- Immune response-based tests (used to diagnose TB in low incidence settings)
  - Interferon gamma release assays
  - Tuberculin skin test
- Serodiagnostic assays (currently recommended against by STAG-TB)
- Volatile organic compounds (no evaluation by STAG-TB yet)
- Phage-based systems (no evaluation by STAG-TB yet)
  - Luciferase reporter phage assay
  - Mycobacteriophage-based assay
- Alternative antigen assays.

The WHO has strongly recommended against the use of existing commercial serodiagnostic assays for the diagnosis of pulmonary or extra-pulmonary TB due to inconsistent and imprecise findings. The immune response-based tests are not endorsed for the diagnosis of active TB, but these tools can be used to diagnose LTBI in low TB incidence settings. The tuberculin skin test cannot distinguish between latent and active disease and there is a possibility of a positive response occurring in BCG vaccinated individuals. Interferon gamma release assays can distinguish between active and latent disease but are more costly and technically complicated. Both tests are not suitable in situations with a high TB and/or HIV burden and, thus, are not recommended for use in LMICs.

Another limitation of many diagnostic tools is the use of sputum for TB diagnosis. Sputum is not suitable for detection of extra-pulmonary TB and collecting an adequate specimen can be challenging in HIV-positive and paediatric patients. Although several tests have been endorsed by WHO, there are currently no simple blood tests or other point-of-care assays suitable for use in resource-poor settings in LMICs.

1.2.2 Treatment

The WHO advises supervised treatment, (e.g. directly observed treatment (DOT)), to ensure treatment adherence and completion. The current treatment regimen for new cases of pulmonary TB consists of a three to six month treatment regimen with four different drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) with daily or three times weekly dosing under DOT. These different medicines may be combined into single Fixed Dose Combination (FDC) tablets to reduce pill burden. The treatment success rate for drug-sensitive patients with this regimen is high. Patients with previously treated TB have a high chance of a drug-resistant strain of TB and require a different approach depending on the availability of drug-sensitivity testing (DST). Where DST is routinely available, a new treatment regimen should be commenced according to the results. In situations where DST is not routinely available, patients are treated empirically with an eight month retreatment regimen containing five first-line drugs or an MDR-TB regimen including second-line drugs. The MDR-TB regimen can last from 18 months to up to 30 months and contains at least four different drugs including the use of at least one injectable medicine but has a relatively low success rate. Several of the first-line or second-line TB treatments can cause liver damage and...
show drug-drug interactions with HIV therapy (antiretroviral drugs, ARVs). In addition these regimens have a high pill burden and require commitment from the patient and care providers.\textsuperscript{3}

The current treatment for LTBI recommended by WHO consists of a six month treatment with daily or three-weekly intake of four different drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol).\textsuperscript{3} The United States Centers for Disease Control (CDC) and the United Kingdom National Institute for Health and Clinical Excellence (NICE) have recently approved a three month once-weekly regimen of isoniazid plus rifapentin (CDC) or rifampicin (NICE). However, this novel treatment is not suitable for young children, pregnant women, and HIV-positive patients on ARVs.\textsuperscript{13,14}

1.2.3 Vaccines

The only available vaccine (Bacille-Calmette-Guérin, BCG) is almost 100 years old. This vaccine protects against severe progressive TB in children, but its protective effects in adolescents and adults are variable. The vaccine is not suitable for use in HIV-positive children. New vaccines that are safe and effective against all forms of TB in all age groups, including the HIV-positive population, are needed.\textsuperscript{1,15}

1.3 Summary

Global trends show that TB incidence, prevalence and mortality rates are gradually declining. However the increase in MDR- and XDR-TB cases is worrisome. Tuberculosis remains a disease of poverty with a high burden of disease in the LMICs and in countries with a high HIV prevalence. Within the EU/EEA region the incidence rates are declining in most countries. The percentages of drug resistant TB cases are also declining within Europe.

Overall, the existing TB tools are not sufficient to eradicate tuberculosis. A substantial number of new diagnostics tools have been endorsed by WHO-STAG, but none of these tests are suitable for use in a point-of-care setting in the LMICs. The current treatment regimens are lengthy, have a high pill burden, require commitment from the patient and can have severe side effects. There is currently only one vaccine available for prevention of TB; however, its protective effects are highly variable. New TB tools are needed and must be suitable for all forms of TB in people of all ages, including the HIV-positive population. These tools must deliver quick results and be suitable for use in the LMICs.

2. Developments in TB Tools; Past and Present

2.1 Basic research

Basic research to improve understanding as to how TB “works” in the human host, how the human immune system responds to infection with \textit{M. tuberculosis} and identification of biomarkers that distinguish all stages of TB are essential to develop effective diagnostics, pharmaceuticals, and vaccines.\textsuperscript{1,16} Basic research is done mainly by academic institutions and through Public Private Partnerships (PPPs).
The Stop TB Partnership was founded in 2001 and brings together nearly 1000 organizations, such as international and technical organizations, government programmes, research and funding agencies, foundations, non-governmental organizations (NGOs), civil society, and community groups and the private sector. The Stop TB Partnership and WHO launched the TB Research Movement to develop an overview of research priorities.

The EC’s Innovative Medicines Initiative (IMI) has funded the PreDiCT-TB project with €14 800 000 to tackle pre-clinical research barriers to the discovery and development of new TB treatments. PreDiCT-TB aims to develop new laboratory-based models and generate a database of patient data from previous and on-going clinical trials. Through these activities the project aims to enable researchers to design better clinical trials.

The EU has funded several projects under the Sixth and Seventh Framework Programme (FP6 and FP7) on fundamental research into TB. An overview of these projects are listed in Annex 6.8.3. The EU has funded a total of 38 projects with a main focus on TB basic research under the FP6 and FP7. The New Medicines for Tuberculosis (NM4TB) project is an example of successful transition from basic research to preclinical development. This project led to the discovery of the class of benzothiazinones and resulted in a novel compound now in preclinical development.

The United States National Institute of Allergy and Infectious Diseases (NIAID) supports basic research into the mechanisms of latency and the TB bacterial genome and cell wall.

### 2.2 Pharmaceuticals

During the past decade, efforts to develop new pharmaceuticals for TB have intensified and considerable progress has been made. The original 2004 report indicated that the TB product pipeline was thin in all stages of development. Since the 2004 report, one novel pharmaceutical has obtained market authorization by the United States regulatory authorities.

In 2004, the product development pipeline was nearly empty. The current pharmaceutical development pipeline is illustrated in Table 6.8.1 and contains only new chemical entities (NCEs). Repurposed antibiotics and novel regimens are listed in Annex 6.8.4. The late clinical pipeline (phase II/III) of new compounds, repurposed antibiotics and new treatment regimens is promising. Two novel compounds have filed for market authorization with stringent regulatory authorities. Otsuka Pharmaceutical’s delamanid is currently under evaluation by the EMA for its use for MDR-TB. Janssen, a pharmaceutical company of Johnson & Johnson, announced that it submitted market approval applications in 2012 to both the FDA and EMA for bedaquiline for the treatment of MDR-TB. In December 2012, the FDA announced the approval of bedaquiline for treatment of MDR-TB. The early clinical pipeline is empty with no novel pharmaceuticals currently in phase I.

#### 2.2.1 Public and Not-for-Profit Private Sector

The public and not-for profit private sector consists mainly of Product Development Partnerships (PDPs) and PPPs. The organizations that do not work on development of specific products but rather work on the development of concepts and pharmaceuticals.
regimens will be referred to as PPPs. In the field of TB R&D, these PDPs and PPPs play a pivotal role, particularly in basic research, regimen development, and redirecting existing antibiotics towards a TB indication.

**Pharmaceutical development**

In 2004, the TB Alliance was the sole PDP working on novel drug development, this is still the case. Currently the TB Alliance has a portfolio with several novel regimens in phase II/III, a NCE (PA-824) in phase II, a lead compound (TBA-354) in preclinical development and several projects in lead identification and optimization.\(^{25,31}\) The TB Alliance collaborates with six large pharmaceutical companies AstraZeneca, GlaxoSmithKline, Johnson & Johnson/Janssen, Bayer Healthcare AG, Novartis Pharmaceuticals, and SanofiAventis to develop novel drugs and treatment regimens.\(^{25}\)

The Stop TB Partnership is a PPP founded in 2001 and housed with the WHO. The Stop TB Partnership brings together nearly 1 000 organizations, such as international and technical organizations, government programmes, research and funding agencies, foundations, NGOs, civil society, and community groups and the private sector. The Stop TB partners have formed working groups in several areas, including the Working Group on New TB Drugs (WGND).\(^{17}\) The WGND is a group of experts dedicated to the acceleration of development of effective and affordable therapies for TB. The WGND provides information on the current developments in TB pharmaceutical development.\(^{32}\)

In 2006, the New Medicines for Tuberculosis (NM4TB) was founded through FP6. This PDP aims to develop new drugs for TB through collaborations with academia, a large pharmaceutical company (Astra Zeneca), and three Small and Medium Enterprises (SMEs).\(^{20}\) The NM4TB has identified and validated several targets for new anti-TB agents, including the benzothiazinone BTZ043 that is now in preclinical development.\(^{21}\) In 2011, the More Medicines for Tuberculosis (MM4TB) research consortium evolved from the NM4TB under the FP7. This research consortium will continue the work started under NM4TB.\(^{22}\) Other projects funded under the FP6 and FP7 are listed in Annex 6.8.3. The EU has funded a total of 14 projects related to TB pharmaceutical research under the FP6 and FP7.

The European and Developing Countries Clinical Trials Partnership (EDCTP) was founded in 2003 under the FP6. It is still mainly funded by the EU. It currently unites 14 participating European Union (EU) Member States plus Norway and Switzerland with sub-Saharan African countries. The EDCTP aims to accelerate the development of new or improved drugs, vaccines, and diagnostics for TB, HIV/AIDS, and malaria. The EDCTP supports multicentre projects in partnerships with sub-Saharan countries that combine clinical trials, capacity building, and networking.\(^{33}\) The EDCTP investigated the use of moxifloxacin in the REMox I trial and is currently conducting the RIFAQUIN and PanACEA-ReMox II, PanACEA-HIGHRIF and PanACEA SQ-109 trials.\(^{34}\) An overview of EDCTP funded tuberculosis projects is listed in Annex 6.8.5. It is anticipated that in 2014, the second phase of the EDCTP programme (EDCTP-II), funded by the EC Framework Programme Horizon 2020, will commence. The planned ten-year budget for EDCTP-II is a minimum of €1 billion. This programme will continue with clinical trial capacity building in sub-Saharan Africa. The EDCTP-II plans to invest in new TB vaccines, novel pharmaceuticals, novel treatment regimens, and point-of-care diagnostic tools.\(^{35}\)
The NIAID is involved in several clinical trials into novel TB treatments and treatment regimens. In collaboration with Sequella the NIAID developed SQ-109, a NCE now in phase II for treatment of active TB. The NIAID is also involved in the development of AZD5847 with AstraZeneca. This pharmaceutical is currently under investigation in a phase IIa trial.

New Treatment Regimens

One of the challenges in treatment of latent and active TB is the lengthy duration of treatment regimens. Research into new drug regimens has led to a reduced treatment time of 6 months for active drug-sensitive TB and consequently higher patient compliance. The treatment for latent TB infection (LTBI) has been reduced to 3 months by the CDC and NICE, but not WHO. However, these shorter regimens are not suitable for all age groups or in HIV patients on ARVs. The current treatment regimens for MDR-TB and XDR-TB can last up to 30 months. An overview of repurposed antibiotics and novel regimens is provided in Annex 6.8.4.

More research into novel regimens is required. To facilitate research in this field the Critical Path to TB Drug Regimens (CPTR) initiative was co-founded by the Bill & Melinda Gates Foundation, the Critical Path Institute, and the TB Alliance and launched in March 2010. Industry, academia, regulatory agencies and civil society organizations work together in this initiative to speed the development of new and markedly improved drug regimens for tuberculosis. The partners of the CPTR are listed in annex 6.8.6. Traditionally individual TB drug candidates were developed and registered separately. The CPTR stimulates advances in preclinical and regulatory frameworks and development of infrastructure necessary to allow testing of promising novel drug candidates in combination with other promising candidates or registered TB drugs. As such aiming to decrease regimen development time and reduce development costs.

A second organization working in the field of drug regimen development is the Tuberculosis Trials Consortium (TBTC) founded by the CDC. The TBTC works closely with academia, government researchers, non-governmental organizations (NGOs), and the private sector. The PREVENT TB study led by the TBTC, in collaboration with Sanofi Aventis, resulted in the development of a 12 week regimen for LTBI containing rifapentine/isoniazid once-weekly under directly observed therapy. This study included substudies in children and HIV-positive patients. The TBTC is currently planning the iAdhere study to evaluate the adherence to this new regimen under self-administrated therapy. Another TBTC trial (Opti-Q) will investigate levofloxacin and moxifloxacin as part of a new regimen. The TBTC study 35, in collaboration with the AIDS Clinical Trials Group (ACTG) and International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), will investigate regimens for preventing TB in persons with household contact with MDR-TB patients. Originally the investigators planned to compare the use of bedaquiline to isoniazid, but bedaquiline’s sponsor (Janssen, a pharmaceutical company of Johnson & Johnson) has not made the drug available for research in LTBI studies. However, the company is investigating bedaquiline in a murine LTBI model to develop an ultra-short regimen.

The Special Programme for Research and Training in Tropical Diseases (TDR) is currently investigating the use of gatifloxacin for a four month treatment of TB. Results of this trial are expected near the end of 2013.
2.2.2 Industry

The 2004 Background paper stated that only three of world’s largest companies conducted research on TB pharmaceuticals, with only one company conducting this research as a part of its mainstream R&D activities. These three companies were all European based (AstraZeneca, GlaxoSmithKline, and Novartis). Since the 2004 report, efforts from the large pharmaceutical companies have increased. There are currently ten multinational companies working on TB pharmaceutical development. Of these companies five are EU-based, (i.e. AstraZeneca, Bayer Healthcare AG, GlaxoSmithKline, Novartis and SanofiAventis).

The two novel compounds currently under evaluation with the regulatory authorities were developed by multinational pharmaceutical companies. Delamanid was developed by Japan-based Otsuka Pharmaceutical Co., LTD. Bedaquiline was developed for the treatment of MDR-TB by Janssen Infectious Diseases BVBA (formerly known as Tibotec BVBA). Janssen provided the TB Alliance with a worldwide license to develop bedaquiline for Drug-Sensitive (DS)-TB in 2009.

The 2004 background paper addressed the issue of investigating broad-spectrum antibiotics, particularly the fluoroquinolones, for a TB indication. The original paper stated that pharmaceutical companies were reluctant to make these patented pharmaceuticals available for clinical trials. Currently there are several fluoroquinolones under investigation as part of novel treatment regimens. Two of the most promising fluoroquinolones under investigation are moxifloxacin (Bayer) and gatifloxacin (Bristol-Myers Squibb). Both are in phase III trials for drug-sensitive TB. Clofazimine (Novartis) is a registered drug for leprosy (a condition related to tuberculosis) that is currently under investigation for a MDR-TB indication. This drug is under investigation in the STREAM trial that is conducted by the United Kingdom Medical Research Council and The International Union against Tuberculosis and Lung Disease. These redirected pharmaceuticals are generally being investigated by PPPs.

An issue addressed by the WHO is the necessity of FDCs to reduce the pill burden for patients and, thus, enhancing patient adherence. In a clinical trial conducted by The International Union Against Tuberculosis and Lung Diseases the efficacy and safety of an FDC was established thus confirming the validity of WHO’s approach. Sandoz, the generic arm of Novartis, has developed an FDC with the four essential first-line TB pharmaceuticals and provides global access to this treatment. SanofiAventis is working on a FDC and dispersible form (suitable for children) of isoniazid and rifapentine for the treatment of LTBI.

The 2004 Background chapter discussed the foundation of specialized infectious disease research institutes by large pharmaceutical companies. These institutes still exist and are often linked with PPPs. Examples include Eli Lilly’s TB Drug Discovery Initiative, the Novartis Institute for Tropical Diseases, and GlaxoSmithKline’s Tres Cantos Medicines Development Campus.

Recently seven large pharmaceutical companies and four research institutions, in collaboration with the Bill & Melinda Gates Foundation, launched the TB Drug Accelerator (TBDA) partnership. This partnership will aid TB drug research by collaborating on early-stage research. The participating pharmaceutical companies will open up sections of their
compound libraries and share data with each other and the four research institutes. An overview of the participants is listed in Annex 6.8.7.

Another collaboration amongst developers of novel pharmaceuticals is the FP7 funded project ORCHID (Open Collaborative Model for Tuberculosis Lead Optimisation). The Orchid consortium, led by GSK, comprises 12 partners. It aims to identify new candidates that could enter into clinical development, to promote the development of new preclinical tools and elucidate the mode of action of anti-tubular compounds discovered in early stage development.

Smaller pharmaceutical and biotech companies still play an important role in TB pharmaceutical development. These companies particularly collaborate with PDPs to develop their products. Examples of SMEs and smaller pharmaceutical companies with TB pharmaceuticals in the current pipeline are Otsuka, Sequella, Qurient Therapeutics, and Daiichi-Sankyo Pharmaceutical.

2.3 Diagnostics

The 2004 Background paper, pages 8 and 10-11, stated that one of the limitations of the DOTS strategy was the lack of cheap, quick, and reliable tests for detection of LTBI, TB diagnosis, and MDR-TB diagnosis. Since 2004, the WHO has endorsed several diagnostic tools for active TB disease. In particular the endorsement and rollout of the Xpert MTB/RIF assay has revolutionized the diagnostic landscape (see Box 6.8.1).

In the LMICs the access to TB health care is variable and limited due to several factors, including poor health-care infrastructure and a lack of trained laboratory professionals. The laboratories with the greatest test capacity and most accurate methods are often located in urban setting. The peri-urban and rural communities are often deprived of these high-quality diagnostic centres. The diagnostic healthcare infrastructure can roughly be divided in three levels, (i.e. the community (point-of-care), intermediate (district and sub-district laboratories, microscopy centres) and reference (National Reference Laboratories or equivalent) level). In the LMIC most patients access healthcare at the community level with only basic diagnostic tools available for use. Despite the endorsement of several novel diagnostics there is currently no test suitable for use at the point-of-care. As a result of these limitations, TB patients in LMICs are often diagnosed late and, thus, these patients remain capable of infecting others. Drug-resistant TB often remains undiagnosed and as such is not treated appropriately.
Box 6.8.1: Xpert MTB/RIF Test

In 2006 FIND, Cepheid, Inc. and the University of Medicine and Dentistry of New Jersey started work on the development of the Xpert MTB/RIF test with support from the NIH and the Bill & Melinda Gates Foundation. In 2006 FIND, Cepheid, Inc. and the University of Medicine and Dentistry of New Jersey started work on the development of the Xpert MTB/RIF test with support from the NIH and the Bill & Melinda Gates Foundation.\(^2\)\(^3\)\(^4\)

The amplification of nucleic acids (DNA or RNA) for the diagnosis of TB or to detect drug resistance is a sensitive method that can produce faster results than conventional culture methods. Polymerase chain reaction (PCR) is the most common method of amplification. The Xpert MTB/RIF cartridge is a disposable plastic cartridge that contains all reagents required for the detection of *M. tuberculosis* and rifampicin resistance with PCR. Rifampicin resistance is an indicator of MDR-TB. The Xpert MTB/RIF cartridge uses Cepheid’s fully automatic GeneXpert device. The assay can be performed directly on a sputum sample. The test has similar sensitivity to culture, is specific for *M. tuberculosis* and results can be obtained within two hours.\(^2\)\(^3\)\(^4\) The GeneXpert device ensures a closed system with no risk of contamination and thus reduces the requirement of bio-safety facilities. The training of laboratory technicians generally lasts one to two days.\(^4\)

In 2010 the WHO-STAG endorsed the use of this test for the detection of TB and rifampicin resistance. The WHO-STAG concluded that this diagnostic tool does not eliminate the need for conventional smear microscopy and DST. In addition several operational conditions need to be met, most importantly stable electrical supply, trained personnel and a maximum ambient temperature of 30°C. The WHO Stop TB Department developed a Rapid Implementation plan which contained an outline with requirements for a global, systematic roll-out of the Xpert MTB/RIF assay.\(^5\) The expected impact of the Xpert MTB/RIF endorsement and roll-out is a three-fold increase in diagnosis of drug-resistant TB and a two-fold increase in the diagnosis of TB in HIV-positive patients.\(^6\)

The next step after the endorsement of the MTB/RIF assay in December 2010 was the roll-out of the Xpert MTB/RIF assay. FIND, in collaboration with PEPFAR, USAID, UNITAID and the Bill & Melinda Gates Foundation, has negotiated with Cepheid to obtain price reductions for the 145 countries on the FIND list.\(^7\) UNITAID, in collaboration with the WHO and Stop TB Partnership, has launched the TBXpert project to provide approximately 1.4 million Xpert MTB/RIF test cartridges and over 200 GeneXpert instruments for 21 recipient countries in 2013-2015.\(^8\) Since the WHO endorsement, 77 countries have procured 966 GeneXpert instruments and 1 891 970 Xpert MTB/RIF cartridges under concessional prices.\(^9\)

The development, endorsement and roll-out of the Xpert MTB/RIF assay and the GeneXpert instruments at concessional prices have revolutionized the diagnosis of TB in LMICs. The most striking example is the roll-out in South-Africa. In March 2011 the South African National Department of Health, in conjunction with the South African National Health Laboratory Service (NHLS), announced a nationwide scale up of access to Gene Xpert. Gene Xpert platforms where placed in 25 laboratories across the country.\(^10\) The goal is a phased scale-up that will eventually lead to the placement of 238 instruments in laboratories nationwide, leading to a test capacity of 11 428 tests per day in 2013.\(^10\) The training of laboratory staff has been centralized and standardized. All instruments were interfaced with the NHLS Laboratory Information System to allow troubleshooting and
By November 2012, 805,571 specimens had been processed with 14.92% positive for TB infection, of which 7.18% were Rifampicin-resistant. Implementation was 53% complete. By December 2012 a total of 153 instruments were placed in 108 testing centres, leading to a 57% implementation rate. By December 2012 a total of 875,964 specimens were processed. It is expected that coverage will reach 74% by the end of March 2013 due to placement of an additional 44 instruments.

The (cost) effectiveness of the Gene Xpert MTB/RIF roll-out in South-Africa will be evaluated in the EXTEND trial. The EXIT-RIF trial will evaluate the effects of MDR-TB diagnosis with Xpert MTB/RIF on treatment outcomes.

References
1 WHO report 2011 GLOBAL TUBERCULOSIS CONTROL;WHO; WHO/HTM/TB/2011.16
2.3.1 Current Research & Development

The 2004 Background paper, pages 10-11, stated that much of the commercial R&D for TB was undertaken by small and medium sized biotechnology companies, with the western market in mind and, thus, these tests were not suitable for use in the LMICs. The current market incentive towards developing diagnostics suitable for LMICs has increased due to the engagement of not-for-profit/public organizations, NGOs, national TB programs and funding agencies. R&D is being undertaken by SMEs in collaboration with PDPs and with support from the public and not-for-profit sector. Projects funded by the EU under the FP6 and FP7 are listed in Annex 6.8.3. Under the FP6 and FP7 the EU funded a total of 11 projects related to research into TB diagnostic tools.

An overview of TB diagnostics currently in use and under development is listed in Annex 6.8.8. Five diagnostic tools are in the late stage of development and are expected to undergo evaluation by WHO/STAG-TB shortly. One of these tests, Determine® TB-LAM, is suitable for use at the point-of-care. Three tests are suitable for use at an intermediate level, and one test is suitable for use at a reference level. The TB-LAM assay uses urine samples, is low in costs, gives rapid results, and can detect extra-pulmonary TB. However, the major drawback of this test is the poor performance in persons without HIV infection and in HIV-positive patients with well-controlled disease.

Public and Not-for-Profit Private Sector

The Foundation for Innovative New Diagnostics (FIND) is a PDP established to drive the development and implementation of diagnostic tests suitable for low-resource settings. FIND’s pipeline currently contains four new diagnostic tools suitable for use at the point-of-care, all are in an early stage of development. FIND’s pipeline also contains three new tools suitable for use at an intermediate level. Since 2004, FIND has successfully co-developed five WHO endorsed diagnostic tools, among which is the Xpert MTB/RIF assay.

The Stop TB Partnership’s New Diagnostics Working Group (NDWG) facilitates the development and adoption of new diagnostic tools for TB. The NDWG has produced a scientific blueprint to aid the R&D of new TB diagnostics. The TDR and WHO launched the TB specimen bank and TB strain bank to assist R&D. The specimen bank contains sputum samples from people with and without TB. The strain bank contains MDR- and XDR-TB samples.

The TDR has investigated diagnostic tools suitable for use at the point-of-care, such as same-day microscopy tests, low-cost fluorescence microscopy and commercially-available serological tests. TDR is also aiming to improve the diagnosis of TB in children.

The IMI has invested €6 828 438 in the development of rapid point-of-care test platforms for infectious diseases (RAPP-ID) project. This project aims to develop a point-of-care test for rapid detection of pathogens and markers of infection involved in several infectious diseases including tuberculosis. The RAPP-ID consortium involves ten academic partners, four SMEs, and five pharmaceutical companies from across Europe, who will work together over a five-year period. The industry has invested €5 848 470 in this project.
In 2009, the NIAID and John Hopkins University established the Tuberculosis Clinical Diagnostics Research Consortium (CDRC). The CDRC offers support to researchers by providing several clinical trial sites with a diverse population of patients to evaluate diagnostic tests in TB endemic countries.65

2.4 Vaccines

As stated earlier there is currently only one vaccine available (i.e. the BCG vaccine). The partial efficacy of this vaccine suggests that an effective vaccine is possible. The 2004 Background report, pages 18-20, indicated that research into new TB vaccines increased substantially since the 1990’s with a vast majority of candidates in a preclinical stage and only three vaccine candidates in phase I. Since the last decade, much progress has been made in TB vaccine research. A rich pipeline of new vaccine candidates has emerged, research into new biomarkers for vaccine safety and efficacy is promising, and capacity for large-scale clinical trials is being developed.15,66 There are two strategies improving the TB vaccination. The first is the “prime-boost” strategy in which previously BCG vaccinated subjects will receive a new vaccine as a booster dose. The second strategy is the development of a vaccine that will replace BCG, such as an improved version of BCG or an attenuated live M. tuberculosis vaccine.1, 66 Research into promising vaccine adjuvants can further increase the efficacy of TB vaccines.15, 66 The TB vaccines under development can have several goals (e.g. to prevent (latent) infection, to prevent development of active disease (either from recent infection or reactivation of LTBI), or to shorten the course of treatment by improving the response to pharmaceuticals).67

The Stop TB Partnership’s Working Group on New TB Vaccines (STBVAC) has compiled an overview of the current TB vaccine pipeline. This overview is described in Annex 6.8.9. This pipeline shows there are currently 16 vaccines in clinical trials, with two vaccines in phase III (M. indicus pranii and M. vaccae).67 The M. vaccae vaccine is under investigation for therapeutic use in active TB.66 The M. indicus pranii project is being developed as a therapeutic vaccine; however, there is no information on the company website (Cadila Pharmaceuticals Ltd.), no clinical trials are listed with the United States or EU trial register, and no results of previous clinical trials have been published in the Medline database. The MVA85A vaccine was tested in a phase IIb trial and whilst it was well tolerated, results did not show efficacy.68 It is anticipated that further analysis of the trial data may be helpful for the development of new vaccine candidates.69

2.4.1 Public and Not-for-Profit Sector

Aeras is the sole PDP working in the area of vaccine development. Aeras currently has six vaccine candidates in clinical trials with two vaccines in late phase II (MVA85A and Aeras-402), one vaccine in early phase II (GSK M72), and three vaccines in phase I (H4-IC31, H56-IC31 and ID93).70 When looking at the global pipeline, Aeras plays an important role in the development of new vaccines. Four of the six phase II candidates have been co-developed by Aeras.67 Aeras collaborates with several partners in industry, academia, NGOs, foundations, and governments.70

Recently STBVAC, in collaboration with Aeras and the TuBerculosis Vaccine Initiative, coordinated the assembly of a blueprint for TB vaccine development. This blueprint offers an outline of the strategy for developing and introducing safe and effective TB vaccines over the
next decade. The strategy contains five critical areas and key questions that need to be addressed to ensure successful vaccine development in the future. These five areas are creativity in research and discovery; correlates of immunity and biomarkers; harmonization and cooperation in clinical trials; rational selection of potential candidates; and the need for advocacy, community acceptance and funding.15

The TuBerculosis Vaccine Initiative (TBVI), funded by the FP7 amongst others, is a PPP that provides a link between several EC supported projects (FP6 and FP7) and global initiatives aimed at the development of new TB vaccines. The TBVI aims to develop both priming and boosting vaccines against TB. The TBVI is also active in the development of biomarkers and offers support to increase clinical trial capacity.71 One of the projects managed by TBVI is the FP6 funded TBVAC project. This project resulted in four new vaccine candidates in preclinical stages, four candidates in early clinical stages, 15 candidate biomarkers, and three adjuvants. The TBVI expects that the most advanced vaccine candidate, if successful in further clinical trials, can be licensed by 2017.72 Other projects funded under the FP6 and FP7 are listed in Annex 6.8.3. The EU has funded a total of 12 projects related to TB vaccines under the FP6 and FP7.

The NIAID provides support and funding for TB vaccine development.73 Recently, the NIAID joined Aeras and Crucell N.V. to further develop the phase II vaccine candidate Aeras-402.74 The NIAID is also involved in development of the phase II M. Vaccae and phase I rBCG30 vaccines.67, 75

2.5 TB tools; future needs

The elimination of TB will only happen if the way TB is diagnosed, treated, and prevented undergoes a radical change and TB tools deliver quicker results, are affordable for the LMICs, and are safe and effective in all populations.8 To ensure a steady flow of new technologies into the TB tool pipelines continues and adequate attention to basic research is necessary. A solid knowledge base of the TB pathogen is required to engineer new diagnostics, pharmaceuticals, and vaccines.8 The currently available therapies are lengthy and require patient commitment. Shorter and simpler treatments for drug-sensitive and drug-resistant TB are needed urgently. For drug-resistant TB, the introduction of novel pharmaceuticals would be most welcome.8 While the available TB treatment regimens are slowly improving, the lack of an effective point-of-care diagnostic is delaying the early diagnosis of TB and hampering with the elimination of this disease. The introduction of the GeneXpert MTB/RIF has had a profound impact on the diagnosis of TB, but this test is expensive, requires continuous supply of electricity, and is not suitable for use at the community level.8 In the past decade research into new vaccines against TB has resulted in several candidates advancing into clinical trials. However, no preventive vaccine has reached phase III yet. The introduction of a new effective TB vaccine will be crucial to the eradication of TB. The current momentum for TB vaccine research needs to be maintained.8

Progress has occurred since 2004 but more needs to be done. The EC (FP6&7 and EDCTP) have been crucial in the support provided to PPPs and PDPs. Continued support through Horizon 2020 will be required.
3. Existing resource flows for TB R&D

The Global Plan to Stop TB 2011-2015 states that global investments in TB research and development have decelerated since the launch of the Global Plan to Stop TB 2006-2015. The Global Plan to Stop TB 2011–2015 calls for an investment of US$ 9.8 billion over five years to reach the Partnership’s 2015 research and development targets. The Global Plan contains five R&D areas: fundamental research, diagnostics, medicines, vaccines, and operational research.8 For the sake of this report, the resource flows for operational research will not be discussed.

Policy Cures is an independent group providing information on R&D data, strategic analysis, decision-making tools, economic modeling, and policy advice on neglected diseases such as tuberculosis.76 Since 2007, Policy Cures conducts the annual G-FINDER survey, which encompasses global R&D funding on basic research, diagnostics, pharmaceuticals, and preventive and therapeutic vaccines for 31 neglected diseases.77 The Treatment Action Group (TAG) is an independent AIDS research and policy think tank, that conducts an annual funding survey for TB research, similar to the G-finder. The TAG 2012 Report on Tuberculosis Research Funding Trends 78 and G-finder report different numbers due to differences in methodology.

G-finder estimated that tuberculosis received US$ 525.8 million (adjusted for inflation and reported in 2007 US$) in R&D funding in 2011. This was a minor decrease from 2010 when total funding was estimated at US$ 575.4 million. This is probably due to uneven grant disbursement and completion of several large multi-year grants. This funding estimation does not include funding from multi-disease organizations (e.g. the WHO/TDR, EDCTP and FIND), leading to a slight underestimation of annual funds.79 The EDCTP has funded several TB projects during 2004-2010 for a total amount of €19 178 113.80 The funding received by multi-disease organizations for TB R&D in 2010 was estimated at US$ 14.2 million. This would increase the total funding annual funding to US$ 589.5 million in 2010.81 An overview of the 2007-2011 TB R&D total funding amounts, excluding multi-disease organizations, is depicted in Figure 6.8.4.

The top 12 funders of TB R&D in 2011 were:
1. United States NIH
2. Pharmaceutical industry (multinational pharmaceutical companies and SMEs combined)
3. Bill & Melinda Gates Foundation
4. European Commission
5. United Kingdom Medical Research Council (MRC)
6. United Kingdom Department for International Development (DFID)
7. United States Centers for Disease Control and Prevention
8. Wellcome Trust
9. United States Agency for International Development
10. Dutch Ministry of Foreign Affairs - Directorate General of Development Cooperation
11. Institut Pasteur
12. Statens Serum Institute (SSI)79
Update on 2004 Background Paper, BP 6.8 Tuberculosis

Figure 6.8.4: Annual global tuberculosis R&D funds in million US$ for 2007-2011.

Together, the top 12 accounted for 90.9% of total TB R&D funding in 2011. The majority of 2011 funding was supplied by the pharmaceutical industry, the US NIH and the Bill & Melinda Gates Foundation, who together accounted for 74.1% of global TB R&D funding. In 2011, the EC funded US$ 23 561 224* for TB R&D, this equals 4.7% of funding globally making them the fourth largest funder. Funding decreases from 2010 to 2011 came from all organizations in the top 12, except the Dutch Ministry of Foreign Affairs (increased from US$ 2 828 608* in 2010 to US$ 3 108 734* in 2011) and the United Kingdom MRC (from US$ 15 108 715* in 2010 to US$15 701 044* in 2011). The funding decrease from the Bill and Melinda Gates Foundation was mainly due to completion of large multi-year grants. Funding decrease from the DFID was due to uneven disbursement across the funding cycle. The EC cut back funding with 20.8% compared to 2010.79

The largest contributor to global TB R&D is the public sector with 51.6% of global funding in 2011. Industry and the philanthropic sector contributed 28.8% and 19.6% respectively of global R&D funding in 2011.79 An overview of the trends in global TB R&D funding by funder type is illustrated in

Figure 6.8.5. The investments done by the private sector have increased from 16.1% in 2007 to the current 28.8% in 2011. Funding by the public sector has decreased since 2007. These

* adjusted for inflation and reported in 2007 US$
changes have been driven by renewed interest from the large multinational pharmaceutical industry in TB pharmaceuticals, diagnostics, and vaccines.\textsuperscript{79}

In 2011, the majority of TB R&D funding went to pharmaceuticals (42.5%), followed by basic research (26.8%), vaccines (18.8%), and diagnostics (9.1%) research.\textsuperscript{79}

**Figure 6.8.5: Trends in global tuberculosis R&D funding by funder type.**

Source: Neglected Disease Research and Development: A five year review. (2012) Policy Cures G-finder.\textsuperscript{79}

### 3.1 Basic Research

In 2011, the global spending of TB R&D funds on basic research was US$ 140.8 million\textsuperscript{*} (adjusted for inflation and reported in 2007 US$).\textsuperscript{79} Approximately 24.6% of the 2010 budget directed to basic research was disbursed by Europe based funders (including the EC) and the EC contributed to 7.4% of these global funds in 2010.\textsuperscript{82} The Global Plan to Stop TB 2011-2015 estimates an annual total funding need of US$ 400 million, with a five-year total funding need of US$ 2.1 billion to reach their objectives.\textsuperscript{8} With the current global funds for basic research this goal will not be met.

### 3.2 Pharmaceuticals

The global funds available for TB pharmaceuticals research reached a total of US$ 223.7 million\textsuperscript{*} in 2011.\textsuperscript{79} Europe based funders (including EC) contributed to 11.0% of available funds in 2010. The EC donated a mere 1.8% of these global funds.\textsuperscript{82} The Stop TB Partnership estimates that the 2011-2015 Global Plan requires a total of US$ 3.7 billion for research into new pharmaceuticals and new regimens. The annual funding needs increase from US$ 0.6

\textsuperscript{*} adjusted for inflation and reported in 2007 US$
Update on 2004 Background Paper, BP 6.8 Tuberculosis

billion in 2011 to US$ 0.8 billion in 2015. Of the four research areas described in this background paper, pharmaceuticals require the largest amount of funding, but this area is closest to reaching its funding goals.
Update on 2004 Background Paper, BP 6.8 Tuberculosis

The 2004 background paper elaborated on the United States Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF). In 2010, the TAACF programme ended.83

3.3 Diagnostics

Approximately US$ 47.9 million was available for diagnostics research in 2011.79 The EC contributed 3.9% and the Europe based organizations (including EC) donated 15.1% of the global funds available for diagnostics in 2010.82 Estimations from the Global Plan indicate that the five-year funding need is US$ 1.7 billion, with annual needs increasing from US$ 300 million in 2011 to US$ 364 million in 2015.8 The field of diagnostics research is furthest away from reaching its funding goals. Increased funding is required to boost the search for new diagnostics and biomarker candidates.

3.4 Vaccines

In 2011, the global expenditure of TB R&D funds on vaccines (both preventive and therapeutic) was US$ 99.8 million.79 Approximately 31.0% of the 2010 budget was provided by Europe based funders (including the EC) and the EC contributed 4.1% of these global funds in 2010.82 The development of vaccines is a lengthy and costly process and will require approximately US$ 1.9 billion from 2011-2015. The annual funding requirements increase from US$ 250 million in 2011 to roughly US$ 440 million in 2015.8

An overview of the 2010 global TB R&D funding for basic research, pharmaceuticals, diagnostics and vaccines versus the Global Plan to Stop TB 2011-2015 funding requirements is shown in Figure 6.8.6.

Figure 6.8.6: The Annual Global Plan to Stop TB 2011-2015 funding targets versus the actual TB R&D 2010 investments.

Source: Created using G-finder 2011 report and the Global Plan to Stop TB 2011-2015 report.8,84

* adjusted for inflation and reported in 2007 US$
4. **Research gaps**

As stated before the current TB tools are not sufficient to eradicate tuberculosis. There is a need for quick and reliable point-of-care diagnostics; effective, safe and shorter TB treatments including for those living with HIV; new pharmaceuticals that are effective against drug-resistant TB; and reliable vaccines suitable for all populations.

The Stop TB Partnership created the Global Plan to Stop TB 2011-2015, which includes a chapter on research and development with a roadmap for meeting the 2015 research goals. Building on this Global Plan, the Stop TB Partnership and WHO’s Stop TB department created a roadmap (*An International Roadmap for Tuberculosis Research*) with detailed objectives and prioritized research questions.

4.1 **Basic Research**

Research aimed at increasing knowledge of *M. tuberculosis* can lead to new discoveries and ultimately results in the development of new, improved TB tools. The Stop TB partnership has defined three major objectives for basic research in the next five years.

The first objective is to better characterize TB in humans through modern biomedical, clinical, and epidemiological approaches. Infection with *M. tuberculosis* is chronic and not every infected person develops active disease in the same manner. The highest priority is to further investigate the steps (both bacterial and human) that mark and predict the different stages of TB. It is feasible that this research priority can be clarified in 6-10 years’ time.

Although the pathogen that causes TB was discovered in the 19th century, it is not yet known where the bacteria are located in the body, how the host and pathogen interact, and how the genetic make-up of *M. tuberculosis* influences the course and outcome of disease. There is evidence that different subsets of *M. tuberculosis* exist and that these subsets respond to treatment differently. Thus the second objective of the Stop TB Partnership is to clarify the key molecular features of both host and pathogen, their interaction and how these features influence disease and treatment outcomes. This objective contains several high priority research questions:

- How does *M. tuberculosis* interact with the immune system during the various phases of progression from infection to disease?
- What components of the immune system and what components of the pathogen are responsible for elimination of *M. tuberculosis* or for preventing reactivation of latent TB infection?
- Can an immune response to the pathogen or a vaccine prevent infection?
- Why and how, in some individuals, does *M. tuberculosis* subvert the immune response, to induce a chronic inflammatory state with ineffective elimination of bacteria?
- Is persistence a natural occurrence in TB, or does it reflect the inability of current regimens to reach the persisting bacteria?

These research questions will take approximately 6-10 years’ time to answer. For those questions that require a thorough investigation of the human host, the Stop TB Partnership
estimates that it is moderately feasible that answers will be available within the set timeframe.\textsuperscript{16}

The answers to the aforementioned objectives will give rise to the development of novel biomarkers that may be useful in the development of new diagnostics, treatments and vaccines. The third objective is to identify those biomarkers that will distinguish the various stages of TB infection, allow accurate identification of patients and predict which patients are likely to develop active TB from LTBI.\textsuperscript{8} \textsuperscript{16} The Stop TB Partnership finds it feasible that this objective can be realized in 6-10 years' time.\textsuperscript{16}

\subsection*{4.2 Pharmaceuticals}

As stated before, there is a need for shorter regimens that are safe, well tolerated, effective against drug-resistant TB, suitable for children and compatible with ARVs. There are still many challenges to overcome in order to produce a better TB treatment.\textsuperscript{85} Keeping the pharmaceutical pipeline filled is essential for further advances in better TB treatments.

Data from basic research can be used to develop new targets and novel pharmaceuticals with new mechanisms of action. Understanding of mechanisms of action of current medicines and of how \textit{M. tuberculosis} acquires resistance against these medicines would add important knowledge. It is feasible that basic research will lead to better understanding within five years. Optimization of cell- and target-based compound screening by developing better models for TB will very likely deliver results in 6-10 years' time.\textsuperscript{16} \textsuperscript{86}

The highest priorities in TB novel pharmaceutical and regimen development are:

- Early clinical investigation of treatment regimens containing novel and redirected medicines. Shorter and more effective treatments against drug-sensitive and drug-resistant active TB and shorter treatments for drug-sensitive and drug-resistant LTBI are necessary;
  - Testing these regimens in HIV-positive patients and children of all ages;
  - Develop FDC of these new regimens;
  - Develop suitable paediatric formulations;
- Further shorten the treatment of both drug-sensitive and drug-resistant LTBI;
- Investigate the optimal timing of initiation of ARVs in TB-HIV co-infected people;
- Studying interactions between novel TB pharmaceuticals and ARVs;
- Determine which biomarkers or combination of biomarkers would allow for early evaluation of efficacy of novel pharmaceuticals and regimens, so as to shorten clinical trial duration.\textsuperscript{16}

The Stop TB Partnership estimated that these goals are feasible. The study of drug-drug interactions can be done relatively quickly and should generate results in under five years. However the development of new regimens and pharmaceuticals will require at least 6-10 years of investments.\textsuperscript{16}

Several challenges exist for the development of these novel regimens. First, novel pharmaceutical candidates will need to be available for testing in regimens.\textsuperscript{87} Pharmaceutical companies are not always eager to cooperate and to make their compound available for clinical trials. Secondly, the companies with ownership of each medicine or pharmaceutical candidate will need to collaborate. Thirdly, the regulatory agencies can assist by developing
clear guidelines as to how to develop novel regimens that contain new chemical compounds.\textsuperscript{87}

Another research opportunity is to reengineer new chemical entities from compounds with known anti-TB activity. Reengineering may lead to improved activity, better safety, and tolerability or superior pharmacokinetic profiles. Although improvement of existing pharmaceuticals is a good strategy to fill the development pipeline, the increasing resistance to several existing medicines can limit the use in MDR- and XDR-TB.\textsuperscript{88}

When a draft of this background paper was sent out for review one reviewer stated that from an industry perspective the key research issues are:

- A lack of diversity in both targets and chemical starting points;
- Need for new \textit{in vitro} tools to assess which combinations of drugs are more appropriate;
- New imaging tools for \textit{in vivo} studies to accelerate Drug Discovery and minimize the use of animals;
- Faster trials and more predicted of cure than current Early Bactericidal Activity studies.\textsuperscript{89}

### 4.3 Diagnostics

The goal of research in the field of diagnostics is to increase detection of TB at the point-of-care or in resource-poor settings; detect LTBI; predict disease progression; identify those cases with drug-resistant TB; and develop tools suitable for use in the HIV-positive and paediatric population.

Four research objectives have been identified by the Stop TB Partnership. The first objective is to evaluate biomarkers identified in basic research. These biomarkers need incorporation in reliable, simple to use, and affordable platforms. These biomarkers would ideally differentiate between active disease, LTBI, and those not affected with the disease. It is feasible that this objective can be reached in the next 6-10 years.\textsuperscript{16}

The second objective is to develop novel tools for rapid diagnosis of drug-sensitive and drug-resistant active TB and LTBI that can be used in high-burden settings, including point-of-care facilities with limited resources. These diagnostics would ideally not only use sputum, but other samples that are easier to collect such as urine, blood, or breath. It is feasible that such novel tools will become available in the next 6-10 years.\textsuperscript{16}

A quicker solution to the current TB diagnostics problem is to improve existing diagnostic tests for use at various health-care levels in diverse patient groups in high-burden settings. The existing tools may be more efficiently combined to shorten the time required for diagnosis. It is very feasible that newer algorithms and test combinations will be developed within the next five years.\textsuperscript{16}

The development and endorsement of novel diagnostic tools does not automatically ensure implementation. The Xpert MTB/RIF is revolutionizing the field of TB diagnosis and research into operational aspects of the roll-out of this test could provide valuable information regarding barriers to implementation in high-burden settings. The study of cost-effectiveness and impact on TB epidemiology and patient-outcomes can show how truly useful a tool is in
resource-poor and high-burden situations. Translation of these findings into policy and practice guidelines could ensure adaptation of implementation of novel tools. These questions regarding TB diagnostics are very likely to be answered within the coming five years.\textsuperscript{16}

The retrieval of adequate sputum samples can be challenging, in particular in paediatric and HIV-associated TB. A number of alternative ways to obtain a sputum sample have been developed (e.g. nebulizer systems, nasopharyngeal aspiration, lung flute and string test), but these methods have practical limitations and as such have not been widely adopted. Identification of TB in samples from blood, urine, biopsies, aspirates, gastric lavage fluids, or effusions could offer welcome alternatives for the use of sputum.\textsuperscript{90}

4.4 Vaccines

To reach the 2050 TB elimination target, the introduction of new and effective TB vaccines is crucial. Several questions need to be answered before vaccines safe and effective in all age groups and for use in HIV-infected and other immunosuppressed patients can be developed.

Basic research should be aimed at discovering the components of the human immune system that are crucial to the control and elimination of \textit{M. tuberculosis}, including research in different populations (HIV-positive and –negative, age groups). Research directed towards discovering new \textit{M. tuberculosis} antigens can give way to novel vaccines or novel vaccine additives to boost BCG efficacy. Another essential goal is to better understand how the current BCG vaccine triggers and maintains an immune response. Answering these questions are feasible, but will require 6-10 more years of research and investments.\textsuperscript{16}

There is currently no robust animal model for evaluation of TB vaccine efficacy. As a result different regulatory authorities require different preclinical tests. Due to the wide range of preclinical approaches reported in literature, comparison of TB vaccine candidates is challenging. New affordable, standardized animal models of TB infection and disease, and new tests that can predict whether a vaccine candidate is likely to be effective in humans are needed. Developing or improving preclinical (animal) models is feasible within the next 6-10 years. The development of preclinical tests is considered very feasible and could be completed within five years’ time.\textsuperscript{16}

There are currently no reliable biomarkers of vaccination-induced protection against TB. As a result clinical trials are lengthy and, thus, expensive. Validation of biomarkers should take place in phase II or III trials of new vaccines that have proven to be effective. This will, in the long-term, reduce clinical trial length of novel vaccine candidates. The Stop TB Partnership estimates that validation of biomarkers is moderately feasible and can take up to ten years.\textsuperscript{16}

Clinical trials of TB Vaccines are generally conducted in countries with high TB incidence rates, many of which are LMICs. In these countries there is often a lack of knowledge of local TB incidence and baseline mortality and morbidity. A good understanding of the epidemiology of TB at trial sites is essential as a basis for trial design and sample size calculations.\textsuperscript{15} With the current TB vaccine pipeline and the large sample sizes that are required, the available clinical trial sites are inadequate. The work of organizations such as the EDCTP, NIH, TBVI and Aeras and collaboration of vaccine developers can ensure optimal use of existing trial sites for testing of multiple vaccine candidates, but there is the
question of how many vaccine candidates can be reasonably tested in a single location.\textsuperscript{15} Thus epidemiological studies to assess TB incidence rates are crucial for the development of more suitable clinical trial sites. This goal is moderately feasible and will require global collaboration.\textsuperscript{15, 16} As mentioned on page 19 of this background chapter the EDCTP-II will most likely invest in clinical trial capacity building for TB vaccine development, as well as capacity building for the development of TB diagnostic tools and TB treatments.

As stated before, current animal models are limited and may not reflect human disease accurately. Regulatory authorities require different preclinical tests and standardization could make comparisons between researches easier. Harmonization of regulatory requirements is very achievable within the next five years. This issue is discussed further in chapter 8 of this report. Development of novel animal models of TB infection and disease will require more effort and time.\textsuperscript{16}

A high priority is the development of improved vaccines for prime-boost vaccination strategies. This includes improvement of the current prime (BCG) vaccine through optimization of adjuvants. A second issue is the determination of optimal vaccination strategies (e.g. number of boosts, duration of intervals, and boosting dose). The estimated timeframe to answer these questions is 6-10 years.\textsuperscript{16}

5. Conclusion

Tuberculosis remains a global threat. While there has been a decline in the number of cases due to intensive control efforts and economic development, new forms of TB have emerged. These drug-resistant forms of TB have proven progressively more difficult to treat. Considerable progress has occurred since 2004 in the development of new treatments, diagnostics, and vaccines often with EC support. However, TB is a long-term disease and long-term support for research will be needed in all areas. Continued and increased support from the EC is required to ensure that TB does not pose a threat to the people of Europe and to reduce the present disease burden that TB causes in the LMICs. Support granted by the EC needs to be a long-term commitment to ensure that the progress made gets seen through.

References


Update on 2004 Background Paper, BP 6.8 Tuberculosis


23 National Institute of Allergy and Infectious Diseases, Tuberculosis basic research. Available from: http://www.niaid.nih.gov/topics/tuberculosis/research/basicresearch/Pages/default.aspx (accessed 18-09-2012)


Update on 2004 Background Paper, BP 6.8 Tuberculosis

36 National Institute of Allergy and Infectious Diseases, Tuberculosis research into treatment. Available from: http://www.niaid.nih.gov/topics/tuberculosis/research/treatment/Pages/default.aspx (accessed on 18-09-2012)


41 Treatment Action Group (TAG) and HIV i-Base. 2012 PIPELINE REPORT HIV, Hepatitis C Virus (HCV), and Tuberculosis (TB) Drugs, Diagnostics, Vaccines, and Preventive Technologies in Development. Available from: http://www.treatmentactiongroup.org/pipeline-report/2012


45 MRC Clinical Trials Unit, Study details STREAM trial. Available from: http://www.ctu.mrc.ac.uk/research_areas/study_details.aspx?s=117 (accessed on 14-09-2012)


Ottenhoff THM, Kaufmann SHE. Vaccines against Tuberculosis: Where Are We and Where Do We Need to Go? PLoS Pathogens, 2012, 8 (5): e1002607


Aeras. Available from: www.aeras.org (accessed on 03-10-2012)

Update on 2004 Background Paper, BP 6.8 Tuberculosis


81 Personal communication with Policy Cures.

82 Policy Cures, G-finder database. Available from: http://g-finder.policycures.org/gfinder_report/search.jsp Survey data on tuberculosis collected for the year 2010 were accessed on 10-10-2012 and analysed using Microsoft Xcel 2010 by the author of this background document.


89 Personal communication.

Table 6.8.1: Overview of the current pipeline for TB pharmaceuticals.

<table>
<thead>
<tr>
<th>Lead Identification</th>
<th>Lead optimization</th>
<th>Preclinical Development</th>
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<th>Phase III</th>
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<td>BTZ043</td>
<td>AZDS847</td>
<td>Delamanid</td>
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<td>Novel Hit to Lead Program (Lilly)</td>
<td>THPP series</td>
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<td>PA-824</td>
<td>Bedaquiline</td>
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<td>Gyrases B Inhibitors</td>
<td>Pyrazinamide analogs</td>
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<td>SQ-109</td>
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<td>Folate Biosynthesis Inhibitors</td>
<td>Diaminoquinolines</td>
<td>DC-159a</td>
<td>Sutezolid</td>
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<td>RNA Polymerase Inhibitors</td>
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<td>Energy Metabolism Inhibitors</td>
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<td>Oral M. vaccae (V7)</td>
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<td>ATP Synthesis Inhibitors</td>
<td>MGyrX1 Inhibitors</td>
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<td>DNA Metabolism</td>
<td>Ruthenium(II)phospine/picolinate Complexes</td>
<td>Rifalazil</td>
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<td>Topoisomerase I Inhibitors</td>
<td>Spectinomides</td>
<td>TGFβ inhibitor + COX-2 inhibitor</td>
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<tr>
<td>Fungal Metabolites</td>
<td>Translocase-1 Inhibitors</td>
<td>IL-4 inhibitor</td>
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<td>Indigoids</td>
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<td>Malate Synthase Inhibitors</td>
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<td>Menaquinone Synthase Inhibitors</td>
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<td>Protein Splicing Inhibitors</td>
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Only new chemical entities are shown. This overview was created using the TB Alliance and WGND databases. The United States Clinical Trial Register ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) was searched to obtain extra information on on-going clinical trials to judge in which phase of human research the depicted pharmaceuticals currently are. 24, 25, 26
Annexes

Annex 6.8.1A  TB Burden in the EU/EEA Region in 2010
Annex 6.8.1B  MDR-TB Burden in the EU/EEA Region in 2010
Annex 6.8.2  PreDiCT-TB Partners
Annex 6.8.3  EC Sixth and Seventh Framework Programmes focused on TB
Annex 6.8.4  Redirected Pharmaceuticals and Novel Regimens for TB
Annex 6.8.5  EDCTP Funded TB Projects
Annex 6.8.6  CPTR Initiative Founders and Partners
Annex 6.8.7  TB Drug Accelerator Participants
Annex 6.8.8  Tuberculosis Diagnostics currently in Use and under Development
Annex 6.8.9  Global TB Vaccine Pipeline
Annex 6.8.1A  TB Burden in the EU/EEA Region in 2010


Case notification rates and mortality rates are reported as cases/deaths per 100,000 population.
Annex 6.8.1B  MDR-TB burden in the EU/EEA in 2010

(data from European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2012. Graph prepared by LA Rook, September 2012)

MDR-TB burden is represented as the percentage drug resistant TB of all TB cases.

[Graph showing the percentage drug-resistant TB of all TB cases for various countries in the EU/EEA in 2010]

Source: WHO Tuberculosis country data 2010.

Annex 6.8.2 PreDiCT-TB Partners


European Federation of Pharmaceutical Industries and Associations

GlaxoSmithKline Investigación y Desarrollo SL, Spain
Sanofi-Aventis Research & Development, France
Janssen Infectious Diseases – Diagnostics BVBA, Belgium

Universities, research organizations, public bodies, non-profit groups

University of Liverpool, United Kingdom
École Polytechnique Fédérale de Lausanne, Switzerland
Erasmus University Medical Centre Rotterdam, the Netherlands
Health Protection Agency, United Kingdom
Institut Pasteur, France
Liverpool School of Tropical Medicine, United Kingdom
Max Planck Gesellschaft zur Förderung der Wissenschaften E.V., Germany
St George’s University of London, United Kingdom
Universidad Carlos III de Madrid, Spain
University College London, United Kingdom
University of Leicester, United Kingdom
University of St Andrews, United Kingdom
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Uppsala universitet, Sweden

Patients' organisations
Vrije Universiteit Medisch Centrum, the Netherlands

SMEs
Microsens Medtech Ltd, United Kingdom
ZF-Screens BV, the Netherlands
Annex 6.8.3 EC Sixth and Seventh Framework Programmes focused on TB

(List prepared by Laurien Rook. Searched on cordis.europa.eu for “tuberculosis” under the FP6 and FP7 programme. Search was conducted on 18-09-2012.)

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<td>TBIRIS</td>
<td>Pathogenesis and identification of predictive factors of TB-IRIS in HIV patients under HAART.</td>
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<td>NEOTIM</td>
<td>Innate and adaptive immunity in clinical and experimental mycobacterial infection in neonates and infants</td>
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<td>TB-MACS</td>
<td>Identification and characterization of <em>Mycobacterium tuberculosis</em> virulence genes involved in macrophage parasitism</td>
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<td>CSI-LTB</td>
<td>The role of chromosome stability in persistence, latency and reactivation of <em>Mycobacterium tuberculosis</em></td>
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<td>MYCOMANCY</td>
<td>Transcriptional regulation and cellular localization of mycobacterial cell cycle proteins during dormancy</td>
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<td>TB TREATMENT MARKER</td>
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<td>The diversity of <em>Mycobacterium tuberculosis</em> strains in China: tracing the origins of the worldwide dispersion of the multidrug-resistant Beijing genotype</td>
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<td>Outer membrane protein complexes of <em>Mycobacteria</em></td>
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<td>Drug mechanism and protein function in live <em>Mycobacteria</em></td>
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<td>GLYCOMIGS</td>
<td>Sugar Mimetics: Multicomponent Inhibitors of Glycosyltransferases</td>
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<td>Genomic screens to identify and characterize mechanisms of mycobacterial killing by macrophages</td>
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<td>New medicines for tuberculosis</td>
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<td>NEWTBDRUGS</td>
<td>New drugs for persistent tuberculosis: Exploitation of 3-D structure of novel targets, lead optimisation and functional in-vivo evaluation</td>
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<td>SCRIN-SILICO</td>
<td>Finding promising drug candidates against tuberculosis with multidisciplinary protocol based non-conventional search.</td>
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<td>TB-DRUG</td>
<td>A SME-STREP for tuberculosis drug development</td>
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<td>02-SENSITIVE TARGETS</td>
<td>Oxygen-sensitive enzymes of the mevalonate-independent isoprenoid biosynthesis pathway as targets for new antimalarial and anti-TB drugs</td>
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<td>NOTB</td>
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<td>TB REACT</td>
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<td><strong>Diagnostics</strong></td>
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<td>Development of a molecular platform for the simultaneous detection of <em>Mycobacterium tuberculosis</em> resistance to rifampicin and fluoroquinolones</td>
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<td>SERO-TB</td>
<td>Development of a specific serological kit for the diagnosis of TB</td>
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<td>OPTOLABCARD</td>
<td>Mass Produced Optical Diagnostic Labcards Based on Micro and Nano SU8 Layers</td>
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<td>FASTEST-TB</td>
<td>Development and clinical evaluation of fast tests for tuberculosis diagnosis</td>
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### Vaccines

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<td>Host and microbial molecular dissection of pathogenesis and immunity in tuberculosis</td>
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<td>Proprotein convertase furin as a regulator of immune responses</td>
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<td>Application of Lithiated Carbamates to the Asymmetric Synthesis of Sulfolipid-I</td>
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<table>
<thead>
<tr>
<th>Project Code</th>
<th>Description</th>
<th>Grant Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORCHID</td>
<td>Open Collaborative Model for Tuberculosis Lead Optimisation</td>
<td>261378</td>
</tr>
<tr>
<td>NATT</td>
<td>New approaches to target tuberculosis</td>
<td>222965</td>
</tr>
<tr>
<td>CHEMBIO4TB</td>
<td>Chemical Biology for Tuberculosis Research</td>
<td>255152</td>
</tr>
<tr>
<td>GLYCOTUP</td>
<td>Novel chemical probes for tuberculosis diagnosis and treatment</td>
<td>221149</td>
</tr>
<tr>
<td>DPRETB</td>
<td>Exploring decaprenyl-phosphoryl ribose epimerase (DprE1) as a validated target for TB drug discovery: Assay development, high-throughput screening and search for novel DprE1 inhibitor scaffolds</td>
<td>252802</td>
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<tr>
<td><strong>Diagnostics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TM-REST</td>
<td>A new platform for fast molecular detection of MDR and XDR resistant strains of <em>M. tuberculosis</em> and of drug resistant malaria</td>
<td>202145</td>
</tr>
<tr>
<td>FAST-XDR-DETECT</td>
<td>Development of a two-approach plate system for the fast and simultaneous detection of MDR and XDR <em>M. tuberculosis</em></td>
<td>201690</td>
</tr>
<tr>
<td>STOPLATENT-TB</td>
<td>Latent tuberculosis: new tools for the detection and clearance of dormant <em>Mycobacterium tuberculosis</em></td>
<td>200999</td>
</tr>
<tr>
<td>AU-NANOPROBES FOR TB</td>
<td>Disposable Point-of-Care DNA kit for <em>Mycobacterium tuberculosis</em></td>
<td>247439</td>
</tr>
<tr>
<td><strong>Vaccines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INYVAX</td>
<td>Optimisation of the development of Poverty-Related-Diseases (PRD) vaccines by a transversal approach, addressing common gaps and challenges</td>
<td>223532</td>
</tr>
<tr>
<td>ESI-TBVI</td>
<td>Establishment, strategy and initial activities of the tuberculosis vaccine initiative: coordination of European efforts with global research initiatives</td>
<td>223064</td>
</tr>
<tr>
<td>NEWTBVAC</td>
<td>Discovery and preclinical development of new generation tuberculosis vaccines</td>
<td>241745</td>
</tr>
<tr>
<td>TRANSVAC</td>
<td>European network of vaccine development and research</td>
<td>228403</td>
</tr>
<tr>
<td>TILIM</td>
<td>The T cell immune response against latent infection with <em>Mycobacterium tuberculosis</em></td>
<td>253706</td>
</tr>
<tr>
<td>ADJUTUB</td>
<td>Rational design of a lipopolysaccharide adjuvant for tuberculosis vaccines</td>
<td>252934</td>
</tr>
</tbody>
</table>
Annex 6.8.4 Redirected Pharmaceuticals and Novel Regimens for TB

The United States Clinical Trial Register (clinicaltrials.gov) was searched for trials that contained the term ‘tuberculosis’. This search strategy produced 599 trials. Trials were globally screened on relevance. All trials on extrapulmonary TB, vaccines, diagnostics, biomarkers, dietary supplements, drug-drug interactions, adverse drug reactions, epidemiology, behavioral interventions and operational management were excluded. Those studies that remained were more closely studied and judged on relevance. The tables below contain studies investigating redirected pharmaceuticals (table 1) and novel regimens in development (table 2).

Table 1: Redirected pharmaceuticals

<table>
<thead>
<tr>
<th>Phase</th>
<th>Pharmaceutical</th>
<th>Indication/population</th>
<th>Sponsors</th>
<th>Status (Estimated completion date)</th>
<th>Clinical trial ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Levofloxacin</td>
<td>MDR-TB</td>
<td>SanofiAventis</td>
<td>Completed</td>
<td>NCT00495339</td>
</tr>
<tr>
<td>3</td>
<td>Gatifloxacin</td>
<td>Active TB</td>
<td>Institut de Recherche pour le Developpement</td>
<td>Unknown</td>
<td>NCT00216385</td>
</tr>
<tr>
<td>3</td>
<td>Moxifloxacin</td>
<td>Active TB</td>
<td>TB Alliance</td>
<td>Ongoing (June 2013)</td>
<td>NCT00864383</td>
</tr>
<tr>
<td>3</td>
<td>Levofloxacin</td>
<td>MDR-TB</td>
<td>Seoul National University Hospital</td>
<td>Completed</td>
<td>NCT01055145</td>
</tr>
<tr>
<td>2</td>
<td>Moxifloxacin</td>
<td>Active TB</td>
<td>Johns Hopkins University</td>
<td>Ongoing (October 2012)</td>
<td>NCT00728507</td>
</tr>
<tr>
<td>2</td>
<td>Moxifloxacin</td>
<td>Active TB</td>
<td>CDC</td>
<td>Ongoing (October 2012)</td>
<td>NCT00728507</td>
</tr>
<tr>
<td>2</td>
<td>Moxifloxacin</td>
<td>Active TB</td>
<td>FDA</td>
<td>Unknown</td>
<td>NCT00082173</td>
</tr>
<tr>
<td>2</td>
<td>Moxifloxacin</td>
<td>Active TB</td>
<td>CDC</td>
<td>Completed</td>
<td>NCT00144417</td>
</tr>
<tr>
<td>2</td>
<td>Metronidazole</td>
<td>MDR-TB</td>
<td>NIAID</td>
<td>Completed</td>
<td>NCT00425113</td>
</tr>
<tr>
<td>2</td>
<td>Linezolid</td>
<td>MDR-TD</td>
<td>CDC</td>
<td>Completed</td>
<td>NCT00664313</td>
</tr>
<tr>
<td>2</td>
<td>Linezolid</td>
<td>XDR-TB</td>
<td>NIAID</td>
<td>Ongoing (January 2015)</td>
<td>NCT00727844</td>
</tr>
<tr>
<td>2</td>
<td>Prednisone</td>
<td>Active TB HIV+</td>
<td>Ottawa Hospital Research Institute</td>
<td>Completed</td>
<td>NCT00414414</td>
</tr>
<tr>
<td>2</td>
<td>Prednisone</td>
<td>Active TB HIV+</td>
<td>NIAID</td>
<td>Completed</td>
<td>NCT00057421</td>
</tr>
<tr>
<td>2</td>
<td>Pascolizumab</td>
<td>Active TB</td>
<td>National University Hospital Singapore</td>
<td>Ongoing (December 2013)</td>
<td>NCT01638520</td>
</tr>
<tr>
<td>1/2</td>
<td>Linezolid</td>
<td>MDR- and XDR-TB</td>
<td>CDC</td>
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<td>NCT00691392</td>
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<tr>
<td>1/2</td>
<td>Gatifloxacin</td>
<td>Active TB</td>
<td>NIAID</td>
<td>Completed</td>
<td>NCT00396084</td>
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</table>
## Table 2: Novel regimens

<table>
<thead>
<tr>
<th>Phase</th>
<th>Pharmaceuticals</th>
<th>Regimens</th>
<th>Indication/population</th>
<th>Sponsor</th>
<th>Status (Estimated completion date)</th>
<th>Clinical trial ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Rifampicin</td>
<td>three regimens for reintroducing TB treatment</td>
<td>Active TB TB-treatment induced liver damage</td>
<td>Institute of Liver and Biliary Sciences, India</td>
<td>Completed</td>
<td>NCT00405301</td>
</tr>
<tr>
<td>3</td>
<td>Isoniazide</td>
<td>four week combination versus nine month isoniazid</td>
<td>HIV+ LTBI</td>
<td>NIAID</td>
<td>Ongoing (September 2016)</td>
<td>NCT01404312</td>
</tr>
<tr>
<td>3</td>
<td>Pyrazinamide</td>
<td>three month combination versus nine month isoniazid</td>
<td>LTBI</td>
<td>CDC</td>
<td>Ongoing (December 2013)</td>
<td>NCT00023452</td>
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<tr>
<td>3</td>
<td>Rifapentine</td>
<td>four month Rifampicin versus nine month isoniazid</td>
<td>LTBI</td>
<td>McGill University</td>
<td>Ongoing (March 2016)</td>
<td>NCT00931736</td>
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<tr>
<td>3</td>
<td>Isoniazid</td>
<td>four months rifampicin versus nine months isoniazid</td>
<td>LTBI Children</td>
<td>McGill University</td>
<td>Ongoing (March 2016)</td>
<td>NCT00170209</td>
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<tr>
<td>3</td>
<td>Rifapentine</td>
<td>five different regimens two to three months</td>
<td>Active TB</td>
<td>Tuberculosis Research Centre, India</td>
<td>Ongoing (February 2015)</td>
<td>NCT01154959</td>
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<tr>
<td>3</td>
<td>Rifampicin</td>
<td>four different regimens</td>
<td>LTBI HIV+</td>
<td>NIAID</td>
<td>Completed</td>
<td>NCT00057122</td>
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<tr>
<td>3</td>
<td>Pyrazinamide</td>
<td>four months versus six months</td>
<td>Active TB</td>
<td>NIAID</td>
<td>Completed</td>
<td>NCT00130247</td>
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<tr>
<td>3</td>
<td>Ethambutol</td>
<td>Daily versus intermittent versus part daily treatment</td>
<td>Active TB HIV+</td>
<td>Tuberculosis Research Centre, India</td>
<td>Ongoing (June 2015)</td>
<td>NCT00933790</td>
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### Update on 2004 Background Paper, BP 6.8 Tuberculosis

<table>
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<tr>
<th>Study</th>
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<th>Details</th>
<th>Comparator</th>
<th>Phase</th>
<th>Sponsor</th>
<th>Status</th>
<th>NCT Number</th>
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<tr>
<td></td>
<td>Rifampicin</td>
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<tr>
<td></td>
<td>2/3</td>
<td>Isoniazid Kanamycin Levofloxacin Protonamide Cycloserine p-aminosalicylic acid</td>
<td>High dose versus low dose isoniazid</td>
<td>MDR-TB</td>
<td>GSVM Medical College</td>
<td>Completed</td>
<td>NCT00513396</td>
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<td>Omitting Isoniazid versus Substituting Isoniazid with Moxifloxacin</td>
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<td></td>
<td>AIDS Clinical Trials Group</td>
<td>Not yet recruiting (May 2013)</td>
<td>NCT01589497</td>
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<td>Low dose versus high dose pyrazinamide regimens</td>
<td>MDR-TB</td>
<td>TB Alliance</td>
<td>Ongoing (June 2013)</td>
<td>NCT01498419</td>
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<tr>
<td></td>
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<td>Five different regimens versus standard treatment</td>
<td>Active TB</td>
<td>TB Alliance</td>
<td>Completed</td>
<td>NCT01215851</td>
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<tr>
<td></td>
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<td>Six different regimens versus standard treatment</td>
<td>Active TB</td>
<td>TB Alliance</td>
<td>Ongoing (July 2013)</td>
<td>NCT01691534</td>
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<tr>
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<td>Three different regimens with high dose rifampicin</td>
<td>Active TB</td>
<td>Radboud University</td>
<td>Ongoing (January 2012)</td>
<td>NCT00760149</td>
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<tr>
<td></td>
<td></td>
<td>Three regimens containing rifapentine versus one rifampicin containing regimen</td>
<td>Active TB</td>
<td>CDC</td>
<td>Ongoing (December 2013)</td>
<td>NCT00694629</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Rifapentine versus rifampicin</td>
<td>Active TB</td>
<td>Johns Hopkins University</td>
<td>Ongoing (September 2013)</td>
<td>NCT00814671</td>
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</tbody>
</table>
### Update on 2004 Background Paper, BP 6.8 Tuberculosis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Regimens</th>
<th>Description</th>
<th>Study</th>
<th>Status</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid</strong>&lt;br&gt;<strong>Pyrazinamide</strong>&lt;br&gt;<strong>Ethambutol</strong></td>
<td>Four regimens with high dose rifampicin</td>
<td>Active TB</td>
<td>Radboud University</td>
<td>Ongoing (June 2012)</td>
<td>NCT01392911</td>
</tr>
<tr>
<td><strong>Rifampicin</strong>&lt;br&gt;<strong>Isoniazid</strong>&lt;br&gt;<strong>Ethambutol</strong>&lt;br&gt;<strong>Pyrazinamide</strong></td>
<td>Two regimens with high dose rifampicin</td>
<td>Active TB</td>
<td>Harvard University Faculty of Medicine</td>
<td>Not yet recruiting (November 2013)</td>
<td>NCT01408914</td>
</tr>
<tr>
<td>NS</td>
<td>One regimen</td>
<td>Active TB Isoniazid resistant or intolerance</td>
<td>CDC</td>
<td>Completed</td>
<td>NCT00023374</td>
</tr>
<tr>
<td>NS</td>
<td>Four different regimens</td>
<td>Active TB Chronic liver disease</td>
<td>Institute of Liver and Biliary Sciences, India</td>
<td>Ongoing (September 2014)</td>
<td>NCT01677871</td>
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</tbody>
</table>

Annex 6.8.5 EDCTP Funded TB Projects

(The European and Developing Countries Clinical Trials Partnership, Information on tuberculosis trials. Table prepared by LA Rook using the EDCTP database, available from: http://www.edctp.org/Project_Profiles.245.0.html?&no_cache=1, accessed on 18-09-2012)

The EDCTP database was searched for projects focused on TB diagnostics, TB vaccines and TB treatments. Projects mainly focused on capacity building, epidemiology and other diseases were deemed irrelevant to this background paper and were removed. The remaining EDCTP projects are listed in the table below.

<table>
<thead>
<tr>
<th>Year</th>
<th>Project title</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Evaluation of multiple novel and emerging technologies for TB diagnosis, in smear-negative and HIV-infected persons, in high burden countries</td>
<td>TB Diagnostics</td>
</tr>
<tr>
<td>2009</td>
<td>The risk of pulmonary tuberculosis associated with intestinal helminth infection among children at two tuberculosis vaccine trial sites in sub-Saharan Africa</td>
<td>TB vaccines</td>
</tr>
<tr>
<td>2009</td>
<td>The evaluation of Mycobacterium tuberculosis specific host cytokine signatures in whole blood culture supernatants as diagnostic biomarkers for active TB infection</td>
<td>TB Diagnostics</td>
</tr>
<tr>
<td>2009</td>
<td>Evaluation of new and emerging diagnostics for childhood tuberculosis in high burden countries</td>
<td>TB Diagnostics</td>
</tr>
<tr>
<td>2008</td>
<td>The effect of HIV co-infection on the immune response to Mycobacterium tuberculosis in the lung</td>
<td>TB vaccines</td>
</tr>
<tr>
<td>2007</td>
<td>A Multicentre Phase II Trial of a New TB Vaccine in African Infants</td>
<td>TB vaccines</td>
</tr>
<tr>
<td>2007</td>
<td>Human M. tuberculosis-specific lung innate and adaptive immune responses in a high-burden setting</td>
<td>TB Diagnostics</td>
</tr>
<tr>
<td>2007</td>
<td>The impact of rapid molecular diagnosis of tuberculosis on tuberculosis services and patient care - a cluster randomized trial</td>
<td>TB Diagnostics</td>
</tr>
<tr>
<td>2004</td>
<td>BCG-induced immune correlates of protection against TB disease</td>
<td>TB vaccines</td>
</tr>
<tr>
<td>2004</td>
<td>Shortening and simplifying the treatment of tuberculosis</td>
<td>TB treatment</td>
</tr>
</tbody>
</table>
Annex 6.8.6 CPTR Initiative Founders and Partners


Cofounders
TB Alliance: Global Alliance for TB Drug Development
The Bill & Melinda Gates Foundation
Critical Path Institute

Partners
Anacor
AstraZeneca
Bayer
Celgene
Cepheid
European & Developing Countries Clinical Trials Partnership (EDCTP)
GlaxoSmithKline
Johnson & Johnson
Novartis
Otsuka
Pfizer
Reagan-Udall Foundation for the FDA
Sanofi
Sequella
Treatment Action Group (TAG)
Vertex
Annex 6.8.7 TB Drug Accelerator Participants


Pharmaceutical companies
Abbott
AstraZeneca
Bayer
Eli Lilly
GlaxoSmithKline
Merck
Sanofi Aventis

Research institutes
Infectious Disease Research Institute
National Institute of Allergy and Infectious Diseases, part of the United States National Institutes of Health
Texas A&M University
Weill Cornell Medical College
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Annex 6.8.8 Tuberculosis Diagnostics currently in Use and under Development


UNITAID created an overview of TB diagnostics in the late stage of development. It is expected these tools will be reviewed by WHO STAG-TB soon.

<table>
<thead>
<tr>
<th>Pipeline Tools</th>
<th>Status</th>
<th>Test Location</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensititre*, improved second line DST</td>
<td>Under development/demonstration. Estimated WHO review, 2013.</td>
<td>Reference</td>
<td>Liquid culture: MTBC in addition to first and second line DST.</td>
</tr>
</tbody>
</table>
The overview below was created by UNITAID. Currently available diagnostic tools are marked with * and those under development are marked with §. Not all currently available diagnostics are endorsed by the WHO-STAG. Those diagnostic tools that have been endorsed by WHO-STAG are listed in the background chapter on tuberculosis.

<table>
<thead>
<tr>
<th>Diagnostic Platform</th>
<th>Manufacturer</th>
<th>Platform Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture-based</td>
<td>Beckton Dickson</td>
<td>Bactec960 MGIT*</td>
<td>Liquid culture system. Fully automated systems that use either fluorimetric or colorimetric detection of mycobacterial growth and can be used for the identification of MTBC and for DST for both first and second line drugs.</td>
</tr>
<tr>
<td></td>
<td>bioMérieux</td>
<td>BacT/ALERT*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trek Diagnostic Systems Inc.</td>
<td>Myco-ESP Culture System II*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hardy Diagnostics</td>
<td>CE-marked MODS kit*</td>
<td>A low cost microscopic observation drug-susceptibility assay that uses liquid culture and microscopy to predict MTBC and identify resistance to rifampicin and isoniazid</td>
</tr>
<tr>
<td>MTBC identification from culture</td>
<td>TAUNS Corporation</td>
<td>Capilia TB Neo Test*</td>
<td>Antigen detection-based lateral flow strip tests for MPB64 to provide a rapid confirmation of MTBC from mycobacterial cultures derived from either liquid or solid media.</td>
</tr>
<tr>
<td></td>
<td>Beckton Dickson</td>
<td>TBC ID*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gen Probe</td>
<td>Accuprobe*</td>
<td>A nucleic acid-based test that confirms the presence of MTBC from positive culture media (in addition see LPA assays below)</td>
</tr>
<tr>
<td>Phage-based</td>
<td>Biotec Laboratories</td>
<td>FASTPlaque-TB§, FASTPlaque-TB-MDR§, FASTPlaque-Response§</td>
<td>Currently not recommended for use by WHO. Mycobacteriophage-based assay (MBA) assays.</td>
</tr>
<tr>
<td>Smear microscopy</td>
<td>Carl Zeiss</td>
<td>Primo Star ILED™</td>
<td>LED microscopes for improved TB microscopy</td>
</tr>
<tr>
<td></td>
<td>Partec</td>
<td>CyScope™</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QBC Diagnostics</td>
<td>ParaLens™</td>
<td>LED conversion kits to provide fluorescence capability to conventional microscopes. Improved TB microscopy</td>
</tr>
<tr>
<td></td>
<td>Fraen Corporation</td>
<td>FluoLED™</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LW Scientific</td>
<td>Lumin™</td>
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</tbody>
</table>
## Update on 2004 Background Paper, BP 6.8 Tuberculosis

<table>
<thead>
<tr>
<th>Diagnostic Platform</th>
<th>Manufacturer</th>
<th>Platform Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR-based NAAT</td>
<td>Hoffmann-La Roche</td>
<td>Amplicor®</td>
<td>Polymerase chain reaction assay to detect MTBC</td>
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<tr>
<td></td>
<td>Cepheid</td>
<td>GeneXpert MTB/RIF®</td>
<td>A instrument that uses nested real time PCR to identify MTBC and common rifampicin resistance mutations</td>
</tr>
<tr>
<td></td>
<td>Innogenetics</td>
<td>Inno-LIPA RifTB®</td>
<td>Line probe assays that use PCR generated amplicons to detect MTBC and first-line drug resistance</td>
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<tr>
<td></td>
<td>Hain Lifescience</td>
<td>GenoType MTBDRplus®</td>
<td>Line probe assay that uses PCR generated amplicons to indicate MTBC and resistance to one first-line drug resistance and two second line drugs</td>
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<td>BD Probe Tec®</td>
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<td>Isothermal based NAAT</td>
<td>Eiken and FIND</td>
<td>Loopamp® Tuberculosis Complex Detection Reagent Kit®</td>
<td>A manually prepared Loop-mediated amplification assay designed to diagnose MTBC with a test kit that can be used in intermediate facilities or microscopy centres</td>
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<td>Epistem</td>
<td>Genedrive®</td>
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<td>GenProbe</td>
<td>AMTD®</td>
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<td>Ionian Technologies</td>
<td>NEAR®</td>
<td>Nicking enzyme amplification reaction assay to identify MTBC</td>
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<td>TwistDx</td>
<td>RPA®</td>
<td>Recombinase polymerase amplification assay to identify MTBC</td>
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<td>Ustar Biotechnologies</td>
<td>CPA®</td>
<td>Cross priming amplification assay to identify MTBC</td>
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<td>Immune response-based</td>
<td>Qiagen</td>
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<td>Not recommended for MTBC diagnosis. Interferon gamma release assays to identify active MTBC infection</td>
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<tr>
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<td>Oxford Immunotec</td>
<td>T-spot®</td>
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<td>Alternative antigen assays</td>
<td>Alere</td>
<td>Clearview® TB ELISA®</td>
<td>Not recommended for MTBC diagnosis. Laboratory based ELISA Antigen assay to detect MTBC from urine sample via LAM</td>
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<td>Determine® TB-LAM®</td>
<td>Not recommended for MTBC diagnosis. Health centre-based RDT to detect MTBC from urine sample via LAM</td>
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<tr>
<td>Volatile organic compounds</td>
<td>Menssana Research Inc.</td>
<td>No product name®</td>
<td>Not recommended for MTBC diagnosis. Determination of pulmonary TB from compounds exhaled in breath</td>
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Annex 6.8.9 Global TB Vaccine Pipeline

(Tuberculosis Vaccines in Clinical Development. Available at http://www.stoptb.org/wg/new_vaccines/assets/documents/Global%20TB%20Vaccine%20Pipeline_Aug%202012.ppt)

For further information, see Tuberculosis Vaccines Pipeline – 2011 (http://www.stoptb.org/wg/new_vaccines/assets/documents/TB%20Vaccine%20Pipeline_rAug%202012.pdf)

TB Vaccine Types
Viral-vectorized: MVA85A, AERAS-402, AdAg85A
Protein/adjuvant: M72, Hybrid-1, Hyvac 4, H56, ID93
rBCG: VPM 1002
Killed WC or Extract: Mw, RUTI

Source: Tuberculosis Vaccine Candidates – 2011
Background Paper 6.9
Neglected Tropical Diseases

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Neglected tropical diseases cause immense suffering and death, mostly in the poorest regions of the world, resulting in a substantial socio-economic burden. A huge medical need exists for appropriate treatments, vaccines and diagnostics for such diseases. There is a significant lack of translation from early stage scientific research into real products for patients and impossible barriers for some products and technologies to become affordable for the poor people most affected by these diseases. Access to the solutions that exist is also limited. The Research and Development (R&D) pipeline has been more populated in the last few years, than ever before, although movement to real products and thereafter control, elimination, or eradication is limited. Two reasons account for this neglect: (a) market failure and (b) a failure of public policy to correct this perverse logic of “no money – no cure”.

Redressing this imbalance requires public responsibility and commitment to the:

1. Development of a global needs-driven (as opposed to market-based) essential health R&D agenda for neglected tropical diseases, and;
2. Creation of appropriate mechanisms, incentives and monitors to allow the effective implementation of such an agenda towards sustainable, achievable solutions for these neglected tropical diseases.

Developing a needs-based R&D agenda for neglected diseases is an essential first step, but current practice in prioritising pharmaceutical research does not meet this goal. This paper explores various criteria to help identify and characterise neglect, which could guide priority setting in building an essential health R&D agenda for neglected tropical diseases. The first part of this paper addresses the needs of the agenda, the health tools available and what is currently being done in the area of neglected tropical disease R&D and programmatic interventions. A detailed and patient-focused needs analysis must be done for each disease, and matched to scientific, technological and programmatic opportunities, taking into account the specific circumstances of neglected poor patients.

The second section of this paper uses the examples of visceral leishmaniasis, Buruli ulcer and schistosomiasis with a needs-based approach to drafting an essential health research agenda. For each disease, we provide a concrete list of high-priority research projects to be initiated, with tangible results for patients. The examples also illustrate that much can already be achieved by supporting innovative and adaptive R&D to make better use of existing medicines (or compounds), diagnostics and technologies, even though radically new solutions remain critically needed if the situation is to improve in the longer term. In all cases, translational research to transform the results of basic research into useful applications is the key. We propose a “3T” approach to develop R&D projects, where a Therapeutic intervention (be it medicines, vaccines or diagnostics) is invented or adapted, there is appropriate Technology to make it useful and produce the intervention and that the intervention can be Transferred to the populations that need it, and complementary to existing programmatic interventions.

The third and final section of the paper suggests gaps that could make a difference to reducing the burden on the affected populations by accelerating the research and development of new solutions to these diseases. Opportunities to mobilise needs-driven
innovation for neglected diseases is also discussed. The EU, while supporting some excellent initiatives, can address the growing problem of neglected tropical diseases. By a careful and needs-based allocation of sustained funding, the EU can and must mobilise an appropriate response. There is a moral and ethical imperative to seriously address neglected diseases in developing countries. The EU-ACP (EU-African, Caribbean and Pacific Group of States) Joint Parliamentary Assembly resolution on poverty-related diseases and reproductive health in ACP states explicitly calls for European action for neglected diseases: “[The Assembly] Calls on the European Commission to include the most neglected diseases, such as sleeping sickness, Chagas disease and leishmaniasis, among its priorities and to ensure that effective, appropriate, easy-to-use medicines are developed and placed on the market in the developing countries at an affordable price”.

A follow up UN Assembly resolution addresses this point and has led to some efforts in reallocating EU support towards neglected tropical disease R&D (through the EU Framework Program and government support for product development partnerships (PDPs)). Not all diseases or even needs are addressed by these supported grantees, and as such there needs to be more mechanisms. Pharmaceutical industry-driven agendas for the development of new therapeutics (such as the Innovative Medicines Initiative, IMI) have not yet addressed R&D efforts for these diseases. With this background paper, we hope that the support will be increased substantially and sustained (in the Horizon 2020 program and beyond), and R&D priorities will be based on societal and health values and not be solely market driven. The medical and public health needs and achievability of solutions to cater to these needs should drive priorities.

In addition to appropriate (sustainable) funding, governments must establish incentives and obligations to encourage neglected disease research and development in both the public and private sectors. Collaborative efforts are necessary, as the sharing of complementary resources and knowledge and the building of an integrated platform for neglected tropical disease R&D is necessary to keep costs low and impact high. Such a programme could include in-kind contributions from the (local and multinational) pharmaceutical industry, preferential funding of translational research projects (by public-private partnerships, public-driven R&D, integrated academic platforms and PDPs), risk mitigation from drivers of product development, reducing regulatory costs and developing of alternative, needs-based models for the setting of research priorities.

Organizations active in this area should be encouraged to pool their resources and work together to increase the opportunities for successful results. These include epidemiological tools and data (including drug resistance and monitoring), products developed, operational research outcomes and recommendations for implementation strategies.

Recommendations to help achieve this are:

- **Mobilise and sustain adequate funding** for neglected diseases. To ensure minimal impact, committed funding of several hundreds of million euros over a number of years must be freed to support the execution of a needs-based priority R&D agenda for neglected diseases;

- **Encourage translatable research** using the “3T” approach (“Therapeutics, Technology and Transfer”) to transform the results of basic research into useful technologies for medical applications, adapted to the needs of neglected tropical disease patients and connected to existing programmes for neglected tropical diseases;
Establish adequate incentives for collaborative research, based on shared values including appropriate training, funding, and specific career incentives based on a reassessment of the way merit is evaluated in public research;

Mobilise the pharmaceutical/diagnostics industry by a mix of incentives and obligations to contribute to the development of needed medical interventions and commit to donate or provide sustained access to medical interventions, based on shared value;

Engage the innovators from emerging economies, biotechnology, along with pharmaceutical/diagnostic companies, SMEs, PDPs and academic institutions through shared (societal and economic) values;

Monitor the performance of PDPs, integrated academic platforms and pharmaceutical companies (including those in emerging economies) for public accountability for resources spent;

Expand the activities of PDPs and integrated academic platforms to include product development for medicines, vaccines, diagnostics, drug resistance platforms and control strategies for these diseases along with strengthening health systems of affected countries. Support integrated academic platforms, where product development and operational research is directly done by academic innovators for neglected diseases;

Strongly encourage the expansion of the activities of the European and Developing Countries Clinical Trial Partnership (EDCTP) to include several of the most neglected diseases as well as other phases of clinical development (phase I, phase IV), (and connect this to the efforts of the pharmaceutical industry-driven TransCelerate);

Create a centre for preclinical research to bridge the continual gap of developing medicines and vaccines into clinical candidates for neglected diseases. This is a pool of resources available for preclinical research which should complement the activities of the EDCTP;

Investigate the possibility for centralized technology platforms for adaptive R&D (adapting current and new medicines, vaccines and diagnostics to tropical countries, fixed dose combination, paediatric formulations, etc). This includes assessing medicines availability, stability, pricing dosing, using appropriate platforms and databases. (This should complement activities of existing organizations and should be a mandate for the recently established non-profit TransCelerate).
Introduction

Of 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis. Of the 756 new drugs approved between 2000 and 2011, 29% (3.8%) were indicated for malaria, TB and neglected tropical diseases, of these there were no new chemical entities for neglected tropical diseases, even though these diseases account for 10.5% of the global disease burden. Such diseases predominantly affect poor patients in populations that do not represent a market of sufficient interest for the pharmaceutical industry. For this reason, no medicines, vaccines, or diagnostics are being developed to specifically address the health needs of these neglected populations, even if these needs are huge. Millions of people, mostly in the poorer regions of the world, are suffering and dying from neglected tropical diseases. Over 200 million people are estimated to be at risk for visceral leishmaniasis, over 700 million at risk for schistosomiasis, and over 60 million people are at risk of developing sleeping sickness in Africa.

People at risk of contracting a neglected tropical disease mostly have a very limited access to health care, and the illness is often made worse by chronic malnutrition or co-morbidity, such as an accompanying HIV infection. These diseases have a profound negative impact on the economies of these countries and are responsible for enormous suffering. The most shocking aspect of this, however, is that with sufficient resources and coordination, a major part of this suffering could be eliminated. Building on the impressive advances in science and technology, simple but innovative solutions can be developed and delivered that will have a dramatic impact on the lives of many of these people.

The diseases often referred to as “neglected” are diseases that are (a) common in defined areas; (b) fatal or disabling; and (c) for which no suitable treatments exist. They affect poor populations that are large but have little or no purchasing power.

New medicines are needed to replace the cumbersome or toxic existing treatments for sleeping sickness and leishmaniasis. No specific treatments exist for dengue fever or rabies. Simple diagnostics are unavailable for acute dengue, Buruli ulcer or yaws. Methods to monitor disease prevalence and accurate data to contain infectious epidemics are limited. Drug resistance also continuously threatens to reduce the existing arsenal of medicines. The few solutions that are safe and effective in treating neglected tropical diseases are often not well adapted to conditions in the developing world—for example medicines that requiring cold-chain storage or difficult administration, or that require costly production methods—or diagnostics that are inaccurate, difficult to use or taking too long to give a useful result. Substantial advances in molecular biology, pathophysiology and genetics have been made, including the recent genome sequencing of organisms causing leishmaniasis and Buruli ulcer. However, the rate at which these results are being processed into new products directed at the needs of patients is far from optimal.

Most medicines development (innovative and adaptive) is driven by the pharmaceutical industry, which sets the R&D agendas. For many other diseases this leads to new products, for neglected diseases this is lacking. Interestingly, in the last 10 years, there has been significant commitment from the pharmaceutical industry through their Corporate Social Responsibility (CSR) programs to improve access to medicines through R&D, philanthropy,
drug donation programs, patent pooling, pricing and participating in capacity strengthening through collaborative programs. Dedicated centres for tropical disease R&D have been set up, and although largely catering to malaria, HIV/AIDS and tuberculosis (TB), these centres are aiming to be committed to the most neglected diseases.

Some 13 major pharmaceutical companies donate products at an estimated value of US$ 2 billion, which reach approx 800 million people each year. More than 710 million preventive chemotherapy treatments were delivered in 2010, and the costs can be as little as US$ 0.4-0.5 per person per year. Many of these neglected tropical diseases could have already been eliminated or eradicated with more global support. Public policies have largely contributed to this unethical discrepancy by focusing on the need for performance and competition in a knowledge-based market economy.

In the last 15 years product development partnerships (PDPs) have been set up for some of the neglected tropical diseases, along with several integrated academic platforms (academia-driven R&D consortia sharing know-how and expertise for several neglected tropical diseases). PDPs develop medicines for sleeping sickness, Chagas, visceral leishmaniasis and vaccines for schistosomiasis and some soil transmitted helminths. PDPs also exist for technology applicable to several neglected diseases, or those that perform adaptive research to use innovative technologies that can be used for general global health. Integrated academic platforms manage the control of diseases (like PCPs), and perform research on epidemiology and drug resistance, and product development for Buruli ulcer, schistosomiasis (among others). Public-private partnerships also fill the R&D pipeline, although these efforts rely on sporadic, not sustained funding. Individual companies and organizations are also involved in product development, although this is more seen in diseases where there may be a paying market (like dengue and leishmaniasis).

While the global commitment exists to eliminate/reduce the neglect, a targeted international response to reduce the numbers affected is urgently needed. Europe, as a global leader, must respond to the crisis and provide a solid vision for the future of humanity, as acknowledged in the preamble to the European Constitution. These are problems that seemingly may not directly impact EU citizens today, but globalisation, including global climate change, extensive international travel and population movement, and the changing political power equilibrium, may also globalise diseases that so far have remained in distant parts of the world.

A prerequisite for starting to address the research gap in neglected diseases is the need for an adequately funded, needs-driven and rational priority R&D agenda for these diseases towards achievable short and long-term goals. Appropriate mechanisms and incentives need to be established to allow the actual implementation of the priority-based essential R&D agenda. Encouraging commitments from both the private and public sectors were recently announced in the London Declaration for Neglected Disease, at which several organizations pledged their commitment to donate, perform essential neglected tropical disease R&D and fund projects.

The current commitment of the EU into developing a response to this global imbalance is better than when the first priority medicines report was published in 2004, but still limited. In recent years, with the financial crisis, the European investment and aid to global health seems to be decreasing. The total budget for research into neglected tropical diseases is
limited to around twenty million euros at most, woefully inadequate to address any aspect of
the problem. Since the last Priority Medicines Report in 2004, the European Commission
contributed 22% of government investments and 15% of total global investments. 76% of
which went to malaria, HIV/AIDS and TB, with most of the money going towards PDPs and
EDCTP (leaving several academic and SME innovators with minimal benefit). While this has
led to 43 new diagnostics, vaccines and medicines registered to tackle neglected diseases and
poverty related disease (including malaria, HIV/AIDS and TB) ²⁰, there could have been more
progress and products if investments and incentives were substantially higher. The
Innovative Medicines Initiative (IMI) which supports precompetitive collaborations, is
driven directly by research priorities of major pharmaceutical companies. The majority of
the programme supports diseases relevant to European public health, and out of 30 projects,
only two projects, accounting for 7.5% of the total IMI budget have poverty-related
relevance, and not at all in neglected tropical diseases. Neglected tropical diseases deserve
the attention of mechanisms like IMI. R&D in neglected tropical diseases could benefit the
pharmaceutical industry (and other stakeholders) through shared values. Reputational
benefits, opportunities for skilled personnel and knowledge sharing of emerging diseases
and markets, access to data relevant to developed-country diseases are only some obvious
benefits.

With the upcoming Horizon 2020 funding scheme, one hopes that there will be more
commitment for innovative and adaptive R&D priorities for neglected tropical diseases,
perhaps using the Framework Program for translatable research (including
epidemiology/resistance research), IMI for product development (through PDPs, SMEs,
integrated academic platforms, public-private partnerships and EDCTP), and a new
mechanism for operational research and capacity strengthening, with adequate monitoring
and milestone reporting.

1. Characterising a Disease as Neglected

The ideas developed in this section come from a thorough analysis of priority-setting in the
context of neglected diseases.

1.1 The neglected tropical diseases

The neglected tropical diseases are 17 diseases (19 if soil transmitted helminths are
considered as three separate diseases) affecting global communities.²¹ One hundred and
fourty-nine countries are endemic for these diseases, and billions of people are at risk of
contracting these diseases. They cause a huge health and socio-economic burden in the
world, mostly in developing countries. Please refer to Appendix 1 for the list and analyses on
the burden of these diseases.

The definition of neglect is due to economic reasons. Neglected tropical diseases affect a
large number of people who are unable to pay for access to health care (even if it is less than
a US dollar) and thus represent an uninteresting market for the development of new
medicines. Medicines that are effective and available for some of these diseases are being
donated by several pharmaceutical companies (see below) towards preventive
chemotherapy programs, but the amounts of medicines available and the capacity of programs to deliver these medicines is limited and has failed to eliminate or eradicate these diseases up to now. More resources is needed (including financial ones) to put these medicines to better use, along with resources to develop new medicines, diagnostics and vaccines for the rest of the diseases that are not currently treatable.

Relevant criteria to describe neglect deal with the magnitude or severity of the disease and the quantity and quality of resources (available and foreseen) to prevent, diagnose and treat these diseases in a sustainable manner.

1.2 The global health, societal and socioeconomic burden of neglected tropical diseases

Existing statistics on the size and nature of the burden of neglected diseases show that the magnitude and severity is large for these diseases, but they are sometimes misleading due to the unavailability of accurate and reliable data. Please refer to Appendix 1 for the burden of the neglected tropical diseases.

There are many aspects of neglect. These include the political, socio-economic and historical conditions in the different regions, leading to the existence of large neglected populations, and the specifics of the biology of the neglected disease itself. Other factors, such as malnutrition, lack of access to healthcare, sanitation and poorly developed infrastructure all contribute to the problem. However, the fundamental need that we address here is the lack of effective, safe, affordable and easy-to-use medicines to treat these terrible, often life-threatening diseases.

While the role that pharmaceutical companies play in developing and implementing new solutions to neglected tropical diseases has been disappointing, there have been pledges to increase that commitment in recent years through donations and R&D activities. R&D in these diseases are mostly done by public institutions and partnerships. Since 1996, a few product development partnerships (PDPs) have arisen to integrate resources and mobilize them towards the neglected tropical diseases. All the efforts which employ a strong shared value attitude to collaboration have led to many successful breakthroughs, even if they subsist on non-sustainable funding. Several new products, tools and knowledge of the disease are all useful end-points for many of these efforts. There are still few integrated platforms to accurately assess where to place resources so as to use existing knowledge and to advance in the most efficient ways possible. One important aspect in doing so is to consult directly with the people involved (patients, health workers, clinical researchers) to target health research using a needs-based strategy.

1.3 The health tools available for managing these diseases and the persistence of the problem

A concerted effort must be made towards management, elimination and then eradication of these diseases. While many control strategies exist, there is a dire need for better, more affordable care for patients affected by these diseases.
1.3.1 Control strategies

Resolutions of the World Health Assembly lead the way as to how global intervention programmes can affect elimination and eradication of these diseases. Efforts of the neglected tropical disease community when focused on realistic achievable milestones can lead to elimination of some of these diseases in many countries. The enhanced commitment of various members to eradicate guinea-worm was noted in a resolution passed in 2011. Guinea-worm eradication was a campaign started in the early 1980s. We have seen a 99% decline in annual incidence from almost 900,000 cases in 1989 to about 1,000 cases in 2011. A resolution related to yaws passed in 1978 saw 460,000 cases worldwide in 1999. It was due to effective campaigning and case management using treatment available that yaws was eliminated from India in 2006. Furthermore, the South-East Asia region in 2011 pledged the elimination of yaws in the last two countries in the region.

There are essentially two main approaches taken in the last decade, both steered by the World Health Organization (WHO). The first approach is preventative chemotherapy (which began shortly after 2003) targeting the helminthiases (namely lymphatic filariasis, oncocercosis, schistosomiasis and soil-transmitted helminths) and trachoma. These rely on large donation programmes from various large pharmaceutical companies, with an annual value of US$ 2 billion and delivery costs of US$ 0.4-0.5 per person per year, and support from large donors to mobilize these medicines. The 2012 London Declaration saw more than US$ 785 million pledged to accelerate R&D for neglected diseases and expand drug distribution. One would expect that a generic market could circumvent the main supply and procurement challenges and lower incidence; however this has not been the case, as in the example of praziquantel and ivermectin. Mass drug administration interventions now reach some 800 million people each year.

The second approach was the start of intensified case management; this is done for 10 other neglected tropical diseases, and where caring for those affected and at risk, with existing tools and medicines, was prioritized.

The WHO estimates that these two approaches remain usable. For preventative chemotherapy, increased access to effective medicines, sustained donations, a continuous committed stream of funding, effective management and monitoring of control programs at country level and limiting the transmission is greatly needed. For proper case management, early diagnosis and access to appropriate treatment to lower infection rates, disease severity and morbidity and the management of complications is needed. There is a wealth of opportunities for pharmaceutical interventions and new R&D programs for this approach.

Simple diagnostics that are less invasive and have a high diagnostic accuracy must be developed to ensure no delay in treatment initiation. Improved appropriate medicines that are safe and have short regimens are also needed for these interventions to be completely effective.

Vector control while underemphasized, is a key factor toward elimination of many of these diseases. Of significance is that 68 vector-borne disease endemic countries have established national policies for integrated vector management (IVM). The need for better infrastructure, including better healthcare, education and access to sanitary conditions are some of the main problems facing control strategies.
1.3.2 New treatments

The treatment of the neglected diseases relies on relatively old medicines, some more than 50 years old. The number of NCE’s marketed in the last 25 years can reflect the interest of the pharmaceutical industry in a specific disease or therapeutic area, and certainly reflects their investment in R&D. The assessment of NCE’s reveals the staggering discrepancy between the allocation of resources for diseases affecting mainly high or low income countries. 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis, and of the 756 new drugs approved between 2000 and 2011, 29% (3.8%) were indicated for malaria, TB and neglected tropical diseases, of these there were no new chemical entities for neglected tropical diseases, even though these diseases account for 10.5% of the global disease burden. 1.4% of almost 150,000 registered clinical trials were for products for neglected tropical diseases, with only a few new chemical entities among them, thus showing that there needs to be more effort in designing new medicines.

With the efforts of product development partnerships, such as the Drugs for Neglected Diseases initiative (DNDi), some substantial steps have been taken towards combination treatments for these diseases. Notably, in 2009, DNDi (with partners) launched the first new therapy in 25 years, a Nifurtimox-Efornithine Co-administration (NECT) for stage 2 Human African Trypanosomiasis (HAT). They have also launched co-administration of pentavalent antimonials and paromomycin for Visceral Leishmaniasis (Africa), a single-dose liposomal amphotericin B (AmBisome®) and new combination therapies (Asia) and (pediatric) benznidazole for Chagas disease (approved in Brazil 2011), though the availability of some of these medicines is uncertain.

Safety and toxicity of available treatments

For some neglected diseases, such as visceral leishmaniasis and HAT, only a few treatments existed before 2009 (most dating from the colonial era) and these have many side effects. For example, melarsoprol, used since the 1940s to treat human African trypanosomiasis, causes a life-threatening encephalopathy in 5-10 % of cases with 50% mortality, for reasons that remain unknown. Other toxic medicines in widespread use are the antimonials used to treat leishmaniasis, medicines that would not pass regulatory approval for use in humans, were they to be developed now. While these medicines have saved many lives relative to having no treatment at all, considering the general progress in medicine, it is unacceptable that the same toxic medicines still remain the mainstay of treatment for these diseases today.

The effectiveness of available treatments

Many of the medicines in widespread use have limited efficacy data. For example, despite widespread use, there have been limited standardised assessments of the efficacy of benznidazole and nifurtimox in treating chronic Chagas disease. Some other medicines have limited efficacy, notably because of growing resistance. Chloroquine, which was developed in the 1940s, was still used until recently as a first-line treatment for malaria in many places, despite widespread resistance, and several of the other more recent antimalarials are being lost due to resistance as well. Resistance levels of over 60% against antimonials have been documented in Indian visceral leishmaniasis, making this first line drug useless in the area with the highest incidence of this fatal disease.
The affordability of available treatments

Many medicines are not affordable, purely because the affected people are too poor to pay for healthcare. As an example, the current most effective treatment for visceral leishmaniasis is AmBisome®, a lipid-encapsulated form of the antifungal agent amphotericin B. The product is expensive even at the preferential price offered by its producer (US$ 18 per vial, hence between US$ 126 and US$ 378 for an average 35 kg patient, depending on the necessary dosage) and it is seldom used to treat kala azar patients, and certainly not as a first line treatment.\(^\text{25}\)

The appropriateness of available treatments

The medicines have to be appropriate for use in tropical countries and for specific situations of the patient. For example, many medicines need to be stored cold, or require reconstitution in clean water. Adapted dosage forms may not always exist (for example, oral rather than parenteral, short treatments rather than extended periods)? Some medicines are seen to be effective, but exist only in dosage forms that are highly impractical in the conditions encountered. Eflornithine, often termed a “miracle drug” because of its rapid action on even moribund sleeping sickness patients, needs to be administered as four daily infusions over 14 days, severely limiting its use in endemic areas such as rural South Sudan, Angola or the Democratic Republic of Congo.

1.3.3 Availability of appropriate diagnostic tests

A first step towards effectively treating patients (right drug, rational use, protect against resistance, etc.) is to make the right diagnosis and tests-for-cure. A huge gap has been identified in many neglected tropical diseases, including sleeping sickness, kala azar, Buruli ulcer and Chagas disease, for which no tests exist that are cheap, simple to use in the field, and of sufficient sensitivity and specificity. While technologies exist to detect these diseases, many of them are not suitable for “closed system” diagnostics (meaning requiring no complex sample handling steps. Simple lateral flow systems, dipsticks, and recently the LAMP technology appear to be the most suitable for field use.\(^\text{11}\) This is due to their simple steps, single temperature requirements and easy readouts. Diagnostics for acute viral neglected tropical diseases such as dengue could dramatically improve care for severe disease and is lacking.

1.3.4 Vaccines against the neglected tropical diseases

With the continued success of mass drug administration programs, there could be indeed elimination of several of the neglected tropical diseases. To reduce the burden of high prevalence diseases (such as schistosomiasis, Chagas disease and leishmaniasis, apart from new drugs, vaccines are urgently needed. These diseases exhibit extensive geographical overlap\(^\text{26,27}\), and there is widespread polyparasitic infections commonly in these developing countries.\(^\text{28}\) It is thus important to integrate drugs with vaccines or vaccine-linked chemotherapy for global eradication.\(^\text{29,30}\) At present there are no available vaccines for any of the neglected tropical diseases, although several are in early stages of development. With more appropriate resource allocation towards elimination tools, we could see some vaccines and packages of vaccines and drugs to be available within the next decade or so.
1.3.5 Areas of “hidden neglect” in a disease

For certain diseases that receive a lot of attention in general, it may still be that specific aspects remain neglected. For example, paediatric formulations are needed in HIV/AIDS treatment, especially in Africa, as are fixed dose combinations of the most frequently used antiretroviral medicines to simplify treatment and increase compliance. Another example is that while praziquantel is available (even in the generic market) for schistosomiasis, elimination is still far from being achieved, and a paediatric formulation for children, especially pre-school level children is not available. Schistosomiasis is a disease that affects adults and also children. Such hidden aspects of neglect are too often not appreciated. Some patients being treated for Chagas disease are children, but no adapted dosage forms existed until recently. Health care workers had to cut up adult tablets to obtain a roughly correct dose.

1.4 Efforts currently being made to address neglected tropical diseases and expectations in the future.

1.4.1 Medicines and diagnostics under development

In the past decade there has been a substantial commitment for development of new medicines and diagnostics for neglected diseases. While efforts in operational research are difficult to monitor, product development information is available through a recent source. A remarkable undertaking has been performed recently by the Bio Ventures for Global Health. This organization tracks and analyzes progress in global health R&D, provides an evidence base to support decision making, policy change and performance and using the innovative WIPO Re: Search platform, brings innovators together to collaborate to address unmet medical needs in global health. Their analysis shows that the PDP model for neglected tropical diseases supports 40% of the overall neglected tropical disease pipeline. Academic participation is mixed in several stages of product development. More than 65% of pharmaceutical companies and less than 3% of biotechnology companies worldwide participate in neglected tropical disease product development. Only a third of the products in development are performed by a single organization alone, showing that for neglected tropical diseases, collaboration and a partnership case can be made for product development.

The full involvement of innovators in the biotechnology sector and more depth of participation of pharmaceutical companies would be highly beneficial. Translational research initiatives targeting public and academic institutions should emphasize product and solution innovation, with increased engagement of emerging market innovators.

An analysis of the products in the pipeline shows a great promise for serious improvements (Figure 6.9.1 and Appendix 6.9.2). For some diseases such as trachoma and leprosy there are excellent medicines available when used correctly, with appropriate diagnostics. For guinea-worm, eradication campaigns to remove worms from people are proving to be very successful. There is a dire need for appropriate diagnostics to match available medicines and initiate early treatment. For diseases such as Chagas disease, sleeping sickness, dengue and leishmaniasis there are still significant efforts being made to develop medicines to suit the global variations in patient needs. In areas where there are no PDPs, such as dengue, a lot
**Fig 6.9.1: The neglected tropical disease product development pipeline**


The figure shows the number of active R&D projects for product development in each of these diseases. Similar figures for basic research (including epidemiology and resistance) and operational research is not available.
of knowledge is spread over many organizations, including private ones (as there is a dual market) while for Buruli ulcer, this comes together in more partnership-based product development.

The pipeline is more populated than ever before, due to the commitment of various stakeholders. Only 10 diseases have products being developed in clinical phases (albeit mostly in early clinical phases). Nevertheless, since their inception, 19 products have been developed by PDPs for poverty associated diseases\textsuperscript{36}, out of which only five are for the neglected tropical diseases. The rest are products for Malaria, HIV/AIDS and TB. It is important to note that with the engagement of appropriate technologies from innovators (for example in diagnostic platforms, enabling technologies and the like) one technology could lead to several new neglected tropical disease products that can be used in developing countries. What is missing is an analysis of the R&D activities and expected milestones for each of these projects, and any information on the landscape of all basic research activities (including mapping, epidemiology and drug resistance studies). Also missing is a landscape of efforts in operational research. Since there is a strong will to develop integrated neglected tropical disease programs in affected endemic countries, it is vital to monitor such activities and so that one can link R&D efforts with programmatic interventions (preventative chemotherapy or intensified case management), and plan for the future implementation of any developed products and solutions.

1.4.2 Number of scientific publications

Instead of screening publication databases such as PubMed, a thorough analysis was recently performed that showed some interesting trends.\textsuperscript{4} This may provide a measure of the general scientific interest for a certain disease, and the current status of knowledge. However, published scientific papers reflect research at all stages, and tends to concentrate efforts in fundamental research, which does not give an idea as to whether the scientific knowledge may lead to any drug development, nor how far along the pipeline medicines are from use in actual therapy. It does illustrate the discrepancy between numbers of people affected and numbers of scientific publications (and thus amount of scientific activity).\textsuperscript{37} Many of the conditions or diseases of global importance were underrepresented in clinical trials published in leading clinical journals.\textsuperscript{38}

For the period from 1992 to 2011, there were 73,212 papers that were about at least one of the Neglected Tropical Diseases.\textsuperscript{4} In the past 10 years most publications have been about dengue followed by soil-transmitted helminths, leishmaniasis and Chagas disease. The most notable increase in the last 10 years has been in the number of papers about Buruli ulcer, indicating more interest and thus activity in the development of solutions for this disease. Particularly since 2005, there has been more use for the term “Neglected Tropical Diseases”, which represents the widespread use of the brand name rather than increased activity. The countries that publish these papers are also widespread.\textsuperscript{4} What is interesting to note is the shift in geography of research, with Brazil and India leading the R&D publication output in regions affected by these diseases. The EU and North America globally are the top producers of publications about neglected tropical diseases.
1.4.3 The future trends of R&D efforts

There is fortune to be had, with estimates looking forward from the current pipeline showing an average of 4.7 new products each year (excluding vaccines) through 2018. If this is realized, it is a striking improvement to the situation from previous decades. There are many valuable lessons that can be learnt from the past efforts and current pipeline of projects. For product development, to accelerate R&D efforts, it is useful to have integrated systems for comparing data of parallel efforts, preclinical and clinical data. The role of PDPs in integrating data and resources to single platforms (for those diseases where there is a PDP) and the role of EDCTP in expanding to integrated clinical trial centers beyond malaria, HIV/AIDS and TB to the neglected tropical diseases will greatly enhance product development. The role of public institutes and alliances between public-public and public-private centers should remain important and supported for development of better tools useful in epidemiological assessment (including drug resistance mapping), product development and operational research. Section 3 of this paper outlines the gaps and opportunities for R&D efforts for pharmaceutical interventions and what should be mobilized by these players and the community in detail.

1.5 Conclusion: The priorities and opportunities must be identified in each unique situation

Using criteria of disease severity and prevalence alone, HIV, TB and malaria, as well as measles and hepatitis B repeatedly appear. However, including other more qualitative criteria to characterise the extent of neglect and need of actual control strategies and better interventions produces a different list. Opportunities lie in the creation of better medicines, vaccines and diagnostics and operational tools. A further complexity is added by the fact that different aspects of a disease and treatment may be neglected for these neglected tropical diseases, while others are not (for example, the lack of paediatric formulations for schistosomiasis or Chagas), and that even when a treatment is available, it may not be adapted (for example, while eflornithine is highly effective for sleeping sickness, a more adapted dosage form, such as an oral formulation, would be better).

Once the importance of commitment and performance in research into neglected diseases is acknowledged, we must then move towards deciding where to allocate available resources (money, time, research funding, advocacy, etc.). Should we use disease burden, disability-adjusted life years, geographical distribution, absence of research or interest, or combinations of these criteria? R&D agendas may focus on the global burden not diseases that are focal. There is no simple formula that can be applied. Rather, what is needed is a case by case assessment of the specific needs (of diseases, populations affected and concerted management of prevention, diagnosis and treatment), the constant evaluation of scientific and technical R&D opportunities linked to existing programs and the achievable solutions to the problems identified.

An important factor in the context of setting research priorities is the expected impact that providing a treatment, diagnostic test or vaccine might have. This is a crucial criterion that is less easily quantified but is often very obvious if the problem is approached appropriately (promising compounds, underexplored ideas, technical opportunities in formulations, finalising a clinical dossier for registration, etc.).
We live in an era of enormous advances in science and technology. An unprecedented knowledge base is available; billions are spent each year to fund public and private biomedical research. What is missing is a coherent and needs-based strategy to identify areas for intervention and to invest time, money and energy in an efficient and effective way. This requires an ongoing needs assessment complemented by an analysis of the “opportunities”—i.e. areas where R&D can provide solutions to these established needs. Also necessary is the ongoing engagement of innovators and stakeholders through creating shared value towards collaborative projects and achievable solutions. However, there is no simple equation, and each situation must be analysed separately and in consultation with a broad range of people who are deeply involved in the problem and the most likely solutions.

Thus:

1. Priority-setting must be based on a needs analysis for each situation
2. The identified needs and an assessment of impact attainable through addressing the needs through achievable solutions must be used to guide the allocation of resources to maximise impact.

In the following section, we will discuss some examples of how to identify specific areas for research and development, and what can be achieved by such a method to develop appropriate solutions by the allocation of resources to create impact. The examples shown here are for visceral leishmaniasis, Buruli ulcer and schistosomiasis. As an update from the 2004 background chapter, human African trypanosomiasis will be briefly mentioned.

2. Needs-Based Assessment to Guide Priority-Setting – Case studies

We outline priority research agendas for three of the 17 diseases, using a needs-based assessment. The examples were chosen to reflect the diversity in the needs of the 17 diseases. Visceral leishmaniasis (VL) was chosen as it has a wide distribution of endemic countries, and affects both patients who can and cannot pay for healthcare. There are medicines available for VL, with severe side effects. R&D for this disease is mainly driven by a PDP, DNDi, although there are several partnerships (including several consortia, and integrated academic platforms and one single innovator company) that are developing products. Buruli ulcer, considered one of the most neglected of the neglected tropical diseases, was chosen as there has been historically little interest in this disease of the poor (Daiichi Sankyo is working in a Buruli ulcer drug discovery program in a partnership, and in vaccine development, there is one of the largest integrated academic platforms for Buruli vaccine development\(^\text{33}\)). Schistosomiasis, was chosen as it is one of the most prevalent of the neglected tropical diseases, and while control strategies rely on medicines donation program, and water and sanitation projects, there are many areas of “hidden neglect” for this disease. R&D involves various partnerships, and is led by all types of innovators (a PDP—the Sabin Vaccine Institute, academic institutions, an integrated academic platform (SCI), pharmaceutical companies (Dafra, Merck Astellas), biotechnology companies (several), and innovators in endemic areas (Brazil)). An update of priority setting for human African trypanosomiasis (HAT) (from the 2004 Priority Medicines Report background chapter on Neglected Tropical Diseases) is given in Annex 1, this was kept as an update as while significant steps have been made for HAT (introduction of a new treatment-NECT-
Update on 2004 Background Paper, BP 6.9 Neglected Tropical Diseases

2009\(^{40}\), and while and the number of reported cases has been declining, the burden of disease is still high in some countries and it is likely to increase dramatically in case surveillance was to be relaxed.

### 2.1 Visceral Leishmaniasis

#### The leishmaniases

Today, the leishmaniases are endemic in 98 countries with an estimated 350 million people at risk. It has been estimated that 12 million people are affected by this group of diseases with around 0.9-1.6 million new cases occurring annually\(^{41}\); and this number is rising in some areas. Leishmaniasis threatens many poor countries and principally affects poor communities in isolated regions, often as devastating epidemics.

In the last decade progress has been made in disease control with the implementation of rapid diagnostic tests (RDTs), clinical trials with mono and combination therapies and a heightened awareness of the disease. In March 2010 the World Health Organization (WHO) convened the expert committee on Leishmaniasis which subsequently issued the first technical report on leishmaniasis after 20 years. In addition, an ambitious elimination program has been initiated in the Indian subcontinent with a target of less than one patient in 10,000 people, at district and sub-district level, by 2020.

There are four main types of leishmaniasis, all transmitted by the bite of an infected female infected sandfly:

- **Visceral leishmaniasis (VL),** is the most severe form of the disease; patients present with fever, wasting, anaemia and an enlarged spleen. If untreated symptomatic VL is considered fatal in less than two years. A large asymptomatic population exists, and only around 10% of patients become symptomatic.
- **Post Kala azar Dermal Leishmaniasis (PKDL)** is a late (usually post-treatment) complication of VL caused by *L. donovani*. Parasites migrate to the skin of patients in around 10% of cases in the Indian sub-continent (ISC) and in up to 50% of cases in Sudan. These patients are thought to be the reservoir of transmission for VL.
- **Cutaneous Leishmaniasis (CL),** the most common form, principally affects the skin, causing simple lesions which usually self-heal but leave scars.
- **Mucocutaneous leishmaniasis (MCL) begins with skin lesions which then spread, causing massive tissue destruction around the mouth and nose.**

Co-infection with leishmaniasis and HIV is emerging as a growing threat. Because both diseases attack the immune system, it means the body has even less chance of resisting the infections and treatment becomes less effective. In Ethiopia, more than 20% of visceral leishmaniasis patients also suffer from HIV co-infection. Diagnosis and treatment of these patients remains difficult.
Pentavalent antimony, the most widely prescribed drug to treat Leishmania patients, has serious side effects, requires a prolonged course of treatment and is losing its efficacy in some regions, especially in India, due to increasing parasite resistance. New treatments have been implemented, including the liposomal amphotericin B; AmBisome® and miltefosine (the only orally available drug), although these are not optimal due to problems of routes of administration (IV for AmBisome®), high price (AmBisome®), risk of resistance (miltefosine) and/or toxicity (teratogenicity for miltefosine). Combination therapies are also available including paromomycin and antimony combination, and other combination therapies have been studied in phase III trials in India to have excellent efficacy (over 96%) and safety outcomes (miltefosine and AmBisome®; miltefosine and paromomycin, and paromomycin and AmBisome®). Single dose AmBisome® with 10 mg could play a pivotal role for elimination programs as well. All these new treatment modalities are currently being studied in a pilot project in India, looking at the feasibility, pharmacovigilance and effectiveness components under field conditions.

The elimination campaign for VL in the Indian subcontinent is underway with aims to reduce the burden to one in 10 000 people in endemic zones by 2015. New rapid diagnostic tests (RDTs) and freely available treatment are enabling the campaign although PKDL and asymptomatic patients in these areas may undermine these efforts. Diagnostic tests and novel therapies in East Africa and South America still remain priority areas for research as does further research into the impact of PKDL patients and asymptomatic patients over disease control efforts. Treatments and diagnostics for CL patients seem a neglected area of disease control and should be prioritized.

2.1.1 Size and nature of the disease burden

Visceral leishmaniasis (VL), the deadly form of the disease, is endemic in 62 countries with a total of 200 million people at risk, and an estimated incidence of 202,200 to 389,100.\(^{41}\) Mortality associated with VL is extremely difficult to evaluate and the WHO tentatively estimate between 20 000 and 40 000 deaths per year.\(^{42}\) As is common for neglected diseases, the exact figures are not known due to limited data and surveillance means. More than 90% of global VL cases occur in six countries: India, Bangladesh, Ethiopia, Nepal, Sudan and Brazil. Population displacement as a result of war, famine, drought or rural-urban migration can underlie epidemics, for example in 2010-11 in South-Sudan. Leishmaniasis is a disease of poverty, with risk factors contributed by malnutrition and especially HIV co-infection, which is changing the face of the disease\(^{43}\) especially in East Africa.\(^{44}\) Communities once less at risk are becoming increasingly exposed to the disease where the urban HIV epidemic and the rural leishmaniasis epidemic are increasingly coming into contact. Co-infected patients may be difficult to diagnose, respond poorly to treatment and relapse repeatedly.\(^{45,46}\)

A complication of VL, especially prevalent in Sudan and South Sudan and to a lesser extent Ethiopia, Kenya and ISC is post-kala-azar dermal leishmaniasis (PKDL)\(^{47}\), occurring in
people who have recovered from VL following treatment. These patients may be a reservoir for ongoing transmission of disease.

Cutaneous Leishmaniasis (CL) is the most common form of the disease with between 0.7 and 1.2 million new cases per year. CL is more widely distributed than VL, with about one-third of cases occurring in each of three regions, the Americas, the Mediterranean basin, and western Asia from the Middle East to Central Asia. The countries with the highest estimated case counts are, Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica and Peru.

2.1.2 Progress in the last decade of VL research

In the last 10 years much progress has been made by a number of multilateral groups working on leishmaniasis. In March 2010, the World Health Organization (WHO) convened the expert committee on leishmaniasis which subsequently issued the first technical report on leishmaniasis after 20 years. Other groups including the WHO-TDR Visceral Leishmaniasis Laboratory Network, the Drugs for Neglected Diseases initiative (DNDi) and the Leishmaniasis in East Africa Platform (LEAP), Institute for One World Health (iOWH) and other academic and non-academic groups are working towards the common goal of control of leishmaniasis.

Although pentavalent antimonials do still remain the first-line therapy in most parts of the world, there has been a substantial improvement in the number of treatments available for VL, with both new products and new formulations of old medicines either recently approved or in clinical trials. In Bihar State, India, where there is a high level of resistance to pentavalent antimonials alternative treatments have been sought. Here, single course AmBisome® therapy of 10 mg/kg has been shown to cure 95% of patients. This success has not been repeated in East Africa as the single course is not efficacious enough (personal communication). However, implementation of the combination therapy paromomycin plus sodium stibogluconate (SSG) has been made possible in East Africa, and treatment duration has been reduced from 28 days to 17 days, an improvement.

The VL-Laboratory Network has performed an evaluation of the commercially available rapid diagnostic tests (RDTs) for rapid diagnosis of VL. The evaluation included separate analysis in the Indian subcontinent, East Africa and South America. Whilst all RDTs were found to work at an acceptable level in the Indian subcontinent, there was a significant decrease in sensitivity in East Africa and South America and progress in these areas should now be a priority. The rK39 tests are now being used for the elimination campaign in the Indian subcontinent as a non-invasive and accurate diagnostic test in clinical suspects, which are also used for diagnosis and management of suspected cases in East Africa. However, this still has limitations and cannot be used for relapse cases since it remains positive for a long period of time.

CL continues to be a neglected condition within the leishmaniasis presentations. Treatments, diagnostics and control strategies are limited and a push for research in this area would be of enormous benefit to the estimated 0.7-1.2 million new cases per year.
2.1.3 Current Pharmaceutical interventions

Although improvements have been made, the current range of treatment options for VL is still limited. Products have to be safe, effective and accurate as well as adapted to health systems in resource limited settings. Recently the combination therapy paromomycin plus SSG (antimony) a 17 day treatment was implemented in East Africa, and single dose treatment with AmBisome® showed very good outcomes in the Indian subcontinent. Appendix 3 shows the situation of products available for VL in South Asia.

The new 17-day combination therapy of Paromomycin and SSG has reduced the length of treatment by 11 days, saving patients and their carers both time and money. However, there still remains a need for an orally available, cheap medicine that is not prone to develop resistance. In addition, no new chemical space has been used by recent developments in treatments, and it is important that this option is also fully explored and developed.

AmBisome®, is a liposomal formulation of amphotericin B which was developed as a safer and more effective alternative to conventional amphotericin B to treat fungal infections. In particular in India, the effectiveness of this medicine in a single-course and even single-dose treatment of VL, has been clearly demonstrated. WHO have negotiated a reduced price with the producers (Gilead, Foster City, CA) at $ 18/50 mg ampoule, however this still remains an expensive product as each patient may need several ampoules even in a single course treatment. In addition, this product is administered by intravenous injection and temperature stability remains as issue, as the manufacturer guarantees stability only to 25°C. In December 2011, WHO signed a Memorandum of Understanding with Gilead for the donation of AmBisome® for five years to selected eligible countries. This is also a treatment for HIV and VL co-infections, although treatment programs should be scaled up to reduce the burden.

Miltefosine, was thought to be a breakthrough in VL (and HIV-VL) treatment as the only orally available drug for VL and is the drug of choice for the Indian subcontinent elimination programme. However, the prolonged 28-day treatment regime (not requiring hospital stay) may be a threat for treatment compliance, and thus is a risk for rapid development of resistance. In addition, it has been noted that resistance to this drug can develop quickly and it would be a disaster if this drug becomes ineffective. Clinical trials of combination treatments in East Africa are ongoing and data will be available in the coming months (personal communication). The expense of miltefosine (US$ 200 per treatment in private pharmacies) means that a generic product would allow access for poor rural communities to this drug. There are concerns about the teratogenicity of the drug, and half-life of miltefosine in the body is longer than had been previously assumed. This means that this drug cannot be administered to women of child-bearing age (except if a pregnancy test can be done, and with concomitant contraception to avoid pregnancy within the four months after miltefosine treatment).

Paromomycin, an old and widely used broad-spectrum aminoglycoside antibiotic, has also proved effective against leishmaniasis. Paromomycin also appears to work well in combination with other medicines, such as antimonials. The recent success with SSG combination has reduced treatment to 17 days in East Africa. In addition, it is also a cheaper alternative to other new therapies at ~US$ 10 per course.
Recently, a promising compound sitamaquine, was not taken forward to phase II trials due to less than 90% cure rates in well-conducted phase II trials.\(^5\) This should guide future clinical trials in acceptable efficacy levels.

While interventions for VL are available, scaling up of programs, and (early) access to these medicines is still a problem.

There is as yet no effective vaccine as prevention against any leishmaniasis form. A limited efficacy was seen with whole killed parasites (promastigote forms) up to phase 1 clinical studies. A suboptimal vaccine for *Leishmania* could have a therapeutic effect. Combinations of administration of antimonials and such first generation *Leishmania* vaccines have shown some benefit in PKDL patients. Recombinant vaccines are being developed, along with genetically maniulted parasites as live vaccines are being tested.\(^6\)

**Cutaneous Leishmaniasis**

The majority of CL infections are currently treatment by antimonial therapy. This includes a long course of injections (usually SSG) over 28 days. Miltefosine is also known to be an effective therapy for CL, but is currently only registered in Colombia as a second line treatment.\(^3\)

2.1.4. Current diagnostics

The major toxicity associated with treatment, as well as the life-threatening nature of the disease makes the need for accurate diagnosis crucial before starting treatment for both VL and CL.

The current gold standard diagnostic for VL requires an invasive aspirate from the spleen which carries a severe risk of haemorrhage and is not recommended except under exceptional circumstances. Lymph node and bone marrow aspirates are also taken for microscopy but these samples are still invasive (and potentially harmful) tests. Reading of the microscope preparations to detect the parasites requires trained and experienced staff, usually present only in major health centres.

The Direct Agglutination Test (DAT) was developed in the 1990's to detect anti-leishmania antibodies in serum of patients. The test requires moderate technical expertise, laboratory equipment, reagents, micro-titre plates, and a toxic solution (chemical 2-mercaptopethanol). Despite this, it remains an important part of the diagnostic algorithm in some areas especially in East Africa.

The development of the lateral flow immuno-chromatographic tests (ICT), commonly referred to as rapid diagnostic tests (RDTs) has greatly improved the diagnostic landscape for VL. RDTs have now been adopted widely especially in the Indian subcontinent where they have been shown to have a high diagnostic accuracy (Cunningham 2012).\(^3\) However, in a recent WHO-TDR evaluation, it was shown that these tests perform with decreased sensitivity in East Africa and in South America. Only one test performs with a sensitivity above 85%.\(^8\)

For CL, the diagnostic landscape is poor. Serological diagnostics are not appropriate as there are few circulating antibodies in the blood, and therefore, only the parasitological tests are applicable (microscopy and culture) for case management. Since therapies for CL are
potentially toxic, they should only be administered to those with confirmed leishmaniasis infection. Therefore more efforts into diagnostics techniques (using antigen or molecular methods) is urgently needed.

2.1.5 Other control strategies

As leishmaniasis is maintained by a complex lifecycle between the human host, parasite and sandfly vector and on some occasions an animal reservoir it is unlikely that control will be achieved by a single strategy. Therefore, in addition to case management by diagnosis and treatment other strategies including integrated vector control and reservoir control (if present) are essential. In Sudan and South Sudan, the on-going civil war makes such interventions difficult and the other regions most affected are poor, isolated or lack the necessary infrastructure.

Vector Control

Vector control strategies have been helpful in the past, including spraying of insecticide and use of bednets. However, growing insecticide resistance and lack of infrastructure and government support has limited such programs. The situation is made even more complex by the many species of sandflies that transmit the disease and the large number of animal hosts, including humans.

Vaccines

Accumulated evidence from basic research on the immunology of Leishmania infection points to an important role for the immune system in controlling infection, suggesting that a preventive vaccine could, in theory, be an option. To date, work has been completed on first-generation vaccines, whole-killed parasites or extracts, with inconclusive or negative results for prophylaxis but encouraging for therapy. Second generation vaccines consisting of recombinant proteins and genetic vaccines have been investigated and one, Leish-111f+MPL-SE has entered clinical trials. Trials indicate that this vaccine is safe and immunogenic in healthy subjects with and without history of previous infection with Leishmania as well as in patients with CL and ML. Vaccination of the common reservoir of leishmaniasis, dogs is seen as an important control strategy. Recently, canine vaccines have been commercialised and studies analysing the ability of canine vaccines to interrupt transmission are encouraging.

2.1.6 Current and potential research: a priority R&D agenda for VL

There are many organizations active in R&D for Leishmaniasis, including DNDi and alliances with pharmaceutical companies, a few SMEs and academic institutions. The following list shows some areas where there are opportunities for further R&D in VL. This list is non-exhaustive. The * indicates that some research activity is ongoing.
Combinations therapy to reduce treatment duration, prevent resistance, and obtain better cure rates*

A broad agreement exists within the scientific community that drug combinations are the best ways to protect effective anti-infective medicines against resistance, in particular when only a few medicines are available. Clinical Trials of existing and new medicines combination therapies could be coordinated by EDCTP. Drug combinations also may reduce treatment duration (and possibly hospitalisation), and/or reduce toxicity. A phase III trial in East Africa is currently finishing with investigations into i) single dose AmBisome® and seven days oral miltefosine ii) single dose AmBisome® and 10 days IM paromomycin and iii) 10 days oral miltefosine and 10 days IM paromomycin and results will be available soon.

Fexinidazole* is a drug currently in phase I/II clinical trials for treating African trypanosomiasis. A bacteria-like nitroreductase has been implicated in both the mode of action and the mechanism of resistance to nitro-drugs in the related trypanosomatids, Trypanosoma brucei and T. cruzi. Given the closely related genomes of the Kinetoplastida investigations have begun to see whether fexinidazole could be an effective treatment for VL. Phase I trials are in the planning stage as this drug shows promise in mice and has the potential to become a safe and effective oral drug therapy for treating VL.

Identify new anti-leishmanial compounds*

New high throughput screening techniques of intracellular amastigote stages of the parasite lifecycle, which is relevant to disease in humans gives us the opportunity to identify new (classes of) anti-leishmanial compounds (references include personal communication with Erika Bogaart). Of particular interest is to screen libraries of already existing medicines and compounds currently under development for other indications, in particular antibiotics, medicines for cancer and veterinary medicines for parasitic diseases as this would offer an opportunity for extension of indication research, or parallel development (both scenarios significantly reduce the R&D efforts, time and resources needed to bring a new neglected disease drug to the patient). This would be suitable for the Innovative Medicines Initiative (IMI) programme if IMI were to extend their reach to include the neglected tropical diseases.

R&D for sensitive and easy-to-use diagnostics, including disease monitoring and test of cure*

A recently-developed simple serological test, the rk28 dipstick, has shown promising results (good diagnostic accuracy) for diagnosis of VL. It is hoped that this test will perform well in East Africa where a specific problem exists with low sensitivity of existing rK39 tests and is undergoing evaluation.

Serological tests cannot be used to monitor disease progression (antibodies remain detectable for months after parasite elimination), to diagnose relapses or to establish cure. Research for alternative markers (antigen-based or DNA/RNA-based or surrogate makers) and field-adapted detection of these still is a high priority, both for treatment programmes and as an important tool for future clinical research for improved treatments. The Foundation of Innovative New Diagnostics (FIND) have recently (2011) started working on diagnostics for leishmaniasis, in particular a molecular test called LAMP and an improved antigen detection system to be used as tests of cure.
Update on 2004 Background Paper, BP 6.9 Neglected Tropical Diseases

PKDL

Accurate epidemiological data about PKDL is sparse, and although there is an assumption that these patients are a reservoir of disease relatively little evidence is available. In view of the elimination campaign in the Indian subcontinent there is a priority to work on epidemiology, pathogenesis, diagnostics and treatment of this component of the leishmaniasis.

Vaccines*

Genetic vaccines have become an attainable target, due to the possibility of producing large volumes, standardisation and longevity of response. In addition, on-going analysis of canine vaccines shows that transmission of human disease can be interrupted by vaccination ultimately reducing incidence. Vaccine development, therefore, is a priority area in *Leishmania* research. Novel, second-generation vaccine antigens candidates must be identified and targeted for vaccine development and evaluation must be performed against a range of *Leishmania* species to ensure geographical utility. Prophylactic use of vaccines should be prioritised as well as for therapeutic use.

R&D on topical applications to treat cutaneous leishmaniasis*

While cutaneous leishmaniasis should have a complete chapter on its own, there is a wealth of knowledge from VL that can be applied to CL. Two formulations of topical treatments containing Amphotericin-B, a drug that is active against all species of *Leishmania* tested are in pre-clinical evaluation ready for clinical studies in the fourth quarter of 2012, if they meet all ICH/ European Pharmacopeia requirements. It is possible that the efficacy of any topical formulation could be enhanced by an immunomodulator.

HIV co-infection: epidemiology, diagnosis and possible treatment*

Evidence suggests that prevalence of VL in HIV patients is between 100 and 2320 times greater than in immunocompetent or other non-HIV-positive, immunodeficient groups of people, while the current treatments prove only marginally effective (up to 50% relapse among HIV-positive VL cases). Because the incidence of VL-HIV co-infection is increasing sharply in certain regions, more than 20% of VL cases in Ethiopia, are HIV-positive), research is needed on different aspects of this problem, including epidemiology, diagnosis and possible treatment. New therapies are under investigation by DNDi.

Study mechanisms of drug resistance

Because only very few medicines are available, with very little innovative and new classes of medicines in the pipeline, it is crucial to make all possible efforts to prevent drug resistance. Understanding the mode of action of the existing and new medicines, including the molecular biology of drug resistance mechanisms, is a prerequisite for this, and should include the development of field-adapted standardised methods to assess drug resistance (both for resistance surveillance purposes, and to guide the choice of treatment).
Leishmaniasis in other regions.

The transfer of progress made in the Indian subcontinent and East Africa, to date, has been slow. The new SSG and Paromomycin therapy is undergoing assessment in South America, however, more effort must be directed towards clinical trials and transfer of technology also to Asia, South America, the rest of Africa and the Middle East.

2.1.7 Conclusion for Leishmaniasis

Leishmaniasis continues to affect millions in different parts of the world, with an alarming re-emergence linked to population movement (migration), urbanization, environment-related development activities and HIV co-infection. In the past decade progress has been made with new clinical trials of mono and combination therapies, diagnostic evaluations and screening of novel compounds for *Leishmania* treatment.

However, there are still research goals and objectives that should be urgently met. The diagnostic landscape for VL patients in East Africa and Brazil is inadequate and diagnostics for PKDL and CL patients are poor. Indeed, relatively little is known about PKDL patients are their potential effect on the elimination campaign in ISC, and we require research on epidemiology, pathogenesis, treatment and diagnostics.

New oral therapies which are not prone to resistance are essential as we await results of the combination trials in East Africa. We must also look for new anti-Leishmania treatment.

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**Summary of priority research agenda for visceral leishmaniasis**

- **Basic research**
  - Study on mechanisms of drug resistance
  - HIV co-infection: epidemiology, diagnosis and possible treatments
  - Impact of PKDL patients as reservoirs of disease. Full evaluation of the epidemiology, treatments, pathogenesis and diagnostic algorithm for these patients.
  - Active disease markers for VL

- **Product development**
  - Pharmaceutical research to develop long-acting and/or oral formulations
  - Clinical trials for combination and novel therapies
  - Identify new anti-leishmanial compounds
  - R&D on topical applications to treat cutaneous leishmaniasis
  - R&D on a preventive and therapeutic vaccine for human leishmaniasis
  - R&D for sensitive and easy-to-use diagnostics, including treatment response monitoring and test of cure with increased sensitivity in East Africa and South America

- **Operational research**
  - Delivery of interventions
  - Resistance monitoring
  - Role of asymptomatic leishmanial infection in transmission
  - Health systems strengthening and pharmacovigilance
### Buruli Ulcer

Buruli ulcer is a progressively destructive skin disease caused by *Mycobacterium ulcerans*. The first descriptions of the disease were from Australia and Congo and appeared more than 60 years ago; on the basis of a report on a focus of cases in Buruli county, Uganda (north-east of Kampala, now Nkasongola district) the disease got its current name. At least 33 countries have reported Buruli ulcer, most cases occur in rural communities in Africa and about half of them occur in children under 15. Although the mode of transmission is unknown, hampering prevention, a combination of aquatic reservoirs and (biting) arthropods are probably involved. Yearly 5 000-6 000 cases are reported, but the disease is likely to be underreported and may increase due to man-made changes in the environment which result in an increase in wetlands.

Because of the relative low optimal growth temperature of *M. ulcerans* of 30-33 °C, lesions develop in the cooler tissues, especially skin and subcutaneous tissue. Buruli ulcer presents as a spectrum of clinical forms from localized to disseminated and from an early painless lump to eventually invasive ulcerating lesions. Pathology is caused by the toxin mycolactone which is secreted by *M. ulcerans*. This polyketide-derived macrolide is diffused in the lesion and has necrotizing and immunosuppressive properties, the latter enabling the disease to progress without pain and fever. Available diagnostic tests either lack sensitivity or simplicity.

Currently most patients that are detected early can be effectively treated with antibiotics. Recent studies have confirmed the efficacy of antibiotics in treatment. However the 8-week regimen of daily oral rifampicin and injectable streptomycin is cumbersome, because of the need of repeated visits to health care centres. Issues of treatment failure and drug resistance could be a risk. Surgery is still needed in many cases for wound management and prevention of deformity. Osteomyelitis is a major complication of Buruli ulcer of which care and treatment are difficult. In many cases Buruli ulcer leads to deformity and permanent disability with psychosocial and socioeconomic implications in endemic regions.

A WHO organized international conference on Buruli ulcer control and research in 1998 marked a significant first step in drawing the attention to the suffering caused by this disease. In May 2004, the World Health Assembly (WHA) adopted a resolution to improve the surveillance and control of Buruli ulcer and accelerate research to develop better tools for its control and prevention. In the last decade major progress has been made in both research and translation of this research into control policies. Still, many features of the disease are still unknown, such as the mode of transmission and the pathogenesis. Better tools to control the disease are badly required with simplified diagnostics and improved treatment regimens as the most prominent needs.

**Buruli ulcer remains a neglected disease and much work, at all levels, needs to be done to improve prospects for rational control.**
2.2.1 The size and nature of the disease burden

Buruli ulcer is endemic in humid, rural tropical climates around the world and has been reported from in 33 countries with a case detection rate of between 5000 and 6000 per year, but reliable DALY figures are not available. Buruli ulcer is the third most common mycobacteriosis of humans, after tuberculosis and leprosy. Cases from China, Australia and Japan have been reported, but most cases are from West Africa, notably Benin, Ghana and Côte d'Ivoire, the latter being the most affected country with over 2500 cases/year. Cases are often localized in specific districts within regions. In many countries there is evidence of huge under-reporting of the disease. The exact mode of transmission is not known. Unlike the other mycobacterial disease tuberculosis and leprosy, Buruli ulcer does not likely involve human to human transmission, but is almost always found in association with an environmental source. Recently, a strong relationship between the presence of \textit{M. ulcerans} in the environment and the presence of Buruli ulcer in humans was found in Benin. Moreover the detection of \textit{M. ulcerans} DNA in multiple sample types within a single village was a strong predictor of high Buruli ulcer case burden. It remains unclear though whether the association is a causal relationship, as Buruli patients may be as well the source of the environment contamination.

It has been reported that refugees from non-endemic Rwanda suffered from an epidemic in a refugee settlement in Uganda affecting 9\% of that community; new cases disappeared when they moved to a new camp 150 miles away. Riverine, swampy environments seem to be universally present in endemic areas in Western Africa. Biting arthropods as vectors have been implicated and zoonotic transmission by mosquitos from mammals has been suggested. The negative influence of the use of insect repellent and wearing long trousers on the risk of disease, favor a role of insects in the transmission.

Following infection, \textit{M. ulcerans} proliferates and secretes the toxin mycolactone, a polyketide-derived macrolide, that causes necrosis and also spreads into neighbouring tissue, suppressing the local immune response and causing the severe and disfiguring ulceration. The host target for mycolactone is as yet unknown. Most lesions occur on exposed parts of the body, particularly the limbs. Children under 15 are among the most incident cases. About half of Buruli patients have functional limitations after treatment.

Because Buruli ulcer presents in a spectrum of clinical forms and many other conditions resemble Buruli ulcer, only a few experienced medical practitioners can diagnose the disease on clinical features alone. Laboratory confirmation of diagnosis is required. The available diagnostic assays, direct smear microscopy, histopathology, culture and PCR lack either sensitivity or simplicity to be useful and operational in peripheral health centres where they would be most useful. Because PCR targeting the IS2404 insertion element is the most sensitive technique (over 90\%) and relatively fast (with 48 hours), WHO recommends that at least 50\% of the cases reported should be confirmed by PCR.

2.2.2 Progress in Buruli Ulcer control and research

Multidrug therapy has been shown to be effective in the treatment of tuberculosis and leprosy, is now also the current accepted treatment for Buruli ulcer. The combination of oral rifampicin and injectable streptomycin both administrated daily for eight weeks is now the
standard treatment of which effectiveness has recently been proven in a randomized controlled trial. Antibiotics kill the bacteria, stop further mycolactone production, which arrests the progression of disease and support healing. Complementary treatments such as wound care, surgery, physiotherapy and interventions to minimize disabilities may still be needed depending on the stage of the disease. Surgery can reduce sequelae but its main advantage is shortened treatment duration in some cases and more rapid wound healing.

2.2.3 Current pharmaceutical interventions

While Buruli ulcer is rarely fatal, the deformity and disfigurement it causes can result in serious loss of quality of life. This is why current control efforts focus on early detection followed by adequate treatment with multidrug therapy to minimize suffering, disabilities and socioeconomic burden. However, both detection and treatment have still their shortcomings.

With the introduction of multidrug antibiotic treatment since 2004, new patients with Buruli ulcer have been offered hope for healing without extensive and destructive surgery, which was the standard treatment before. However, patients need to be encouraged to report early for the antibiotic treatment to be most effective and to prevent functional limitations resulting from extensive tissue damage caused by long patient delay. Due to wrong perceptions about treatment and social stigma of the disease, it is thought that a large number of patients never seek treatment, hiding their ulcers, disabilities and scars. A simple diagnostic tool which fulfills the ASSURED criteria (Affordable, Sensitive, Specific, User friendly, Rapid and robust, preferably Equipment-free and Deliverable) in conjunction with information, education and communication at community level are badly needed. Furthermore, health workers and village volunteers need to trained in early detection. More complicated diagnostics may have a useful role at district hospital level.

Development of a simple diagnostic for Buruli ulcer is not likely to be easy. Mycolactone seems to be an obvious target, but this compound is not water-soluble and lipid extractions suffer from a high background due to co-extracted human lipids. Serology, i.e. antibody detection to a number of well-defined protein antigens, has shown to be of little diagnostic value. The search for alternative biomarkers and alternative detection systems seems warranted, including those employing blood and urine.

The current antibiotic treatment is cumbersome, mainly because of the need for daily injection with streptomycin (which is contraindicated in pregnancy) and thus repeated visits to health centres. Oral fluoroquinolones may be alternatives to be used in combination with rifampicin. However, randomized controlled trials are needed to prove that these are as good as, if not superior, to the current treatment. A prerequisite is that the medicines can be procured and dispensed appropriately under field conditions and that patients and providers adhere to effective treatment protocols.

Prevention of the disease would be preferable over cure. However, there are few targets to focus on. If the mode and dynamics of transmission were better understood, control strategies could be focussed at cutting the transmission cycle, for example by vector control. Because the incidence of Buruli ulcer is relatively low, vaccine development efforts specifically targeted at Buruli ulcer will not likely to be cost-effective. However, because the pathology of Buruli ulcer is mediated by an immunosuppressive toxin, passive
immunization may be a way forward. Current research is ongoing, and the BCG vaccine offers some short term protection.\textsuperscript{87}

Since December 1997, when the World Health Organization (WHO), announced that they would take the lead in mobilizing an international response to Buruli ulcer as a serious public health problem, considerable progress has been made. In 1998, WHO launched the Global Buruli Ulcer Initiative (GBUI) to coordinate control and research efforts\textsuperscript{75} and in May 2004, the World Health Assembly adopted a resolution on Buruli ulcer that called for increasing surveillance and control, and for intensified research to develop tools to diagnose, treat and prevent the disease.\textsuperscript{76} The last 10 years have been very productive in terms of research and research outcomes which have led to better control. The total number of research publication has increased by a factor 3.9 from 98 in the 10-year period 1992-2001 to 379 in the period 2002-2011.\textsuperscript{4} Nevertheless, compared with about 16 000 papers per year on HIV/AIDS and with a research budget of only $5.5 million in 2010 (0.2% of the global R&D funding), Buruli ulcer remains a truly neglected disease.\textsuperscript{48}

2.2.4 Current and potential research: a priority R&D agenda for Buruli ulcer

There is a need for focused R&D, divided over basic research, product development and operational studies:

**Basic research**

Basic research to increase understanding of transmission dynamics will eventually lead to clues for better control. Biomarker research will be needed to feed the product development pipeline for diagnostics and high throughput screening. Immunological research will be needed to increase our understanding of fundamental mechanisms of protection (if any) and pathology (paradoxal reactions; interactions with HIV infection) and may lead to recommendation on interventions to prevent or decrease pathological features. Animal studies to determine bactericidal synergisms effects of drug combinations, like in the mouse footpad model, are useful to guide clinical trials in humans.

**Product development**

Appropriate clinical trials with all-oral therapeutic regimens are very much needed. Macrolides and fluoroquinolones could potentially replace injectable streptomycin. A close connection with the research community involved in developing and testing new medicines for treating TB would be useful.

There is a need for modern wound management and access to bandages. Topical applications could assist in facilitating or accelerating wound healing after surgery. In both phases, the protection against opportunistic infections would be an important secondary objective. Applied pharmaceutical research to design a formulation that helps the active compounds to effectively cross the skin and reach the bacteria is needed.

New biomarkers, or entire new concepts of diagnostic testing, are needed to feed POC test development. Simplifying molecular technology may be another way forward. Appropriate tests which could be used in assisting the mapping of the disease would be useful. Test systems employing urine or blood should be explored.
Operational research

Operational research is especially needed as to optimally deliver interventions. The current control of Buruli is dependent on early diagnosis followed by adequate treatment. How to ensure that patients report early with their lesions, how can medicines be procured and dispensed appropriately under field conditions and how to assure that both providers and patients adhere to treatment guidelines are important fields of investigation.

2.2.5 Conclusions for Buruli ulcer

Buruli ulcer is a neglected and re-emerging disease that predominantly affects children in Western Africa and other parts of the tropical world, causing terrible disabling and disfiguring ulcers, often leading to permanent lesions. Drug treatment is available provided the disease is detected at an early stage; extensive surgery followed by skin grafts, often out of reach for the poor in rural populations affected by the disease, is still warranted in many severe cases. The relatedness to other major mycobacterial infections (TB, leprosy), as well as progress in basic science provide a wealth of opportunities for focused adaptive R&D towards improved treatment options, in particular making use of existing topical treatments, oral medicines, and compounds in development for other indications. Coordinated efforts and serious financing is needed to move this essential R&D agenda forward, but major improvements are possible on the short to medium term.

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2.3 Schistosomiasis

2.3.1 Size and nature of the disease burden

Schistosomiasis, or bilharzia, is a parasitic disease caused by trematode flatworms of the genus *Schistosoma*. Schistosomiasis affects at least 200 million people worldwide, is prevalent in tropical and sub-tropical areas, mainly in poor communities without potable water and adequate sanitation. Over 80% of the schistosomiasis burden is concentrated in sub-Saharan Africa (SSA). The burden of disease due to schistosomiasis is underestimated, as chronic manifestations in the liver, bladder, and cancers are not recorded as schistosomiasis.

Urinary schistosomiasis is caused by *Schistosoma haematobium* and intestinal schistosomiasis by any of the organisms *S. intercalatum*, *S. mansoni*, *S. japonicum*, and *S. mekongi*. In urinary schistosomiasis, there is progressive damage to the bladder, ureters and kidneys. The disease is caused primarily by schistosome eggs, which are deposited by adult worms in the blood vessels surrounding the bladder or intestines and initiate immunopathology. In children schistosomiasis can cause anaemia, stunting and a reduced ability to learn. Infection with *S. haematobium* is the cause of a large number of cases of hydronephrosis, renal failure, and bladder cancer, although these may not be recorded as schistosomiasis. Women with urinary/genital schistosomiasis are at an increased risk of acquiring HIV infection. In intestinal schistosomiasis, there is progressive enlargement of the liver and spleen, intestinal damage, and portal hypertension.

Few, if any, of the clinical manifestations are specific to schistosomiasis and overlap with other causes, including other helminth infections, malaria, and viral hepatitis, which often are co-endemic with schistosomiasis. The classical sign of urogenital schistosomiasis is haematuria (blood in urine). In women, urogenital schistosomiasis may present with a range of signs and symptoms including lesions of the cervix and vagina, vaginal bleeding, pain during sexual intercourse and nodules in the vulva. In areas endemic for urogenital schistosomiasis a large proportion of women may have female genital schistosomiasis (FGS). Genital schistosomiasis also affects men, inducing pathology of the seminal vesicles, prostate and other organs. This disease may also have other long-term irreversible consequences, including infertility.

Intestinal schistosomiasis has a nonspecific clinical picture of abdominal pain, diarrhea, and blood in the stool. Liver enlargement is common in advanced cases, frequently associated with ascites and other signs of increased portal pressure. In such cases there may also be splenomegaly.

Schistosomes require a molluscan intermediate host, freshwater snails, in which they undergo development. Humans become infected when cercariae emitted by the snails burrow into human skin; the lifecycle is completed when miracidium in eggs in infected urine or faeces hatch in water and penetrates the snail host. Contact with freshwater is an everyday occurrence in endemic areas and collecting drinking water, washing, bathing and many rural occupations including fishing and agriculture are risk factors for infection. Co-infections with other helminth infections are common and therefore control programmes should synergise efforts for control of multiple diseases.

Mass drug administration (MDA) of individuals is the main intervention for the control of schistosome infections. Within control programmes it is essential that sanitation is also
improved and modifications are made to the environment to reduce exposure to the snail intermediate hosts and to cercaria that have been shed by snails, combined with education to reduce unsafe water contact.\textsuperscript{92}

2.3.2 Progress in the last decade of Schistosomiasis control and research

Praziquantel has been used successfully over the past 20 years to control schistosomiasis in many countries, such as Brazil, Cambodia, China, Egypt, Morocco and Saudi Arabia\textsuperscript{[87]}. In 2001 the World Health Assembly (WHA 54.19) recommended that 75\% of children at-risk of schistosomiasis should be treated with regular chemotherapy by 2010.\textsuperscript{93} In the year following, the Schistosomiasis Control Initiative (SCI) was set up by the Imperial College, UK (acting as an Integrated Academic Platform) with the aim of making progress towards this goal and the reduction of prevalence and intensity of infection and morbidity in sub-Saharan Africa.\textsuperscript{92} SCI is an initiative that helps governments in African countries tackle neglected tropical diseases caused by worms. It was founded in 2002 and funded via grants from the Bill and Melinda Gates Foundation, USAID and Geneva Global.\textsuperscript{94} SCI commenced treatment in 2003 and targeted half a million people, mainly in Uganda where the pilot programme took place. In 2005, close to 13 million doses of praziquantel (PZQ) were administered in the six SCI-supported countries and, by the end of 2008, a total of 45 million praziquantel treatments had been administered.\textsuperscript{95}

SCI has demonstrated that treatment with praziquantel not only benefits those who are treated but also to those untreated members of the communities. In addition SCI showed it is possible to reach school age children and to treat them with PZQ for less than US$ 0.50 per capita and per year.\textsuperscript{95} However, we are still far away from treating the targeted goal of 75\% of school age children living in endemic areas.\textsuperscript{96} SCI has been working with improving schistosomiasis in six countries in Africa, where there is good data that a single administration of praziquantel with effective community involvement works well.\textsuperscript{97} Reports of treatment in the Philippines, emphasizes the need for more community involvement in MDA programs.\textsuperscript{98}

More recently a meeting held in the UK (January 2012) produced a pledge, the ‘London Declaration,’ that public and private partners would unite and co-ordinate to combat 10 neglected tropical diseases by 2020. The aim for schistosomiasis is control by 2020.\textsuperscript{48} An increased commitment for donated praziquantel (from Merck KgaA) was pledged.\textsuperscript{19}

Until there is a vaccine developed for schistosomiasis, there needs to be effective chemotherapy along with proper public health initiatives to control this disease. Facilitating treatment programs using praziquantel at lower prices and health campaigns (for deworming) of school-going children could greatly help reduce the burden.

2.3.3 Current pharmaceutical interventions

The current goals of the WHO and the London Declaration are based on the use of a MDA strategy. Apart from praziquantel, two other drugs metrifonate and oxamniquine were also recommended by the WHO in the essential drug list, however the latter two were not made affordable or accessible. Praziquantel provides effective, safe, single-dose treatment with few side-effects, offering opportunities for improved schistosomiasis control. This is currently the only treatment used in schistosomiasis programmes.\textsuperscript{96} The schistosomiasis community has
observed successful use of MDA in countries where political commitment has been strong, such as China, Brazil, Egypt, and Morocco, if additional measures including sanitation and environmental management are also implemented.\textsuperscript{90,99}

However, the long-term impact of expanded MDA is uncertain and it is possible that this approach could result in emerging parasite resistance. This would alter the dynamics of control programmes and it is, therefore, essential that monitoring and evaluation of MDA, especially at the local community level, is applied.\textsuperscript{96} The presence of schistosome populations that are refractory to praziquantel has already been reported and it has been estimated that around 10\%–20\% of infected patients will continue to excrete eggs after treatment.\textsuperscript{100}

2.3.4 Other control strategies

Efforts to develop antihelminth vaccines have gone on for many years and continue with steady progress in identifying candidate antigens, recently aided with the generation of a number of helminth genomes. Where the transmission involves an animal reservoir it is possible that treatment or vaccination of the reservoir would contribute towards control [89]. It is now possible to create an effective vaccine against a multicellular parasite, as evidenced by the successful porcine cysticercosis vaccine, a massive step for helminth vaccine development.\textsuperscript{101} Very promising leads in the development of schistosomiasis vaccines have been seen.\textsuperscript{48} Vaccines developed could be used in combination with antihelmintics as adjunct prophylaxis, thus accessing the already existing control activities (by MDA) to reduce morbidity, reduce rates of infection and re-infection, and reduce the likelihood of antihelminthic resistance. Recently, an anti-schistosome fecundity vaccine with an efficacy of 50\%–90\% is being evaluated for bovine vaccination.\textsuperscript{102}

2.3.5 Current and potential research: a priority R&D agenda for Schistosomiasis

Basic research (and epidemiology):

As the prevalence of schistosomiasis decreases due to MDA programmes the need for improved diagnostics will increase. There are several important areas for diagnostic development.

1. Diagnostics capable of monitoring treatment response and therefore, ability to monitor and evaluate intervention programmes
2. Disease mapping to guide initiation of interventions including lot quality assurance (LQA) for identifying high risk communities.
3. Assays for individual diagnostics
4. Tools to determine and quantify infection prevalence and intensity
5. Detection of anthelmintic resistance
6. Treatment end-points.

It is likely that a single diagnostic tool will not provide the answer for these multiple problems. Investment in antigen and molecular detection tools may allow quantitative detection of active infection and monitoring of treatment response. It is important that these tools are simple and easy to implement and do not require large investment in laboratory infrastructure. Serological tools are appropriate for disease mapping and monitoring elimination programs.
Product development (and case management):

The London Declaration will see increased donations of praziquantel for MDA programmes. SCI have estimated 128 million school-aged children would need to be given praziquantel on a yearly basis. This is an estimated 192-384 million tablets every year in Africa alone. A persistent reduction in efficacy of praziquantel in schistosomes would represent a grave threat to control programmes, as there are very few alternative medicines. Therefore, research should be focused on the development of alternative treatments to praziquantel. This includes the use of combination anthelmintics; firstly, to increase the spectrum, effectiveness, and convenience of drug administration, and secondly, to slow the development of possible resistance. Specific paediatric formulations of praziquantel should also be developed and evaluated to ensure effective population coverage.

Alternative compounds are also under investigation and recently artemisinin-based compounds have been shown to be active against immature stages of schistosomes, which are relatively refractory to praziquantel. The artemisinins could prove useful should praziquantel resistance become a problem. However, because the artemisinins are currently critically important for malaria chemotherapy artemisinins may not be used for schistosome MDA programmes.

New chemical space should be explored for novel anti-schistosome compounds that can be used in combination or as second line therapies in case of an increased drug resistance or infections which are refractory to treatment.

Other Control Methods:

An essential aspect of control of schistosomiasis is improvement of sanitation in affected communities and access to clean water for washing, bathing etc. Any disease control programme must integrate clean water and hygiene activities into their efforts and promote education and awareness of this disease. Without these elements any control programme will not be sustainable and will fail as soon as MDA is removed. It is imperative that innovative methods to improve sanitation and implement interventions should be encouraged and invested in. As schistosomiasis is transmitted via direct penetration of cercaria through the skin people who work in or around water and who use infected water for washing are most at risk. Sustainable vector control is an important component of elimination programmes. Innovative methods to remove snails as well as prevention of cercaria invasion would be beneficial.

In China, where targets for control of morbidity have been met, multi-factorial efforts for control of transmission are being tested and implemented. These include replacing buffalos (one of the reservoir hosts) with tractors, better livestock management e.g. fencing animals, improved access to clean water, sanitation and human faeces management. Control programmes in sub-Saharan Africa should learn from the experiences in China in control of schistosomiasis including the recognizing the importance and power of political commitment to the campaigns.
Conclusions for Schistosomiasis

Schistosomiasis is a preventable and treatable disease, however even if medicines for this disease exist in the generic market, the disease is far from elimination, let alone eradication. The disease affects mostly children, a target group where existing medicines has to be adapted. A wealth of opportunities exist in enabling technologies to develop more specific forms of treatment (e.g. pediatric forms with appropriate dosing), diagnostic tools and vaccines and must be complemented with substantial infrastructure improvement to be effective in elimination. Coordinated efforts from both the public sector, the private sector (including the engagement of pharmaceutical industry, PDPs, sanitation and education organizations), along with substantial financing can lead to reducing the immense burden of disease and even complete elimination.

Summary of priority research agenda for schistosomiasis

- Basic research
  - Study of resistance mechanisms

- Product development
  - Improvements on existing medicines (including pediatric forms, adapted for tropical conditions)
  - Use of new chemical space for novel therapies
  - Diagnostic assays with increased sensitivity including those that can detect response to treatment and monitor drug efficacy. In addition, diagnostics that are directed towards individual case management are necessary
  - Vaccine development

- Operational Research
  - Better access of existing medicines including combination therapies
  - Novel and innovative ways to improve sanitation and access to clean water for washing, including inventive ideas for implementation of these strategies
  - Sustained and innovative vector control programmes in high risk areas
  - Synergise efforts with other helminth control programmes due to poly-parasitism
  - Acceptance of multi-factorial programmes for control and elimination of schistosomiasis
  - Health systems strengthening and pharmacovigilance

See Annex 1 for a brief update on Human African Trypanosomiasis (HAT)
3. Mobilizing Needs-Driven Innovation to Address Priorities for Neglected Diseases

Research innovation and support is largely driven by market interest. For diseases where a paying market exists, this accommodates an R&D framework that develops new medicines steadily. For neglected tropical diseases, this is not the case. However, the commitment and performance for these diseases has improved significantly since the 2004 Priority Medicines Report was published.

There has been a steady increase in projects involved in neglected tropical disease R&D, and also some amounts of financial support from the EU, various governments and philanthropists towards neglected tropical disease R&D projects. This has led to more engagement of public academic institutions, PDPs and some industry in neglected tropical disease R&D. Support for neglected tropical diseases still lies far behind diseases with a paying market, despite the millions dying or being disabled. Perhaps to increase investments into neglected tropical disease R&D, one needs another approach. Investments into R&D should be based both on economic and societal progress, defined under the term shared value. Companies such as the pharmaceutical, diagnostics and biotechnology industries that define markets through economic needs, need to avoid social harms (and thus take into account societal needs) and can bring down costs and increase opportunity into emerging economies. Many pharmaceutical and medical device companies are already embracing shared value, and are engaging in product development, advocating for affordability, ease of manufacturing and distribution, and are getting more involved in capacity strengthening programs. Neglected tropical disease product development needs more engagement of innovative biotechnologies, and pharmaceutical/diagnostic companies, (including those in emerging economies). PDPs and academic institutions (including integrated academic partnerships) are the source of many innovative inventions used for neglected tropical diseases, and rely currently on such companies to co-develop and market products for patients. If more companies embrace shared value, partnerships with PDPs and academic institutions towards neglected tropical diseases, with sustained financial support from the EU and other sources will greatly accelerate product development, operational research and alleviate disease burden. Ongoing negotiations on intellectual property, pricing of medicines and the incentives for innovation will all influence the setting of current and future R&D agendas. R&D effort should work closely with existing programmes and interventions, using the approach of preventative chemotherapy or intensified case management. Priority research agendas with clear milestones and roles for different stakeholders should be made for each of the 17 diseases, and for enabling technologies for adapting products and solutions to different circumstances of patients.

3.1 From a few diseases to a more comprehensive agenda. Identifying gaps in research issues that are priority to make a difference

The three examples described in Section 2 show how a needs-driven priority research agenda can be conceived and has identified the most pressing areas where resources and action is needed.
In leishmaniasis, having a PDP has elevated visceral leishmaniasis (VL) to one of the most “non-neglected” of the neglected tropical diseases. There is however still a dire need for medicines, diagnostics and organizational research. Here allocation of resources is driven by an R&D agenda for products that will be better than what is currently used. This could not have been done without the innovators that DNDi partners and co-develops solutions with (academia and private companies). In the second case, Buruli ulcer, there is no PDP active in this disease however, there has been more activity from academic institutions and integrated academic platform in the last few years (including one supported by the framework program). Accepting that no pharmaceutical company is going to make R&D for Buruli ulcer a priority (as the number of affected patients is very low and unable to pay), integrated academia-driven R&D projects should continue to be supported, and one can envision an academic-driven platform or PDP to emerge. Research agendas could use what is known from TB (caused by similar bacteria) and find solutions using repurposed products and technologies, and perhaps attract some investments from sources that support TB projects. In the last example, schistosomiasis, there is a PDP for developing a vaccine. An integrated academic platform (at the Imperial College, UK) that manages the Schistosomiasis Control Initiative (SCI) implements and monitors schistosomiasis control programs in various countries. There is a need for enabling technologies to adapt current products and solutions to these diseases (such as paediatric versions of effective medicines, better simpler closed-system diagnostics). In schistosomiasis, the engagement of local private sector involved in water and sanitation and the engagement of the local education system is vital for limiting transmission.

Visceral leishmaniasis, Buruli ulcer and schistosomiasis are only three examples of the many diseases that remain neglected within the current medical innovation framework. A continuous needs-identification process is needed, notably because some of these diseases only affect populations that have no access to decision makers or media attention, and thus do not benefit from organised patient advocacy groups or PDPs. For all of these diseases, the development of solutions and products start in innovators from academia, and are developed further by PDPs or delivered by Integrated Academic Platforms and include endemic countries. In Buruli ulcer, as in several neglected tropical diseases, having no PDP, no pharmaceutical company interest means that the challenge is placed on academic groups and partnerships to develop solutions, and priority setting and funding mechanisms may overlook these partners. Some involvement of pharmaceutical companies for R&D projects related to patent pools or for dual-market diseases exist (such as in dengue, where profit can be made). There are also innovations and technologies that never get translated to real products and solutions at all.

A needs assessment should involve both patients and health professionals in endemic countries and should include identifying the relevant therapeutic goal: primary or secondary prevention, alleviating a symptom, preventing relapse, diminishing mortality, etc. For example, in Chagas disease, there is still a debate as to what constitutes the appropriate therapeutic target. Chronic stage patients have chronic disorders such as cardiovascular complications, of which the link to parasite infections is not well understood. In Buruli ulcer, where available treatment is against the causative *Mycobacterium*, one cannot ignore treating the devastating ulcers and disfigurement itself. It is therefore not clear whether the one therapeutic strategy would be to develop a new drug that eliminates the causative organism, or whether in late stage disease, the presence of the organism is less important than treating...
the other symptoms. Multiple interventions may have to be developed if each disease is to be eradicated.

The next step is to consider the currently available tools in the field and to identify their limits according to the therapeutic goal. For example, even if in the long term the target would be to have every HAT patient cured at stage 1, given the difficulty of identifying patients at this stage, a more relevant initial target is to have a safe and easy-to-use treatment for stage 2 infection. This field reality is glaringly obvious to health care workers treating patients in affected areas, not to innovators in R&D laboratories. The therapeutic target should take into account the field conditions and appropriate technologies that can solve this hurdle.

Development of treatment tools should include means of diagnosis and prevention as well as curative treatment. Indeed, diagnostic tools are key elements in a coherent treatment strategy. Just as there is little rationale in testing patients for a disease without a coherent treatment strategy to follow, there is equally little benefit in having a drug without a satisfactory diagnostic strategy and case management system.

Innovation in drug and diagnostic development is best defined by public health needs, which means that innovation should be assessed in relation to the relevant public health goal and the current treatment and prevention options. An innovative treatment for neglected diseases, and arguably, for all diseases, should address the following criteria: it should be of pharmaceutical quality, efficacy and safety, and it should be available, affordable and easy to use, and with relevant diagnostic tools available (that are themselves sensitive, specific, easy to use and affordable).

Development of epidemiological tools, new medicines and diagnostics and operational tools are largely required in several of these diseases to reduce the burden. We outline some opportunities that could make a substantial difference to the burden of these diseases below.

### 3.2 Opportunities for a priority R&D agenda

In order to ensure solutions for neglected tropical diseases, priorities should be based on the public health need. Current performance of the development of solutions has been largely driven by the priorities of stakeholders and markets. Spending also depends on the short term achievability of each project. It is crucial to make the development of each solution (be it a therapeutic, diagnostic or vaccine) better than current pharmaceutical interventions, applicable to the situation of the patient living in affected countries and economically sustainable.

#### 3.2.1 What needs to be mobilized

To ensure adequate opportunities for neglected disease R&D, several areas have to be fortified. There must be adequate incentives to make R&D projects attractive, so as to engage appropriate innovators from PDPs, academia, biotechnology, and multinational pharmaceutical and diagnostic companies, including those in emerging economies and countries endemic for these diseases. Projects should address products and solutions to be developed to be better than existing interventions or complement existing interventions and
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actually reach the patient in a cost effective way. The setup and support of integrated platforms (such as PDPs, integrated academic platforms, etc) for research, development and the implementation of new medicines are needed. These platforms should be framed within a well-defined cooperation framework between developed countries and those endemic for these diseases if sustainability is to be achieved. These platforms should be able to create necessary therapeutics (products such as medicines, vaccines and diagnostics), technologies (to produce them in an affordable way) and transfer them to patients in countries.

Given that products developed for these diseases does not finish with regulatory approval as it requires validation in the actual countries affected, which is perhaps more variable than than for medicines for developed countries. Significant steps must be made to get health systems ready for some of these products. Of concern if the inability of most countries to conduct the pharmacovigilance activities required for new products.

Incentives for engaging innovators to perform R&D on neglected tropical diseases

Financial, social and training incentives will stimulate more engagement from industry, both large and small companies. Currently the EC framework program includes support for small and medium enterprises (SMEs) involved in partnerships for translatable research and product development projects. Matching in-kind contributions from SMEs, and preferring collaborative R&D projects between public and private partners, supporting training of skilled personnel in these companies are all encouraging to engage more companies. Organizations not usually involved in neglected tropical disease R&D can (and do) contribute as part of their Corporate Social Responsibility (CSR) and enjoy reputational benefits, while increasing their profile to global consumer markets. The current EC Framework program also supports a number of academic institutions and integrated academic platforms which develop basic epidemiological and research tools and technologies and also recently translational product development. Taken together, academic groups and SMEs are some of the main source of R&D for neglected tropical diseases, and these are sources that PDPs rely on as well. These product development activities managed by academic-academic consortia should continue to be supported. The acceptance of any final product depends on the health systems and patients in endemic countries, thus they have to be engaged early in R&D agenda setting for the development of products. One could envision several integrated academic PDPs emerging, especially for the diseases where no PDP exists. After the London Declaration, several pharmaceutical companies and PDPs pledged more focused investments towards neglected tropical disease R&D. Advocacy for these diseases and setting proper R&D agendas for these diseases is vital for engaging innovators.

Necessary integrated platforms

Through shared value, various innovators such as PDPs, academic integrated platforms and public-private partnerships all attempt to address the needs of each disease and situation of patients. Every needs-driven priority R&D effort (or project) must follow a “3T approach”; (a) a better or new Therapeutic approach (diagnostics, treatments and/or prophylactic vaccines), have (b) the Technology to produce it (in the correct, affordable and sustainable form) and have (c) a way to – Transfer- to the users (the patients). Engagement of partners and innovators, financial support must follow this “3T” approach when committing to an R&D effort. Projects will have to address the technical solution with a business model (a cost-
effective way to deliver a solution), a solution vector (that will eventually deliver a solution using the business model) and an expected market landing (pre-arrangements, commercial and practical to ensure swift adoption and an early demand) (see Figure 6.9.2).

**Figure 6.9.2: shows what is necessary for each needs-driven priority R&D project to become viable and successful**

Some examples of the 3T approach are shown in Appendix 6.9.4. While many projects within PDPs follow this principle, several partnerships and integrated academic platforms also have been employing this approach in their programs. Enabling technology projects (not specific to any one neglected tropical disease, but across several diseases) can also follow the 3T approach.

### 3.2.2 How can this be mobilized

To mobilize opportunities towards a priority R&D agenda for neglected tropical diseases, there must be a global call to action. There must be more commitment by innovators, product developers; there must be more steady monitoring of the global landscape of R&D efforts (research/epidemiology, product development and operational research) and monitoring of this commitment into performance. We also need to fortify the partnerships, Integrated academic platforms and PDPs that perform well through adequate funding.

**A call to action. Enhanced commitment**

There are many effective medicines for several of the neglected tropical diseases. Since the cost of these medicines is an issue, patients rely on drug donation programs to gain access to these medicines. Disease elimination programs also need large communities to be mass treated (as in the case of trachoma and schistosomiasis). Donation programs in the past years have been largely led by industry, private foundations and funders that manage and mobilize these medicines, with the WHO guiding many programs (see Appendix 6.9.5). This is an area where industry plays a strongest role in the global fight against neglected tropical diseases, and should continue to do so. One such program is run by an integrated academic platform, SCI, while there are several product control partnership and the WHO who manage the rest of the donation programs. In early 2012, the London Declaration of Neglected Tropical Diseases showed 13 multinational pharmaceutical companies pledging their support to commit, coordinate and collaborate towards the control or elimination of at
least 10 of these neglected tropical diseases by 2020, affecting a total of 1.4 billion people).\textsuperscript{48} The declaration also included non-governmental organizations, product development partnerships and public institutions pledging their support. Countries endemic for these diseases and the international community were also urged to provide necessary resources to remove the primary risk factors for these diseases, poverty and exposure. They were urged to contribute by ensuring “access to clean water and basic sanitation, improving living conditions, vector control, health education, and strengthening health systems in endemic areas”. Many neglected tropical diseases can be eliminated both in the short term and in the long run. For example, it is due to enhanced commitments of expertise and money that will shortly lead to the global eradication of guinea-worm. Appendix 4 gives a table of the medicines donation programs active (from pharmaceutical companies). A tool to measure and monitor the commitments and performance of industry (and others who pledged support) and hold those who pledged accountable is being developed. Those who pledged support must show within a reasonable timeframe the efforts they have made in contributing to these goals and this will develop into a benchmark towards real progress in the eradication of these diseases.

There have been an increased number of academia-driven consortia (integrated academic platforms) towards product development, especially in diseases where there is no PDP. Engagement of several biotechnology companies and companies in developing countries (as early co-inventors) is necessary. Existing partnerships and platforms are adding more diseases to their priority agendas (as evidenced by DNDi adding more neglected tropical diseases to their agenda and the recent proposal by EDCTP to start supporting neglected tropical disease clinical trials). Pharmaceutical companies and SMEs using the WIPO Re:Search tool for example have opened their libraries to share compounds, know-how and expertise for neglected tropical disease R&D.

**Monitoring performance on neglected tropical disease priority agendas**

There is an excellent tool for measuring the portfolio of projects and analyzing these available from the BIO Ventures Global Health Global Health Primer\textsuperscript{33} Their work has been recognized and detailed in Section 1. To measuring the commitment of the pharmaceutical industry, a monitoring tool already exists. The Access to Medicines Index is a biennial report that measures multinational pharmaceutical companies’ policies, practices and performance in contributing to access to medicine (including neglected tropical diseases) globally.\textsuperscript{6} It compares performance of companies with each other and ranks them based on relevant metrics and provides a final chart of the top 20 pharmaceutical companies comparing how they contribute to access to medicine. This is a useful framework for transparent reporting about access to medicines performance, which will help companies inform their stakeholders and investors and also enables the comparison of companies among others. One could engage more companies if lessons learnt and best practices could be shared among these companies, and also engage stakeholders in emerging economies (e.g. generics companies) using this tool. A similar monitor for measuring the performance of PDPs and integrated academic platforms is needed. A monitor of projects supported by the European Commission Framework Program (and other supporters of neglected tropical disease R&D) would be useful to monitor R&D milestones and connect existing research priorities to programmatic interventions, while ensuring adequately prioritized agendas for the future.

Almost every multinational pharmaceutical company has dedicated part of its business strategy to improving access to medicine. While much of this sentiment is because of
philanthropy and corporate image setting, a large part is actually to reach a wider market share, as most products developed by pharmaceutical companies is needed also by patients in low and middle income countries, the challenge is in keeping these medicines affordable and accessible to all patients regardless of their geographical location. Commitment to spending is monitored by the G-FINDER index¹⁰⁹, where governments, philanthropists and other donors play an important position in supporting research priorities across the globe, and influence the rate at which products can be developed.

### 3.2.3 Existing mechanisms and tools

Following the ‘3T’ approach, we outline opportunities for priority R&D using existing mechanisms.

**Therapeutics:**

For almost all of the neglected tropical diseases, one needs better cheaper medicines, vaccines and diagnostics. The different stages of a typical pharmaceutical R&D pipeline is shown in Appendix 6, where in neglected diseases, the **most important gap** is the transition from fundamental research or identified field need to a candidate drug or vaccine in the predevelopment stage. It is crucial to confirm the validity of the chosen development candidate, and if needed, to optimise it (i.e. assuring absence of toxicity, choosing a formulation, assuring ease of production, etc). Unless there is strong commercial interest, few candidates are taken through this phase.

While some big pharmaceutical companies have set up specialized centers for tropical diseases (Novartis, GSK, Astra Zeneca), only some research applicable to neglected tropical diseases is performed at these centres. While this has the potential to change in the coming years due to the increased commitment and increased opportunities with neglected tropical diseases emerging in the (paying) developed world (such as leishmaniasis and dengue), most R&D is done through collaborative efforts with PDPs (usually in drug discovery programs with pharmaceutical compounds tested in neglected tropical disease assays managed by the PDPs), and in smaller capacity through lesser-known, direct R&D with academic groups and SMEs in bilateral or multilateral consortia in disease areas (where there are no PDPs or through integrated academic platforms).³³ PDPs have the biggest ever portfolio of neglected tropical disease products ever, some of which are in late stage clinical trials. Apart from performing R&D, PDPs have extended their work into advocacy and capacity strengthening. There are many new PDPs established in the last decade and new ones are emerging. Some existing PDPs are taking on newer neglected tropical diseases. PDPs are clearly playing an increasing role in neglected tropical disease research¹⁰⁹,¹¹⁰, claiming a bulk of the funding and spending, and playing a role where pharmaceutical industry had traditionally not been active in the past. In the Global Health primer, it is obvious that there are a vast number of other R&D projects that are involved in neglected tropical disease R&D, though these may not have one organized voice, and do not qualify for the typically PDP-oriented funds. EDCTP, when neglected tropical diseases are in the agenda, will play an important role in parts of the clinical trial process for some of these diseases. In September 2012, a non-profit organization called TransCelerate based on 10 pharmaceutical companies was set up to help speed up R&D of new and adapted medicines, by sharing appropriate resources, data and standardizing clinical trial processes. The focus will be on identifying and resolving common issues that delay R&D.¹¹¹ The disease focus has
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not been outlined for this non-profit, and will hopefully include a mandate for neglected tropical diseases. TransCelerate also could offer a unique platform for enabling technologies to affect current and future neglected tropical disease R&D, using knowledge sharing in dosage, bioavailability and pharmacokinetics and pharmacodynamics, areas of hidden neglect within several of these diseases. It could also be a platform to connect complementary R&D activities with drug donation programs offered by these pharmaceutical companies. All of these initiatives will need to also partner with scientists and doctors in endemic countries to create and advance capability and capacity.

Technologies

This is an area widely underestimated in priority R&D agendas. Scanning for technologies not usually used for neglected tropical diseases and engaging innovators, manufacturers of the final products is vital. Biotechnology companies and academic researchers have been developing new technologies at a rapid rate. Although these have been predominantly used in applications for 1st world diseases, they can be “rediscovered” to look for adaptability and affordability in neglected tropical disease product development. New ways of culture, analytical systems, platform technologies and types of delivery methods and innovative therapeutics are emerging. With genome sequences available for more causative organisms (such as *M. ulcerans*, the causative agent of Buruli ulcer) there is a wealth of resources available for creating the next new neglected tropical disease medicine or diagnostic, and producing this in an affordable, sustainable way. Technologies can be used to adapt medicines, vaccines and diagnostics to tropical conditions, while retaining sensitivity, specificity, affordability, and ease of use is important. Adaptive R&D projects in heat stabilizing both medicines and diagnostic reagents, developing closed systems diagnostics, studying (fixed dose) combinatorial drug chemistries for polypills are available and should be tied into neglected tropical disease R&D efforts.

In technology platforms for diagnostics, the most adaptable to developing countries is lateral flow or dipstick type diagnostic technologies (closed system diagnostics requiring simple handling of infected samples), and these can be produced cheaply and correctly. Recently with the commitment of a biotechnology company, Eiken, the proprietary LAMP technology reputed to be highly sensitive and specific, yet requiring simple (albeit multiple) handling is being tested for a range of neglected tropical diseases. Nonetheless a closed extraction and amplification systems should be explored.

Transfer

Health improvement programs and capacity strengthening are vital for the success of any developed solution. Early engagement of manufacturers and distributors, procurers and users, and adapted pricing may be necessary. GeneXpert for TB is an example that uses concessional pricing to roll out quickly into the developing world. The Global Health monitor shows some projects with early engagement of local manufacturers. Adapted packaging, training and education, ensuring multiple suppliers (of reagents or components of each solution) helps to reduce cost and increase emerging opportunities.
3.2.4 Adequate Funding for Neglected Tropical Diseases

Neglected tropical diseases have for too many years been ignored by the private and public R&D sectors. The G-FINDER index was set up to monitor annual funding of several tropical diseases, including Malaria, HIV/AIDS and TB. The global spending on tropical diseases is about US$ 3 billion in R&D of new products in 2011 (which is US$ 443 million increased investment since 2007). Of these, nearly 80% is for malaria, HIV/AIDS and TB. While product R&D was heavily focussed on innovative medicines, vaccines and diagnostics and enabling technologies (for adaptive R&D) received only 0.4% of R&D investments.

Continuous R&D for neglected diseases will mean committing substantial amounts of money. It is a widely contested and controversial topic to deduce the true cost of developing a new pharmaceutical product. Apart from the actual cost of out-of-pocket expenses to develop a drug, capital costs due to the long time it takes to develop, register and market a drug also plays a role. It is approximated that it could be anywhere between 55 million and 1.2 billion, as evidenced by several studies.

It has widely been perceived that the revenues generated from drug sales are to be spent on R&D. Recent reports estimate up to 26% of gross profits for some pharmaceutical companies spent back in R&D, though there are certainly a majority of companies that spend lesser amounts.

It is difficult to determine the exact cost of developing a drug when including the contribution from public-funded research, tax credits, inter-company licensing agreements, etc. Moreover, it is well known that there is significant attrition, meaning that the risk of failure is high, especially in earlier stages of the development process. Moreover, the cost of developing a medicine is not the same for all indications. While industry’s figure may be inflated and may not be relevant at all for the development of a drug for neglected tropical diseases (due to the more needs-based decision-making process and the pooling of resources to cut costs), it remains clear that pharmaceutical R&D is a lengthy and costly process. Not-for-profit drug development initiatives such as the Global Alliance for Tuberculosis Drug Development (GATB) or Medicus Mundi Switzerland and the DNDi project a cost of 35-40 million US dollars to develop a new drug (not including the enormous cost of failure).

A minimum response to the 10/90 gap (where currently less than 10% of global R&D spending is relevant to the health of 90% of the world’s population) will require new funding of the order of several hundreds of millions of euros over a number of years. This is itself only a part of the solution, The Commission on Macroeconomics and Health determined that an additional global yearly investment of US$ 3 billion per year is needed to reach an appropriate level of health R&D to meet the needs of the poor.

In the London Declaration, more than US$ 785 million was pledged to accelerate R&D of new and adapted medicines and expand existing drug distribution was pledged. This amount will at least see significant steps in the elimination of trachoma and some of the helminthiasis.

In the European Union, the European Commission contributed 22% of government investments and 15% of total global investments. 76% of which went to malaria, HIV/AIDS and TB, and most of the money going towards PDPs and EDCTP. This has led to 43 new...
medicines, vaccines and diagnostics registered to tackle neglected diseases and poverty related disease (including malaria, HIV/AIDS and TB).\textsuperscript{20} It is important to note that the main source for products developed by PDPs and EDCTP include academic institutions, Pharmaceutical companies and some private SMEs, who may not have received much of this support themselves. Looking at the landscape developing, one could consider that funding will be also reserved for integrated academic platforms and public-private partnerships (as well as PDPs), knowing especially that for several of the neglected tropical diseases, there are no PDPs and no advocates.

Given the current EU budget for neglected diseases it is clear that a serious effort needs to be sustained if one hopes to have an impact. Furthermore, the current EC-research funding for neglected diseases is structured mainly through the Framework Programmes, where neglected infectious diseases (which are mostly the neglected tropical diseases, with diarrhoeal diseases additionally in the list). In the FP6 program, research projects were mostly supported two or three years with budgets of around 1-2 million euros, and the FP7 program awarded larger amounts of around 3 up to 10 million euros of support.\textsuperscript{120} In the past years the FP6 and 7 programs have focused more and more on translational research, and such a mechanism will hopefully continue. It is important for any such mechanism to keep track of the achieved milestones of each of these projects, and plan for the implementation of any appropriate results, products and solutions.

Moreover, the EU focuses on basic research, and through the European Developing countries Clinical Trials Platform (EDCTP) on phase II and III clinical trials (so far only for HIV/AIDS, malaria and tuberculosis). There is more to be done in EU support for translational neglected tropical disease research, to take the results of basic research through the tedious, costly and time-consuming steps of preclinical research and the initial clinical safety studies (phase I) and link successful product development into existing programmatic interventions.

The Innovative Medicines Initiative (IMI) supports precompetitive collaborations, with scope related directly to the research priorities of pharmaceutical companies.\textsuperscript{121} The majority of the program supports diseases relevant European public health, and out of 30 of such projects, only two projects, accounting for 7.5% of the total IMI budget have poverty-related relevance, and not at all in neglected tropical diseases. This worrying trend of having a market-driven agenda will hamper the already starved for funding pipeline of neglected tropical disease product development. If we take into account the pharmaceutical commitments in the London Declaration and the global need to embrace shared value, an neglected tropical disease mandate must become available in the IMI scheme. It is of great concern to advocates of neglected tropical diseases that IMI have and may in the future overlook these devastating diseases.

With the upcoming Horizon 2020 funding scheme, one trusts that there will be continued stream of support for R&D priorities for neglected tropical diseases.

There are currently some substantial sources of investment, the National Institutes of Health (NIH) through the TRIND program and the private charity, the Bill and Melinda Gates Foundation, and the Wellcome trust that are starting to respond to this problem. Governments such as the UK DFID are also responding to this issue. Recently governments have been investing in neglected tropical disease R&D, mostly through PDPs, leaving product development from public collaborations, integrated academic platforms and public-
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private collaborations in diseases where no PDP exists with limited support. With the current EU budget deficit, one expects member state government support for neglected tropical disease R&D and innovation to also be slashed.

It is clear that money per se is not the limiting factor - rather it is the priority allocation of money that needs to be reassessed. Clearly, when the political will to respond is present, research can be accelerated - for example, a diagnostic test for SARS, deemed a serious threat to the world economy, was developed in an unprecedented three months.\(^\text{122}\)

3.2.5 Involving the private and public sector: capacity building for R&D into neglected diseases

The current pharmaceutical R&D framework has been left by governments in the hands of the private sector, which is not enough to meet the medical need of neglected tropical diseases. The balance of shared value across public and private people and organizations where economic interests and social needs need to drive the priority setting.

The limitations of the market-driven R&D framework

During the few last years, the global community has become more aware of the dramatic health needs in developing countries. The debate about the implication of WTO/TRIPS agreements and patents on drug affordability for the poorest has drawn attention to several key issues regarding access to essential care on the one hand, and stimulation of drug innovation on the other.\(^\text{123}\) At the global level, these two aims should be complementary: we need new solutions (medicines, diagnostics, vaccines), and we want these solutions to reach the patients who need them. In practice, these two aims are potentially contradictory. For instance, when drug innovation is dependent on private investment and is patent-protected – giving a temporary market monopoly to the patent holder – medicines may be marketed at such a high price that only a fraction of patients in need can have access. But, in such a market-driven framework, mandatory very low prices for new medicines would be a strong disincentive for private investment and thus for drug innovation. For prices to be lowered, shared value must be generated. Innovative strategies engaging multinational, local, public and private stakeholders must be encouraged. Means such as reconceiving (emerging) markets, refining productivity, supply chains and manufacturing and adaptive sales and distribution and enabling local cluster development all make opportunity increase and costs decrease in the long term.\(^\text{105}\)

Most public decision makers in industrialised countries still expect new medicines to come from the pharmaceutical industry, an expectation too often arrived at without sufficient analysis of the efficacy and cost of this choice. This expectation implicitly shifts the responsibility for public interest missions to the private sector, which lacks the (financial) incentives to fulfil this role, and seems to be unwilling to accept this responsibility.

A crucial role for public research

While a clear commitment exists within the public research community to work on neglected diseases, as can be seen from the large number of related publications, for instance in the area of trypanosomiasis and leishmaniasis\(^\text{124}\), this research mainly focuses on basic research and epidemiology. Because of the way public sector research is organised, financed and
assessed, there are not enough monitors to determine how much translational projects come from the public sector that directly cause an impact to the burden of neglected tropical diseases. There is clearly a continued focus on “upstream” research has resulted in less than expected research capacity and expertise for pre-clinical R&D phases in the public sector. The exceptions are the few integrated academic platforms (for example the SCI or BuruliVax consortium) who with limited support, engage in disease control strategies and product development. Whether this is because of the lack of interest in even PDPs for these diseases of increased social responsibility, this has led to a stronger role for public organizations in neglected tropical disease priority R&D. A concerted effort to build more centralised pre-clinical research capacities in pharmaceutical sciences in the public sector should be considered, using some of these integrated academic platforms already present.

Furthermore:

- Incentives for public sector researchers need to be adjusted to ensure that their work provides health benefits. Focus needs to shift from publishing or patenting as the end goal of research, to designing and implementation of new effective technologies for patients. Incentives should include for example valuing pharmaceutical development projects, or applied research.
- In parallel, established scientists should be encouraged to publish in open-access websites and in specialist journals, when appropriate, and in this way set an example to show that sharing knowledge freely, especially in the field of neglected diseases, is more important than being caught up in the current evaluation system.
- Career advancement in the public sector should not be dependent on the classical system of number of citations and impact factors of journals, where researchers in the less fashionable and less populated area of neglected diseases are at a disadvantage. Rather, funding agencies should be sensitized about the importance of applied research into neglected diseases and access to funding facilitated.
- Public sector commitment to priority setting and funding within public and private partnerships is crucial. The public sector should be encouraged to provide technical support and external expertise for protocol assistance, legal issues in drug development, and information access.
- Projects emerging from any public sector or public collaborations should ensure that the core principles of the business model, market landing and solution vector are thought of, to ensure achievable solutions.

A role for the private sector

Finally, the role of the private sector needs to be redefined. The pharmaceutical, biotechnology and diagnostic industry (including those in emerging markets) has a responsibility to contribute to the search for essential health tools, even though it may be less profitable economically. Specific incentives (and obligations) could be designed to more actively involve industry, but care should be taken that these remain cost-effective in terms of public investment. Possible measures to be explored include:

- Tax-deductible, in-kind contributions to publicly-driven R&D, for example by doing toxicology studies, pharmaco-kinetic studies, bioequivalence studies (as suggested by the Global Alliance for TB Drug Development);
- Higher tax breaks for in-kind contribution to publicly-driven research rather than industry-driven research to encourage business sector support for essential public health R&D;
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- A tax-deductible requirement for industry to open their compound libraries and knowhow and include data and content.
- A non-working clause on compounds: if a promising compound has not been developed by a drug company after a given period, then it should be put on the market for licensing to a group willing to pursue it, with appropriate remuneration for the originator company in case of profit. Open access to information on all clinical trials remains a priority (as announced by in GSK)\textsuperscript{126}

3.3 Towards a system ensuring commitment and performance to solutions to neglected diseases

3.3.1 A needs-driven priority R&D agenda

As detailed in sections I-II, such an agenda should encompass the following elements:

- For each disease, a definition of the optimal preventative and therapeutic objectives, based on patient needs, the expectations and skill of health professionals and on achievability of the solution; the ultimate goal of obtaining safe, effective, easy-to-use and affordable solutions must guide decision-making;
- An analysis of creative R&D opportunities based on the current state of the art in medical research (engaging multinational and emerging Pharmaceutical and Diagnostic companies, biotechnology innovators, PDPs (where there is one for a disease) and the public sector, and a definition of the innovation expected (medicine, vaccines and diagnostics or enabling technologies) to respond to the identified needs;
- The setting up of incentives/obligations for both the public and private sectors in terms of responding to the priority R&D agenda.

3.3.2 Public responsibility

Addressing the unmet health needs of the world’s population, including those of people suffering from neglected diseases, is a public responsibility. Governments from the North and the South must be more proactive, i.e.

- Allocate sufficient funds
- Design specific policies to strengthen R&D into medicines for neglected diseases. These policies should balance incentives and obligations for the public and the private sector.

It is essential that governments equip themselves with the means to ensure that theoretical advances into priority health needs are translated into practical applications, with the goal being real therapeutic advances for patients. This requires a substantial shift in the current power balance in the setting of priorities, and a change in the current mind-set. Policy-makers must accept the challenge of setting up a paradigm shift, and develop a new and more justifiable health care policy. A not-for-profit model of essential drug development should be explored, at least to address those needs falling outside of market interests. Health and medicine must be treated as strategic sectors requiring large and sustainable investments, as occurs today for weapons and defence, space exploration, the telecommunications industry, etc.

In setting the public research agenda, scientists can be encouraged through specific programmes, sustainable financing and appropriate career incentives to focus on neglected
diseases and particularly on translational research to move basic research results into medical applications. Governments can also target the private sector by a mixture of incentives and obligations. One possibility is a tax analogous to the eco tax, where industries are required to develop their own system of waste elimination or pay a tax subsidising the public waste management system. Initiating these changes requires strong political will and commitment, but is a crucial aspect of the collective responsibility to address neglected diseases.

The pursuit of needs-driven health R&D to generate global public good, in particular in areas such as neglected diseases where the market fails, is an example of “enlightened” self interest for all members of the international community. Examples are the recent emergence of West Nile virus in North America and the growing incidence of primary malaria, tuberculosis and multidrug resistant-TB in the West. Changing global populations, local conflicts and the ongoing economic imbalance mean that diseases that today affect countries far from Europe may soon be found closer to home. Pursuing health R&D as a global public good is not charity, but an endeavour from which all nations stand to benefit through shared value.

3.3.3 Upgrading the international effort to treat neglected diseases

A number of international initiatives have been set up to address the issue of neglected diseases but this can only been seen as a start. The oldest one, the WHO/UNDP/WorldBank/UNESCO programme on Tropical Disease Research (TDR), was created in 1975, in response to a plea from developing countries for an international commitment to their health problems. Although TDR has been instrumental in bringing to the market several new tools for tropical diseases, the increasingly huge needs of neglected patients demonstrate that a much stronger response is needed.

Over the past few years, international awareness has grown around the unacceptable inequities in access to essential medicines, including the lack of adequate treatments for certain diseases. Several types of initiatives have been set up to start addressing some aspects of this vast problem. For instance the Global Fund against AIDS, Tuberculosis and Malaria (GATM) exclusively focuses on access to existing medicines for these three diseases (there is only a limited “end fund” for Neglected Tropical Diseases who are garnering private support in developing countries for operational neglected tropical disease programs); others are donation programmes for a specific medicine (for instance for the helminthiasis and trachoma). A few are public private partnerships (PPP) focused on neglected tropical diseases (See chapter 8.3 of this report), especially those focusing on pharmaceutical or vaccine or diagnostics development, such as the Drugs for Neglected Disease Initiative (DNDi), the Sabin Vaccine Institute (SVI), the Foundation for Innovative New Diagnostics (FIND) and the Institute for One World Health (IOWH) but they are generally engaging pharmaceutical companies and academics and their sustainability is not secured.

Among the major challenges for all these initiatives is access to (proprietary) compound libraries and technologies (from biotechnology, pharmaceutical companies and public innovators), to medicinal chemistry expertise, and to sustainable long term financing that is compatible with the lengthy, complex and costly drug development process.
3.3.4 More than Malaria, HIV/AIDS and TB

Today, malaria, HIV/AIDS and TB receive much media attention, and increasingly also more research attention. However, these diseases present only a part of the global disease burden contributed by neglected diseases. While the ongoing mobilization for these diseases is more than justified, and should be strengthened, it should not create a false sense of having dealt with the problem. The lack of knowledge about other neglected diseases is both a cause and a consequence of their neglect, and serves to entrench a hierarchy of “neglected” and “more neglected” diseases. Unfortunately, the recent attention of wealthy countries of the north, including Europe, to “poverty-related” global disease has been limited to the “big three”, in an exclusive rather than inclusive way. Several of the activities developed to increase R&D efforts into malaria, HIV/AIDS, and TB may also benefit the most neglected diseases. For instance, access to compound libraries or high throughput screening capacity might benefit discovery projects for all neglected diseases, and setting up a joint preclinical research facility would bridge a gap encountered for all non-commercial drug development projects— if clinical trials capacity is built in Eastern Africa for a malaria study (eg by EDCTP or a pharmaceutical company), a subsequent leishmaniasis trial may be run by the same clinical research group, provided disease pattern overlap geographically.

3.3.5 A moral challenge for Europe

Currently, neglected diseases are not a major focus of interest for the EU. Apart from the Framework Program, most of the available funding is for the EDCTP which so far focuses on phase II-III clinical trials for malaria, HIV/AIDS and TB. Recently there is interest for EDCTP to expand into more neglected infectious diseases, although the choice of the disease(s) is pending. This is a very important and laudable commitment, but presupposes that a mechanism exists to develop the medicines to be tested. Such a mechanism is glaringly lacking. To obtain one clinical candidate starting from a characterised lead compound may easily take two to four years and require several millions of euros. Without specific public funding to finance this type of research, and more importantly, a broadly accessible technology platform or facility equipped to do the necessary chemistry, toxicology and lead optimisation research for non-profit drug candidates, there is little hope that new candidate medicines for neglected diseases will reach clinical phases. If the intermediate steps in the development pipeline are not being filled, to go from discovery to clinical studies (gaps 1-2 in Appendix 5), there will be no medicines to test in the clinical trials platform.

There is a moral and ethical imperative to seriously address neglected diseases in developing countries, especially as the EU has existing relations with many of these countries through the ACP agreements.\(^{131}\) The EU-ACP Joint Parliamentary Assembly Resolution on poverty-related diseases and reproductive health in ACP states acknowledges Europe’s responsibility for and commitment to addressing these diseases.\(^{132}\) The Resolution states that “poverty diseases and reproductive health must continue to be tackled through joint efforts from the international community”, while pointing out that “there is an uneven political commitment among donor countries”. The resolution explicitly calls for European action for neglected diseases: “[The Assembly] Calls on the European Commission to include the most neglected diseases, such as sleeping sickness, Chagas’ disease and leishmaniasis, among its priorities and to ensure that effective, appropriate, easy-to-use medicines are developed and placed on the market in the developing countries at an affordable price”.

6.9-52
Politicians will need the courage to strongly promote a paradigm shift in the way that medicines are developed, in order to address the needs of both the European and the global community. It is not enough to focus only on the needs of Europe, wealthy countries can no longer escape the need to stabilize and develop the global economy, and need to redress the imbalance of resources and access to wealth. Furthermore, diseases and health needs are globalizing, and ignoring these problems is more than just shortsightedness - it may also prove to be a gross strategic error.

4. Conclusion

Developing countries carry an enormous burden of (neglected) disease, yet lack the infrastructure and the human and financial resources to develop new medicines for these neglected diseases. This capacity does exist in Europe and other developed countries. Through public sector support for basic and in particular appropriate translational research, product development and operational research through innovative mechanisms such as public-private-partnerships (that act to bridge the gap between industry and the public sector) or public-responsibility oriented initiatives, relatively small investments could have a dramatic impact. Innovative R&D aimed at radically new products and solutions for neglected tropical diseases, or adaptive R&D designed to make better use of existing medicines, vaccines, diagnostics, and technology platforms, should be supported.

Specific recommendations:

- **Mobilise and sustain adequate funding** for neglected diseases. To ensure minimal impact, committed funding of several hundreds of million euros over a number of years must be freed to support the execution of a needs-based priority R&D agenda for neglected diseases;
- **Encourage translatable research** using the “3T” approach “Therapeutics, Technology and Transfer” to transform the results of basic research into useful technologies for medical applications, adapted to the needs of neglected patients and connected to programmatic interventions;
- **Set up adequate incentives for collaborative research**, based on shared value including appropriate training, funding, and specific career incentives based on a reassessment of the way merit is evaluated in public research;
- **Mobilise the pharmaceutical/diagnostics industry by a mix of incentives and obligations** to contribute to the development of needed medical interventions and commit to donate or provide sustained access to medical interventions, **based on shared value**;
- **Engage the innovators** from emerging economies, biotechnology, along with pharmaceutical/diagnostic companies, SMEs, PDPs and academic institutions through shared (societal and economic) value;
- **Monitor the performance** of PDPs, integrated academic platforms and pharmaceutical companies (including those in emerging economies) for public accountability for resources spent;
Expanding the activities of PDPs and integrated academic platforms to include product development for medicines, vaccines, diagnostics, drug resistance platforms and control strategies for these diseases along with strengthening health systems of affected countries. Support integrated academic platforms, where product development and operational research is directly done by academic innovators for neglected diseases;

Strongly encourage the expansion of the activities of the European and Developing Countries Clinical Trial Partnership (EDCTP) to include several of the most neglected diseases as well as other phases of clinical development (phase I, phase IV), (and connect this to the efforts of the pharmaceutical industry-driven TransCelerate);

Create a center for preclinical research to bridge the continual gap of developing medicines and vaccines into clinical candidates for neglected diseases. This is a pool of resources available for preclinical research which should complement the activities of the EDCTP;

Investigate the possibility for centralized technology platforms for adaptive R&D (adapting current and new medicines, vaccines and diagnostics to tropical countries, fixed dose combination, pediatric formulations, etc). This includes assessing medicines availability, stability, pricing dosing, using appropriate platforms and databases. (This should complement activities of existing organizations and should be a mandate for the newly formed non-profit TransCelerate).

Given the enormity of the needs of patients, with literally millions of people dying due to the lack of safe, effective and easy-to-use drugs, real innovation lies in utilizing current knowledge and ongoing technological progress to design, promote and implement treatment options for those in need. Innovative medical research should refer not to the means but to the ends, and the primary criterion should be the impact of R&D efforts on the life and health of neglected patients. The role of the European Community is crucial in this respect, and policy makers are encouraged to follow this global view of their mandate and responsibility.

References


Update on 2004 Background Paper, BP 6.9 Neglected Tropical Diseases


34 BVGH, Developing new drugs and vaccines for neglected diseases of the poor: The product developer landscape. 2012.


44 MSF, HIV/ visceral leishmaniasis co-infection in east africa. 2011.


Update on 2004 Background Paper, BP 6.9 Neglected Tropical Diseases


85 WHO, Provisional guidance on the role of specific antibiotics in the management of Mycobacterium ulcerans disease (Buruli ulcer). 2004: Geneva, Switzerland.


The END Fund. [cited; Available from: endfund.org.

Resolution ACP-EU 3640/04/fin of the ACP-EU Joint Parliamentary Assembly.


TransCelerate Biopharma Inc. http://transceleratebiopharmainc.com
Annexes

Annex 6.9.1: An update on the priority agenda for Human African Trypanosomiasis (HAT)

HAT was covered extensively in the background chapter for neglected tropical diseases in the Priority Medicines Report of the WHO published in 2004. We give a short update on the status of HAT priority setting. There have been significant steps taken recently in medicine development, which has strengthened both clinical case management, however the mortality remains immense.

Human African trypanosomiasis (HAT, also known as sleeping sickness) is a life-threatening disease caused by parasites transmitted by infected tsetse flies. There are two forms of HAT—caused by Trypanosoma brucei gambiense and T. b. rhodesiense, with different geographical distribution. Gambiense HAT is primarily a human disease in West and Central Africa while rhodesiense parasites infect both humans and animals and thus have a large animal reservoir in East Africa.

Patients presenting with early stage disease have non-specific symptoms such as fever and weakness. Without diagnosis and treatment, they go on to develop stage 2 HAT, when the parasite crosses the blood brain barrier. This occurs weeks to years after initial infection. At this point the patient develops neurological and psychiatric symptoms such as confusion, lethargy and convulsions.

The priority for HAT research for the past 10 years was to find a safe and effective therapy for stage II disease to replace the toxic drug melarsoprol. Simplified stage 2 treatment combining seven days eflornithine (two infusions/day) and 10 days oral nifurtimox proved successful for gambiense HAT and this combination therapy was added to the WHO list of essential medicines in 2009 [10, 40]. The WHO secured a donation of nifurtimox through an agreement with Bayer to match the donation of eflornithine by Sanofi-Aventis and created a kit to facilitate the distribution and administration of this cumbersome therapy.

Unfortunately to treat the second stage of rhodesiense HAT, melarsoprol remains the only drug available. Figure A shows the current status of available tools for HAT (Source: Julien Potet, MSF).

Current priorities:

- Today there is clearly a need for the development of an easy to administer, safe and oral drug for stage II HAT. Recently one oral compound, a nitroimidazole called fezinidazole, started phase II/III clinical trials with the HAT platform for clinical trials run by DNDi. This compound was dropped from drug development by Hoechst in the 1980’s and recently rediscovered as a potential new treatment for HAT and is also interesting for the leishmaniasis (see section 2.1).

- New drugs are in development including the oxaboroles which have progressed through HAT lead optimization to pre-clinical phase I trials which are currently in recruitment.

- To identify new drugs the use of medium- to high-throughput screening assays to model crossing of the blood-brain-barrier, and allow screening and lead optimisation based on the capacity to cross the blood-brain-barrier are currently being used.

- In addition to new treatments, sensitive and easy-to-use diagnostic tests are also essential for the control of HAT. New markers need to be identified to accurately detect HAT in blood, or preferably even in saliva or urine, including stage determination (but without invasive lumbar puncture). Two prototype rapid
screening tests are currently under evaluation, and fluorescent microscopy is being investigated.\textsuperscript{33} 

- Today, there are no surrogate markers to assess disease progression or cure in HAT. Analysis of the cerebrospinal fluid (CSF) collected via lumbar puncture to detect the presence of parasites and/or measure the white blood cell count is the only method for stage determination and treatment efficacy. An accurate and preferably non-invasive tool to \textbf{measure treatment efficacy} is essential.

Figure A:
Products available for HAT. A model is shown here to show the tools available and their efficacy and adaptedness to health systems in resource-limited settings.

Safe, Effective, Accurate

Adapted to health systems in resource limited settings

[Diagram showing various tools and their efficacy]

Diagnostics must be affordable, user friendly, rapid, robust, Equipment free and deliverable to those who need them, and medicines must be affordable, short course, oral, with no cold chain, with minimal monitoring and for outpatient use.


Appendices

Appendix 6.9.1:

(a) The 17 Neglected Tropical Diseases (Neglected Tropical Diseases) are as follows:

Chagas disease (American trypanosomiasis)
Fascioliasis (Distomatosis)
Sleeping sickness (Human African Trypanosomiasis)
Leishmaniasis (all forms)
Lymphatic filariasis (elephantiasis)
Oncocercosis (River blindness, Robles' disease)
Schistosomiasis (Bilharzia, Snail fever)
Soil-transmitted helminths - *Ascaris lumbricoides*
Soil-transmitted helminths - *Trichuris trichiura*
Soil-transmitted helminths - hookworm
Trachoma (Granular conjunctivitis, Egyptian ophthalmia)
Buruli ulcer
Cysticercosis / Taeniasis
Dracunculiasis (guinea-worm disease)
Leprosy (Hansen disease)
Dengue / severe dengue
Echinococcosis (Hydatid disease)
Rabies
Yaws
(b) Prevalence of neglected tropical diseases (logarithmic scale). Bubble size represents DALYs of the different diseases.\textsuperscript{1,2,137} For Dracunculiasis, Buruli ulcer, leprosy and cysticercosis, reliable data on population at risk are unavailable.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence/millions</th>
<th>DALYs/000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buruli ulcer</td>
<td>0.05</td>
<td>616</td>
</tr>
<tr>
<td>Cysticercosis / Taeniasis</td>
<td>50</td>
<td>503</td>
</tr>
<tr>
<td>Dracunculiasis (Guinea-worm disease)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Leprosy (Hansen’s disease)</td>
<td>0.4</td>
<td>6</td>
</tr>
</tbody>
</table>

Update on 2004 Background Paper, BP 6.9 Neglected Tropical Diseases

Appendix 6.9.2.

Table on the current product development landscape (from BIO Ventures Global health Accessed Oct 2012). Number of active R&D projects in different stages of product development for each disease is shown below. R&D activities for basic research and operational research is unavailable.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drugs</th>
<th>Vaccines</th>
<th>Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Discovery</td>
<td>Preclinical</td>
<td>Clinical</td>
</tr>
<tr>
<td>Chagas disease</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Fascioliasis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Human African Trypanosomiasis</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Leishmaniasis (all forms)</td>
<td>8</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Lymphatic Filariasis</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Onchocercosis</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>STH-Trichuris trichiura</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>STH-Helminths-hookworm</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Trachoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Buruli ulcer</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dracunculiasis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leprosy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pernique</td>
<td>8</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
Appendix 6.9.3:

Products available for VL in South Asia. A model is shown here to show the tools available and their efficacy and adaptedness to health systems in resource-limited settings.

(Source: Julien Potet, Access Campaign, Médecins Sans Frontières).

Diagnostics must be affordable, user friendly, rapid, robust, equipment free and deliverable to those who need them, and medicines must be affordable, short course, oral, with no cold chain, with minimal monitoring and for outpatient use. The graph below shows the situation of tools available in South Asia only. The situation in other settings, including East Africa is very different, as tools have different levels of efficacy depending upon geographical regions.

Safe, Effective, Accurate

Adapted to health systems in resource limited settings
Appendix 6.9.4:

Table showing the 3T approach, which all needs-driven priority R&D in neglected tropical diseases should follow.

<table>
<thead>
<tr>
<th>Platform</th>
<th>Therapeutics</th>
<th>Technologies</th>
<th>Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priorities (based on)</td>
<td>Unmet medical needs</td>
<td>Resolving main hurdles to delivery</td>
<td>Improving local access and ability to access health</td>
</tr>
<tr>
<td>Examples</td>
<td>Diagnostics for detection</td>
<td>Heat stability for drugs and vaccines, Combination diagnostics, drugs and vaccines, closed system diagnostics</td>
<td>Local infrastructure, Economic and financial stimuli (health improvement programs)</td>
</tr>
<tr>
<td>Basic criteria</td>
<td>Safe, effective, cost effective, affordable.</td>
<td>Effective, Cost effective, affecting a wide range of products</td>
<td>Ensuring self sufficiency and sustainable access to health</td>
</tr>
</tbody>
</table>
**Appendix 6.9.5**: Donation programs of medicines for neglected tropical diseases by pharmaceutical companies (adapted from the Gates Foundation\(^{138}\) and WHO)

<table>
<thead>
<tr>
<th>Donated by</th>
<th>Product</th>
<th>Indication</th>
<th>Donated through</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK</td>
<td>Albendazole</td>
<td>Lymphatic filariasis and Soil-transmitted helminths</td>
<td>WHO</td>
</tr>
<tr>
<td>Gilead</td>
<td>AmBisome</td>
<td>Visceral Leishmaniasis</td>
<td>WHO</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Azithromycin</td>
<td>Trachoma</td>
<td>International Trachoma Initiative</td>
</tr>
<tr>
<td>Eisai</td>
<td>Diethylcarbamazine (DEC)</td>
<td>Lymphatic Filariasis</td>
<td>WHO</td>
</tr>
<tr>
<td>Sanofi-Aventis</td>
<td>Eflorenithine</td>
<td>Human African Trypanosomiasis</td>
<td>WHO</td>
</tr>
<tr>
<td>Merck and Co</td>
<td>Ivermectin</td>
<td>Lymphatic Filariasis and Oncocercosis</td>
<td>Mectizan Donation Program</td>
</tr>
<tr>
<td>Novartis</td>
<td>Multidrug therapy (rifampicin, clofazamine and dapsone) and single-dapsone</td>
<td>Leprosy</td>
<td>WHO</td>
</tr>
<tr>
<td>Johnson and Johnson</td>
<td>Mebendazole</td>
<td>Soil-transmitted helminths</td>
<td>several programs</td>
</tr>
<tr>
<td>Sanofi Aventis</td>
<td>Melarsoprol</td>
<td>Human African Trypanosomiasis</td>
<td>WHO</td>
</tr>
<tr>
<td>Bayer</td>
<td>Nifurtimox</td>
<td>Human African Trypanosomiasis and Chagas disease</td>
<td>WHO</td>
</tr>
<tr>
<td>Sanofi Aventis</td>
<td>Pentamidine</td>
<td>Human African Trypanosomiasis</td>
<td>WHO</td>
</tr>
<tr>
<td>Merck KGaA</td>
<td>Praziquantel</td>
<td>Schistosomiasis</td>
<td>WHO</td>
</tr>
<tr>
<td>Bayer</td>
<td>Suramin</td>
<td>Human African Trypanosomiasis</td>
<td>WHO</td>
</tr>
<tr>
<td>Novartis</td>
<td>Triclabendazole</td>
<td>Fascioliasis</td>
<td>WHO</td>
</tr>
</tbody>
</table>

Appendix 6.9.6: Bridging the gaps in the R&D pipeline: translational research.

The different stages of a typical pharmaceutical R&D pipeline. A schematic view of a typical development pathway, from identification of need in the field or fundamental research, to the development of a drug. This long and costly process is typically quoted as taking 10-12 years. However, a large part of the process can be made more efficient (in terms of cost and time) by identifying the existing gaps and targeting efforts to the necessary area (“making better use of existing knowledge and tools”). In neglected tropical diseases, the most important gap that could make a big difference to innovation and the global burden is the transition from fundamental research or identified field need to a candidate drug or vaccine in the predevelopment stage (gap 1). The pre-development phase is scientifically less exciting for some, but is crucial to confirm the validity of the chosen development candidate, and if needed, to optimise it (i.e. assuring absence of toxicity, choosing a formulation, assuring ease of production, etc). Unless there is strong commercial interest, few candidates are taken through this phase (gap 2). Even clinically developed drugs sometimes do not reach their target population (gap 3), because they are too expensive, or too difficult to use in the field, or because production is not secured.
Background Paper 6.10
Malaria

By Shuichi Suzuki, MPH, BSPharm
February 2013
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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>AMFm</td>
<td>Affordable Medicine Facility malaria</td>
</tr>
<tr>
<td>CC</td>
<td>National Institutes of Health Clinical Center</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CISID</td>
<td>centralized information system for infectious diseases</td>
</tr>
<tr>
<td>DFID</td>
<td>The United Kingdom Department for International Development</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DTP</td>
<td>diphtheria, tetanus, pertussis</td>
</tr>
<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>EDCTP</td>
<td>European and Developing Countries Clinical Trials Partnership</td>
</tr>
<tr>
<td>EIR</td>
<td>entomological inoculation rate</td>
</tr>
<tr>
<td>EPI</td>
<td>expanded program on immunization</td>
</tr>
<tr>
<td>FIND</td>
<td>Foundation for Innovative New Diagnostics</td>
</tr>
<tr>
<td>G6PD</td>
<td>glucose-6-phosphate dehydrogenase</td>
</tr>
<tr>
<td>Global Fund (GF)</td>
<td>The Global Fund to fight AIDS, Tuberculosis and Malaria</td>
</tr>
<tr>
<td>GMAP</td>
<td>global malaria action plan</td>
</tr>
<tr>
<td>GMP</td>
<td>Global Malaria Programme, WHO</td>
</tr>
<tr>
<td>GPARC</td>
<td>Global Plan for Artemisinin Resistance Containment</td>
</tr>
<tr>
<td>GPIRIM</td>
<td>Global Plan for Insecticide Resistance Management in malaria vectors</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline Biologicals</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HRP2</td>
<td>histidine-rich protein 2</td>
</tr>
<tr>
<td>IM</td>
<td>intramuscular</td>
</tr>
<tr>
<td>IPTi</td>
<td>intermittent preventive treatment in infants</td>
</tr>
<tr>
<td>IPTp</td>
<td>intermittent preventive treatment in pregnancy</td>
</tr>
<tr>
<td>IRS</td>
<td>indoor residual spraying</td>
</tr>
<tr>
<td>ITN</td>
<td>insecticide-treated mosquito net</td>
</tr>
<tr>
<td>IUGR</td>
<td>intrauterine growth retardation</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>IVCC</td>
<td>Innovative Vector Control Consortium</td>
</tr>
<tr>
<td>IVM</td>
<td>integrated vector management</td>
</tr>
<tr>
<td>kdr</td>
<td>knock-down resistance</td>
</tr>
<tr>
<td>LBW</td>
<td>low birth weight</td>
</tr>
<tr>
<td>LLIN</td>
<td>long-lasting insecticidal net</td>
</tr>
<tr>
<td>MDA</td>
<td>mass drug administration</td>
</tr>
<tr>
<td>MMV</td>
<td>Medicines for Malaria Venture</td>
</tr>
<tr>
<td>MVI</td>
<td>Malaria Vaccine Initiative</td>
</tr>
<tr>
<td>NGO</td>
<td>nongovernmental organization</td>
</tr>
<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
</tr>
<tr>
<td>NICHD</td>
<td>Eunice Kennedy Shriver National Institute of Child Health and Human Development</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NMCP</td>
<td>national malaria control programme</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PAR</td>
<td>population attributable risk</td>
</tr>
</tbody>
</table>
PATH Programme for Appropriate Technology in Health
PCR polymerase chain reaction
PCW positive control wells
PDP product development partnership
PDS panel detection score
PMI The US President’s Malaria Initiative
RBM Roll Back Malaria
RDT rapid diagnostic test
RR relative risk
SMC seasonal malaria chemoprevention
TB tuberculosis
TI transmission intensity
USAID United States Agency for International Development
USAMRMC U.S. Army Medical Research and Materiel Command
WHO World Health Organization
WHOPES WHO Pesticide Evaluation Scheme
WRAIR Walter Reed Army Institute of Research

Abbreviations of antimalarial medicines

(d) days on treatment course
ACT artemisinin-based combination therapy
AL artemether plus lumefantrine combination
AM artemether
AQ amodiaquine
ART artemisinin
AS artesunate
AS+AQ artesunate plus amodiaquine combination
AS+MQ artesunate plus mefloquine combination
AS+SP artesunate plus sulfadoxine-pyrimethamine combination
CL clindamycin
CQ chloroquine
DOXY doxycycline
DHA dihydroartemisinin
DHA+PPQ dihydroartemisinin plus piperaquine combination
MQ mefloquine
PG proguanil
PPQ piperaquine
PQ primaquine
QN quinine
SP sulfadoxine-pyrimethamine
Executive Summary

In 2010, malaria accounted for an estimated 660,000 deaths (between 610,000 and 971,000) and 219 million cases (between 154 million and 289 million) – down from an estimated 800,000 deaths and 230 million cases in the early 2000s. Overall, the malaria mortality rate has fallen by 26% since 2000. Almost 80% of cases and 90% of deaths occur in sub-Saharan Africa, and most of these deaths (86%) are in children under the age of five. The most vulnerable populations are children aged under five and pregnant women. The substantial reductions in the malaria burden were gained in countries where integrated control programmes were successful, but there are still many areas where the malaria burden is increasing. In Europe, while the number of imported malaria cases is decreasing, indigenous cases are still being reported in countries where malaria was officially eradicated long ago. In 2008, the Global Malaria Action Plan was launched by the Roll Back Malaria Partnership (RBM), addressing the control, elimination and future eradication of the disease.

The control strategy for malaria involves efforts to control the mosquito vector and provide preventive therapies and/or effective curative treatment. The success of vector control approaches in recent years is due to the global mass campaigns to distribute long-lasting insecticidal nets and carry out indoor residual household spraying. As a result, the percentage of households in sub-Saharan Africa owning at least one insecticide-treated bed net has increased from 3% in 2000 to over 50% in 2011. The intervention of intermittent preventive treatment for pregnant women with sulfadoxine-pyramethamine and seasonal malaria chemoprevention for young children has also been increasingly operated globally. No new vaccine has been developed since 2004, but the latest Phase III clinical trial of the malaria vaccine candidate RTS,S/AS01 showed modest protection against clinical and severe malaria among infants.

Since 2004, there have been major improvements in the diagnosis and treatment of malaria. In the WHO African Region, the percentage of suspected cases in public health facilities who received a diagnostic test increased from about 20% in 2005 to 47% in 2011. At the same time, there has also been a major improvement in the quality of the rapid diagnostic tests (RDTs) procured. The number of treatment courses of artemisinin-based combination therapies (ACTs) procured by the public sector has increased dramatically from 11 million treatments in 2005 to 278 million in 2011. The enormous increase in procurement and distribution of diagnostics, antimalarials and vector control tools are financially supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria, the (United States) President’s Malaria Initiative, and the Affordable Medicines Facility – malaria (AMFm).

The major challenge to malaria control is the growth of resistance to both insecticides and treatment. The mosquito vector is becoming resistant to insecticides, especially pyrethroids, and cases of parasite resistance to artemisinin have emerged in the Cambodia-Thailand border region. To counter this, there is a need for medicines and insecticides with new modes of action, as well as effective monitoring systems.

By 1999, the pharmaceutical industry had largely disengaged from innovative drug R&D in tropical diseases due to the lack of market incentives. As a result, the malaria drugs pipeline was virtually empty. However, since the establishment of the Medicines for Malaria Venture (MMV) in 1999, the situation has improved. Using the product development partnership
(PDP) model to discover and develop new antimalarials, MMV has created the largest-ever portfolio of malaria drugs, including completely new classes of medicines. Vaccine research has also accelerated in recent decades, including a promising candidate in Phase III trials managed by a public-private partnership, the PATH Malaria Vaccine Initiative. New active ingredients for insecticides and their new formulation have been developed by the Innovative Vector Control Consortium, and many companies have been involved in the R&D of new diagnostic tools. The European Commission has also been supporting R&D for basic science, antimalarials, vaccines, diagnostics, and vector control tools under the Sixth and Seventh Framework Programmes.

International funding for malaria control has increased dramatically over the past decade, from around US$ 100 million in 2004 to a peak of US$ 2.3 billion in 2011, while global funding for malaria R&D has also been increasing gradually. However, it is estimated that US$ 5.1 billion is required every year to achieve global coverage with malaria interventions. The R&D of new pharmaceuticals is a long process and requires long-term support. Priority needs for research in 2014 to 2020 include: resistance to pyrethroid insecticides and ACTs; malaria vaccine development; and improvements in the sensitivity of RDTs in the detection of low-density infections.

What is new since 2004

- Global malaria incidences and deaths are declining.
- The Global Malaria Action Plan (GMAP) was launched in 2008 to target malaria elimination/eradication.
- There have been intensive vector control activities, introduction of chemoprevention, better access to ACTs, and the advent of qualified RDTs.
- Resistance to insecticides and antimalarials has been growing.
- Several new antimalarials have become available through Product Development Partnerships.
- There have been a growing number of candidates in the medicine, vaccine, diagnostic and insecticide portfolios.
- Global funding for malaria control and malaria R&D has increased since 2004, but it has now been levelling off for the last few years.
1. Introduction

1.1 Background

In 2004, a report Priority Medicines for Europe and the World was written by Warren Kaplan and Richard Laing and published by the World Health Organization (WHO). A chapter (6.10) and background paper on malaria were written by Lise Riopel for this 2004 publication. This background paper is an update of the 2004 paper published at http://archives.who.int/prioritymeds/report/background/malaria.doc.

Malaria is a vector-borne infectious disease, caused by protozoa genus Plasmodium. There are five types of human malarial parasites, *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. The most deadly strain is *P. falciparum*, which is widely spread globally, and *P. vivax*, which is less pathogenic but relapsing.\(^1\)\(^2\) It is estimated that 98% cases of malaria in Africa in 2010 were due to *P. falciparum*, while nearly 50% were due to *P. vivax* in South-East Asia.\(^2\)\(^3\) Malaria is exclusively transmitted by the anopheline mosquito.\(^1\)

One of the major characteristics of malaria is biological diversity during the life cycle of the parasite (Figure 6.10.1).\(^4\) When the mosquito carrying malaria bites a human, parasites in the form of sporozoites are injected into the blood and invade liver cells where they multiply over a few weeks.\(^4\) In the liver the sporozoites become merozoites. The merozoites exit the liver into the bloodstream, start to infect erythrocytes and asexually replicate, before invading more red blood cells.\(^4\) This multiplication process causes clinical signs in infected people such as changes in regional blood flow and vascular endothelium, systemic complications due to anemia, fever and other flu-like symptoms due to the release of cytokines.\(^5\) Some merozoites stay in the red blood cells, developing into sexual forms, called gametocytes.\(^4\) These circulate in the bloodstream, until a mosquito bites the human and ingests the infected red blood cells, and then these gametocytes replicate in the mosquito to form sporozoites.\(^4\) The three forms of malaria parasites are biologically diverse, resulting in different responses to diagnostic tools, vaccines and pharmaceuticals.\(^4\) This is one of the reasons for the difficulties in malarial case management.

Each *Plasmodium* strain has different biological and clinical features.\(^3\)\(^5\) In *P. vivax*, gametocytes appear in the blood earlier than those of *P. falciparum*. They emerge almost simultaneously with merozoites before the clinical threshold of a blood infection is reached, while the gametocytes of *P. falciparum* are developed at least 10 days after the clinical threshold. This difference has important consequences in the pattern of selection of resistance and control strategies. Since *P. vivax* gametocytes are transmitted to mosquitoes during the pre-symptomatic period before the initiation of drug treatment, *P. vivax* will be less vulnerable to transmission control by effective case management due to pharmaceutical therapy.\(^6\) In addition, *P. vivax* and *P. ovale* exhibit clinical relapses weeks to months after the initial infection due to dormant liver forms called hypnozoites, which represent unique stages of malaria for both those strains. Additional therapy targeting hypnozoites is required to treat *P. vivax* and *P. ovale* completely.\(^7\)
Malaria can be a preventable and curable disease, but eradication programs have failed in the developing countries and control measures to stop the progression of this human and economic burden are also not reaching their set goals yet. However, in the last few decades, there have been improvements in the political profile of this disease, resulting in increased funding for malaria prevention and treatment interventions. Antimalarial drugs with selective actions on the different phase of the life cycle have proved effective in the treatment and prophylaxis of the disease. However, widespread resistance has made many of these products less effective. Newer effective drugs such artemisinin-based combination therapies (ACTs) are now recommended as first line treatment by WHO, but are still unaffordable for many of the people and governments of low income countries. To address the cost of ACTs, many organizations, including The Global Fund and the President’s Malaria Initiative (PMI), are assisting in the purchase of ACTs and procurement and distribution systems. The Affordable Medicines Facility – malaria (AMFm) is a financing mechanism to increase access to ACTs by reducing their price to the equivalence of old antimalarials.
In 2008, the Global Malaria Action Plan (GMAP) was launched by the Roll Back Malaria Partnership (RBM), addressing malaria control, elimination as well as eradication in the future. The targets are to decrease the number of preventable deaths worldwide to near zero, to reduce global incidence by 75% since 2000 and eliminate malaria in at least 8 - 10 countries which are in the elimination stages currently. The malaria burden has been decreasing due to increased coverage rate of insecticide-treated mosquitonets (ITNs) and indoor residual spraying (IRS), as well as increased accessibility of rapid diagnostic tests (RDTs) and effective treatment with ACTs. However, more needs to be done to combat growing resistant strains against ITNs, IRSs and antimalarials, as well as to increase the coverage and access to preventive and curative methods all over the world. Progress in developing a vaccine has occurred, but a fully effective vaccine may still be years away.

1.2 Malaria burden in endemic areas

Malaria is a major global health threat, with an estimated 3.1 billion people at risk of malaria in 2011, mostly in sub-Saharan Africa, where 80% of cases and 90% of deaths occurred. In the early 2000s, the estimated number of cases and deaths increased to 230 million and 800 000 respectively. Since then, both new cases and deaths have decreased to 220 million and 660 000 in 2010 (Table 6.10.1). Reduction in incidence rate and mortality rate amongst the risk population is more dramatic, with a 17% and 26% decrease since 2000. However, accurate statistics on malaria are still difficult to collect and report in Africa, where the disease is recognized to be a major obstacle to human and economic development. That is mainly due to the enormity of the disease problem, the weakness of health information systems, and the fact that the treatment of most malaria cases, as well as many deaths, occur outside the formal health system. Therefore, figures published are rough estimates and that the precise number of fatal and morbid events will never be known. However, the existing statistics reflects the trends that can be used for planning proposals.

Most individuals in malaria endemic areas exhibit an explicit clinical response at some stages in their lives, often manifesting febrile events. Chronic, sub-clinical infections may render an individual anemic or predisposed to under-nutrition, conditions that will influence the severity and outcome of other infections. Asymptomatic infection of the placenta of pregnant women significantly reduces the weight of their newborn children. Patients who survive a severe disease may suffer from debilitating sequelae such as spasticity, epilepsy or retinopathy. Behavioral disturbances and cognitive impairment are now also recognized as major consequences of malaria (Figure 6.10.2). Also, a recent study showed detailed information about the risk of malaria among children, in accordance with malaria seasonality and transmission intensity (Figure 6.10.3). It demonstrates that the malaria risk among children under the age of five is clearly higher than in the older age groups. In fact, 86% of those who die are children under the age of five.
Table 6.10.1: Trend in estimated number of malaria cases and deaths, 2000-2010

<table>
<thead>
<tr>
<th>Region</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>% reduction since 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>1750</td>
<td>1790</td>
<td>1830</td>
<td>1880</td>
<td>1900</td>
<td>1910</td>
<td>1890</td>
<td>1870</td>
<td>1820</td>
<td>1790</td>
<td>1740</td>
<td>1%</td>
</tr>
<tr>
<td>Americas</td>
<td>2100</td>
<td>2000</td>
<td>1800</td>
<td>1800</td>
<td>1700</td>
<td>1900</td>
<td>1600</td>
<td>1300</td>
<td>1000</td>
<td>1100</td>
<td>1100</td>
<td>56%</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>1000</td>
<td>9000</td>
<td>9000</td>
<td>1100</td>
<td>8000</td>
<td>8000</td>
<td>8000</td>
<td>10000</td>
<td>11000</td>
<td>11000</td>
<td>10000</td>
<td>0%</td>
</tr>
<tr>
<td>Europe</td>
<td>38</td>
<td>28</td>
<td>24</td>
<td>19</td>
<td>11</td>
<td>6</td>
<td>3.1</td>
<td>1.4</td>
<td>0.7</td>
<td>0.3</td>
<td>0.2</td>
<td>99%</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>33000</td>
<td>33000</td>
<td>30000</td>
<td>30000</td>
<td>32000</td>
<td>33000</td>
<td>29000</td>
<td>28000</td>
<td>29000</td>
<td>30000</td>
<td>28000</td>
<td>15%</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>3000</td>
<td>2600</td>
<td>2300</td>
<td>2600</td>
<td>2900</td>
<td>2400</td>
<td>2600</td>
<td>2100</td>
<td>1800</td>
<td>2000</td>
<td>2000</td>
<td>33%</td>
</tr>
<tr>
<td>World</td>
<td>223000</td>
<td>225000</td>
<td>226000</td>
<td>233000</td>
<td>235000</td>
<td>237000</td>
<td>231000</td>
<td>229000</td>
<td>225000</td>
<td>222000</td>
<td>216000</td>
<td>3%</td>
</tr>
<tr>
<td>Lower bound</td>
<td>170000</td>
<td>172000</td>
<td>173000</td>
<td>175000</td>
<td>177000</td>
<td>181000</td>
<td>172000</td>
<td>169000</td>
<td>165000</td>
<td>163000</td>
<td>149000</td>
<td>13%</td>
</tr>
<tr>
<td>Upper bound</td>
<td>297000</td>
<td>301000</td>
<td>304000</td>
<td>310000</td>
<td>316000</td>
<td>319000</td>
<td>310000</td>
<td>304000</td>
<td>298000</td>
<td>292000</td>
<td>274000</td>
<td>13%</td>
</tr>
</tbody>
</table>

The data comes from 106 malaria endemic countries and territories grouped by WHO regions.13

Figure 6.10.2: The direct, indirect and consequential public health effects of P. falciparum malaria in Africa

Figure 6.10.3: Age-patterns of P. falciparum malaria in Sub-Saharan Africa.

Source: Modified from the figure in Carneiro, I et al. (2010). Age-Patterns of Malaria Vary with Severity, Transmission Intensity and Seasonality in Sub-Saharan Africa: A Systematic Review and Pooled Analysis.

Percentage of uncomplicated clinical malaria, hospital admissions with malaria and malaria-diagnosed deaths per month of age in children under ten years of age, by transmission intensity (TI) and seasonality of malaria transmission.

In addition to children, pregnant women are also vulnerable to malaria due to changes in the immune system of pregnant women. The parasite invasion may cause various adverse consequences for both the mother and the newborn; maternal anemia, placental accumulation of parasites, low birth weight (LBW) from prematurity and intrauterine growth retardation (IUGR), fetal parasite exposure and congenital infection and infant mortality. Steketee et al. in 2001 summarized the malaria population attributable risk (PAR) accounting for both prevalence of the risk factors in the population and the magnitude of the associated risk in African populations between 1985 and 2000. Each PAR from the study is as follows; anemia (2-15%), LBW (8-14%), Pre-term LBW (8-36%), IUGR LBW (13-70%) and infant mortality (3-8%).

Malaria burdens and trends are diverse by region, for example in African countries, cases and deaths are exclusively due to P. falciparum. The majority of populations in Central Africa, West Africa, East Africa and some countries in Southern Africa live in high risk areas. However, the Southern African countries, such as Botswana, Namibia, South Africa, Swaziland and Zimbabwe, are in the control phase of malaria. Cape Verde is in the pre-elimination phase, and Algeria is in the elimination phase. Table 6.10.1 above shows 13%
reduction in the number of deaths in Africa as a whole, but many countries still have an increased number of cases and deaths. For example in West Africa (Figure 6.10.4), Sao Tome and Principe, Cape Verde and Senegal showed significant reductions since 2000, whereas several countries increased the number of deaths by over 50%. The WHO report World Malaria Report 2011 concluded that the substantial reductions of a malarial burden were gained on islands and in small countries along with intensive control programs. Well-developed surveillance systems are also important to detect changes in disease burdens. Also, expansion of diagnostic tools, such as rapid diagnostic tools (RDTs), reveals more precise information about the epidemiology of malaria, resulting in a reduction of presumptive cases of malaria in patients with fever episodes.

Figure 6.10.4: Percentage decrease in admissions and deaths in West Africa, 2000–2010

Note: Upward bars mean decrease, and downward bars mean increase in number

As for the malaria burden outside of Africa, smaller countries showed a clear reduction of malaria burden, while the malaria burden is still high in large endemic areas, such as Africa. One of the concerns outside of Africa is that the disease is caused by various species, such as *P. falciparum* and *P. vivax*. Just over two billion people in Central Asia live at risk of *P. vivax*, which accounts for 82% of the global population at risk of *P. vivax*. As mentioned previously, *P. vivax* is characterized by its unique biological features including dormant liver forms called hypnozoites, which result in clinical relapses weeks to months after the initial infection. It was also demonstrated from the past eradication approaches that *P. vivax* frequently remains longer in the environment than *P. falciparum* does, so that control measures for *P. falciparum* are not adequate against *P. vivax*.

There is also an increasing awareness of an emerging fifth malaria strain, *Plasmodium knowlesi*. The host is usually macaque monkeys and the first human infection was detected in 1965. A human-mosquito-human transmission has only been reported at the experimental level so far. To date, up to a thousand cases have been reported in South-East Asian region, mostly in Malaysia. Several imported cases have also been reported.
Clinically, *P. knowlesi* causes severe and sometimes fatal cases like *P. falciparum*, and selective RDTs for the strain do not exist.\(^{22}\)

### 1.3 Malaria burden in Europe

In European countries, malaria was virtually eradicated by intensive vector control measures in the period before 1970.\(^{27}\) But in the mid-1990s recrudescence of autochthonous malaria has been reported in many countries of the continent, reaching a total of 90 000 cases in 1995.\(^{27}\) In addition, around 10 000 cases of imported malaria were reported by the European Union in the early 2000s.\(^{27}\) However, the number of indigenous cases has been dramatically declining since the middle of 2000s (Annex 6.10.1).\(^{28}\) The number of autochthonous cases reported in 2010 was 182, less than 1% of the number of cases in 2000.\(^{28}\) In terms of eradication perspectives, Azerbaijan, Kyrgyzstan, Tajikistan, Turkey and Uzbekistan are now in the elimination stage.\(^2\) Georgia and Russian Federation are in the stage of prevention of reintroduction.\(^2\) Turkmenistan and Armenia are countries which were certified malaria-free within the last five years with no local transmission reported for over a decade.\(^2\) The number of deaths due to indigenous and imported malaria has also been declining in the last few decades (Annex 6.10.2).\(^{28}\)

Indigenous cases are still reported spontaneously.\(^{28}\) In Spain in 2010, a case of *P. vivax* was reported in a woman without a history of travel and no contact with people visiting malaria endemic areas.\(^{29}\) It was the first case since 1964, when malaria was officially eradicated in Spain. Also in Greece, several cases of *P. vivax* were reported in 2009, which were the first cases since 2000.\(^{30}\) Malaria was eliminated in Greece in 1974 and since then most cases have been imported by travelers, mainly from Africa and Asia.\(^{31}\) As a reason for the resurgence of autochthonous malaria, the impact of a climate change has been discussed\(^{32,33}\) as the malaria parasite cannot proliferate when the temperature is below 16 - 18 degree Celsius, depending on the species.\(^{32}\) In addition, mosquitoes are also influenced by the temperature, because they are cold-blooded.\(^{32}\)

Imported cases of malaria are of great concern in the European regions, because the majority of these cases are due to nationals traveling to endemic countries. Statistically, imported cases are decreasing steadily, with approximately 4 000 cases in 2011 (Figure 6.10.5, Annex 6.10.3)\(^{28}\) compared with a peak of 15 000 cases in 2000. More cases are reported in the summer holiday months (June – October), reflecting the increased number of travelers going to the malaria endemic countries during these periods (Figure 6.10.6).\(^{29}\) Cases due to the emerging malaria strain, *P. knowlesi*, were also reported in several countries, which were confirmed by PCR.\(^{25,26}\) There is a need to increase awareness and use of pre-travel counseling, especially to immigrants who visit friends and relatives in endemic areas.\(^{34,35}\) As malaria is rare in Europe, many doctors do not consider it as a possible diagnosis, and patients may be diagnosed late.\(^{36}\)
Figure 6.10.5: Imported malaria cases of France, UK and Northern Ireland, Germany and Spain 2000 – 2010

Source: Created from Centralized information system for infectious diseases (CISID). WHO/Europe, 2011.

Figure 6.10.6: Trend and number of reported confirmed malaria cases by month, in EU and EEA/EFTA countries, 2006–09

1.4 Summary

Epidemiological data shows that the malarial burden has been decreasing globally as well as in the European region. It is still necessary to increase access to effective malarial treatments, preventive methods and diagnostic tools to vulnerable populations, such as children and pregnant women. Further innovations in pharmaceuticals, diagnostics, insecticides and vaccines are essential to further reduce the malarial burden in the future.

2. Control Strategy

There has been substantial progress in both vector control and malaria case management in the last decade. Technical innovations, especially the development and deployment of rapid diagnostic tests (RDTs), have brought about a dramatic improvement in case management. In addition, global financial initiatives have increased access to preventive methods and treatment; the percentage of households owning at least one insecticide-treated mosquito net (ITN) in sub-Saharan Africa has increased from 3% in 2000 to 50% in 2012. The percentage protected by indoor residual spraying (IRS) increased from less than 5% in 2005 to 11% in 2011. The percentage of reported suspected cases receiving a diagnostic test has also increased from 67% globally in 2005 to 76% in 2010. This section covers current malaria control strategies and discusses their challenges as follows:

- Vector control
- Preventive therapies
- Diagnostic testing and treatment
- Financial approaches to malaria control
- Approaches toward malaria elimination and eradication

2.1 Vector control

In 2007, universal coverage of the population at risk of malaria with effective vector control was recommended by WHO, such as Long-Lasting Insecticidal Nets (LLINs), and Indoor Residual Spraying of insecticide (IRS). Previous to this recommendation ITNs were provided only to the high-risk populations, such as pregnant women and children under the age of five. In specific conditions, other methods such as larval control and environmental management to diminish the breeding sites of mosquitoes and reduce the mosquito population are also suggested in the context of Integrated Vector Management (IVM).

Bed nets impregnated with pyrethroid insecticides provide a chemical and physical barrier between mosquitoes and human beings, and have proven to be effective in vector control. In Africa, almost all ITNs distributed are LLINs. The number of ITNs delivered has dramatically increased from six million in 2004 to 145 million in 2010 in sub-Saharan Africa. However, the numbers distributed in 2011 and 2012 have decreased to 92 million and 66 million respectively from the 2010 peak. Mass campaigns were the most common strategy for distribution, and antenatal clinics were also widely used as a channel in the African regions. Free ITNs were distributed in 38 of 45 malaria endemic countries in Africa and a subsidy was available in 21 African countries. Simultaneously, the percentage of households owning at least one ITN in sub-Saharan Africa has increased from 3% in 2000 to 50% in 2011 (Figure 6.10.7). On average, 91% of people who have access to ITNs use them.

6.10-17
Sprayed insecticides are also an effective tool in vector control, by killing adult mosquitoes and preventing them from surviving for 12 to 14 days, which is the necessary time for malaria to transform into the infective stage inside of the mosquito. The proportion of populations at risk covered by IRS increased, especially from the middle of the 2000s in Africa (Figure 6.10.8). There are four classes of insecticides for IRS; pyrethroids, organochlorines, organophosphates and carbamates. In 2009, pyrethroids accounted for around 80% of IRS coverage in terms of spray area covered. The use of organochlorines, such as DDT, has been declining since 1970s, because of growing resistant strains in mosquitoes.

A serious threat to the current vector control is growing resistance to pyrethroids by the mosquito vector. In terms of safety, effectiveness and cost, pyrethroids are currently the best insecticides for public health use. They are the only class of insecticides for ITNs and are the most frequently used for IRS coverage. It is estimated that more than 55% of the vector control benefits would be lost, if pyrethroids lost their effects. Two types of resistance have been observed; knockdown resistance (kdr) which is a genetic resistance with a point mutation in sodium channels targeted by pyrethroids and DDT, and metabolic resistance, which is based on an increased level of enzyme systems to detoxify the insecticide. There are increasing reports of vectors resistant to pyrethroids, although increased reports are partly due to the increased monitoring. Currently, insecticide resistance has been found in about two thirds of malaria endemic countries. As an approach to insecticide resistance management, WHO recommendations include:

- rotations of insecticides, use of interventions in combination and mosaic spraying, and use of mixtures of insecticides,
- resistance monitoring and effective data management,
- development of new and innovative vector control tools.

Durability of ITNs is also a growing concern. Worn-out nets need to be replaced with the new ones to sustain the efficacy of malaria control. Many ITN distribution programs assumed that nets have a relatively uniform lifespan of about three years based on the WHO guideline in 2005. However in Togo, it was found that 30-40% of ITNs reduced their efficacy biologically or physically in 2009. Therefore, monitoring the performance of mosquito nets treated with insecticide is recommended in order to determine ITN durability and the rate of replacement in each local setting.

Furthermore, current vector control strategies with LLINs and IRSs are not sufficient to eradicate malaria. In the areas, especially where the entomologic inoculation rate (EIR) is high, even 100% coverage of an entire population with ITNs did not reduce the EIR to the threshold required for local elimination. Also, tools aren’t effective enough for all malaria species because their targets are mostly indoor feeding and/or resting female vectors. Allowing outdoor biting and resting species escape from these control measures.

In summary, research opportunities for vector control include the development of new long-lasting chemical products for ITNs and IRSs, monitoring and evaluation of current control strategies, and the development of persistent larvicides.

2.2 Preventive therapies

Malaria preventive therapy is the administration of effective antimalarials to an “at-risk” population regardless of their infectious status. Currently two types of preventive therapy are recommended by the WHO; intermittent preventive treatment for pregnant women with sulfadoxine-pyramethamine (SP-IPTp) and intermittent preventive treatment in infancy with SP (SP-IPTi). SP-IPTp entails the administration of at least two doses of SP during the second and third trimesters of pregnancy. By the end of 2011, 36 high-burden countries in sub-Saharan Africa and Papua New Guinea (PNG) have adopted SP-IPTp as a national policy. Roughly 50% of pregnant women who attended antenatal clinics received a second dose of IPTp in the 2010 survey. The reductions of malaria risk by the SP-IPTp are as follows; placental malaria (relative risk (RR), 0.48; 95% CI, 0.35-0.68), low birth weight (RR, 0.71; 95% CI, 0.55-0.92), and anemia (RR, 0.90; 95% CI, 0.81-0.99). It is also suggested that
SP-IPTp remains beneficial in a context with SP resistance, as measured with treatment failure rates (8%-39%) in children with symptomatic malaria at 14 days.\textsuperscript{3,51} In a study in Kenya in 1998, up to 2% of pregnant mothers reported adverse drug reactions, such as nausea, vomiting, rash, pruritus, and fatigue.\textsuperscript{52} United States prescribing information included boxed warnings about severe dermatological and blood disorders for SP.\textsuperscript{53}

Preventive therapy for infants, SP-IPTi, includes the co-administration of a full therapeutic course of SP with DTP vaccine (diphtheria, tetanus and pertussis), and measles immunization to infants, through the expanded program on immunization (EPI).\textsuperscript{54} This has been a recommendation from the WHO since 2009.\textsuperscript{3} The recommendation is aimed at countries with moderate to high malaria transmission, where the resistance to SP is not high.\textsuperscript{3,50} The protection due to SP-IPTi is as follows; clinical malaria (30.3%; 95% CI, 19.8%–39.4%), anemia (21.3%; 95% CI, 8.3%–32.5%), and hospital admissions associated with malaria parasitemia (38.1%; 95% CI, 12.5%–56.2%).\textsuperscript{54}

The WHO recommendation for IPTi was revised to seasonal malaria chemoprevention (SMC) in 2012.\textsuperscript{55} The new intervention is “the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malarial illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk.”\textsuperscript{55} A complete treatment course of amodiaquine plus sulfadoxine-pyrimethamine (AQ+SP) is given to children in areas with a high clinical attack rate of malaria where over 60% of clinical cases happen within a maximum season of four months.\textsuperscript{35,56} Expected benefits include preventing roughly 75% of all malaria episodes and approximately 75% of severe malaria episodes.\textsuperscript{55} This intervention has been demonstrated to be effective, cost-effective, safe, and feasible.\textsuperscript{55}

The USA Centers for Disease Control and Prevention (CDC) recommends to travelers to malaria endemic countries to take antimalarials for malaria prophylaxis.\textsuperscript{57} The recommended medicines are atovaquone/proguanil, or chloroquine, or doxycycline, or mefloquine, or primaquine, depending on the area of travel.

There are several concerns with intermittent preventive treatment, such as safety, scheduling, drug resistance, cost-effectiveness and susceptibility to malaria in the following year.\textsuperscript{58} Some studies suggest a slight increase in the incidence of clinical malaria among children during the malaria transmission season in the year following IPTc administration compared to children who had not received IPTc.\textsuperscript{59}

The arrival of effective malaria vaccines is another hope. The latest phase III clinical trial of the malaria vaccine candidate RTS,S/AS01 showed modest protection (a vaccine efficacy of about 30%) against clinical and severe malaria among infants six to 12 weeks of age, and approximately 50% reduction of episodes in children five to 17 months of age.\textsuperscript{60,61} Further research is necessary to boost up the potency of the vaccine candidate as well as to develop other potential malaria vaccines.

### 2.3 Diagnostic testing

Effective case management depends on prompt and accurate diagnosis, which is based on clinical suspicion and the detection of parasites in a blood specimen.\textsuperscript{37} Diagnosis with high sensitivity is essential in malaria endemic countries as it helps detect malaria in vulnerable
There have been dramatic changes in malaria diagnosis and treatment since 2004. The reported number of RDTs delivered by National Malaria Control Programmes (NMCPs) has increased greatly, from less than 200,000 in 2005 to 74 million in 2011, while the number of patients examined by microscopy is almost stable. As a result, the percentage of suspected cases in public health facilities who receive a diagnostic test has increased from about 20% to 47% in the African Region during the same period (Figure 6.10.9). The quality of the RDTs procured has also improved dramatically over time (Figure 6.10.10). Nearly 90% of RDTs procured in 2011 had panel detection scores (PDSs) of more than 75%, compared with only 23% in 2007. The PDS measures the performance of RDTs against samples of known parasite presence; WHO recommends procurement of RDTs with PDS greater than 50% scores against low parasite densities of *P. falciparum* in high endemic regions, and PDS greater than 75% scores for areas of low to moderate transmission.

Although more RDTs have been distributed recently, many patients still receive malaria treatment without confirmation by a parasitological test. In the African Region during 2006-2010, the number of ACTs treatment distributed by NMCPs was more than twice the total number of diagnostic tests (microscopy + RDTs) carried out in 2010. The introduction of RDTs can reduce expenditures on antimalarial drugs. In Senegal in 2009 after the introduction of RDTs, the majority of suspected cases were treated with ACTs after confirmation by RDTs. Before the introduction of RDTs in 2007, over 70% of suspected cases were treated with ACTs without diagnostic confirmation. As a result of RCTs, there was the reduction of ACT usage by 70%. Although the cost saving does not fully cover the cost of the diagnostic tests, overall, RDTs are more cost-effective than presumptive treatment, largely because patient outcomes for non-malarial febrile illness improve.

**Figure 6.10.9:** Percentage of suspected malaria cases attending public health facilities that received a diagnostic test, 2000–2011

![Figure 6.10.9](image-url)
The following is the diagnosis methodology and its characteristics.37,64

(a) Symptom-based (clinical) diagnosis37

Common signs and symptoms of malaria (fever, chills, headache and anorexia) are not specific to malaria. The use of detailed weighting and scoring systems may improve the accuracy of clinical diagnosis, but they still have low sensitivity and specificity.

(b) Light microscopy37

Microscopy provides quantification of malaria parasites and identification of the species. Quantified data is useful to assess the response to the therapy and to understand severity of parasite load in a severely ill patient. Sensitivity is generally high, depending on the quality of microscopy. This is one of the two adequate confirmatory methods in endemic areas. Operational costs are relatively low, especially in endemic areas. Technicians need to be trained, and their skill and experience make a major difference in sensitivity. In many settings, malaria patients are treated outside of the formal health care service, which makes microscopy less feasible.

(c) Rapid diagnostic tests (RDTs)37,64

Rapid diagnostic tests detect parasite-specific antigens in a finger-prick blood sample, such as histidine-rich protein 2 (HRP2), which may be specific for P. falciparum, or pan-specific or species-specific Plasmodium lactate dehydrogenase (pLDH) and pan-specific aldolase. Those antigens are detectable when malaria parasites are in the blood stage. Also, HRP2 can be detectable in immature gametocytes with two other antigens which are found in mature gametocytes. The HRP2 antigen persists for a few weeks after viable malaria parasites are eliminated from the blood, while pLDH and aldolase disappear within five to six days. The results of RDTs are available within two hours and a general health care worker can easily use the test without intensive training. Furthermore, this is one of the two adequate
confirmatory methods in endemic areas. However, RDTs cannot distinguish a new case and a treated patient. Additionally, sensitivity can be changeable, depending on the condition of procurement, transportation and storage of the test and sensitivity to other strains than *P. falciparum*.

The choice of RDTs varies according to the prevalence of malaria species. In sub-Saharan Africa and lowland Papua New Guinea (PNG), where *P. falciparum* is predominant, RDTs specific to *P. falciparum* are generally preferable. In Asia, the Americas and some parts of Africa, where several species are endemic, combination RDTs are required to detect all species and to distinguish *P. falciparum* from non-falciparum. Generally, sensitivity for detecting *P. ovale* and *P. malariae* is lower. In East Asia, Central Asia and South America, where *P. vivax* is mostly predominant, RDTs detecting non-falciparum species alone are appropriate.

The quality of RDTs was a growing concern as the access to RDTs expanded. In 2006, the WHO Special Programme for Research and Training in Tropical Diseases (TDR) and the Foundation for Innovative New Diagnostics (FIND) launched an evaluation programme to assess the comparative performance of commercially available malaria RDTs. The panel detection scores (PDSs) is one of the quality parameters which measure the performance of RDTs against samples of known parasite presence. Detailed information about the performance of RDTs is given on the WHO report “Malaria Rapid Diagnostic Test Performance Results of WHO product testing of malaria RDTs: Round 3 (2010-2011).” The success of this programme in improving the performance of RDTs is a notable achievement of the past decade.

(d) Immunodiagnosis (serology)  
This technique detects antibodies to the parasites in human blood. This technique is not effective for clinical diagnosis, because antibodies appear in the blood several days after infection and present after cure. It results in an inability to distinguish between current and past infections, and to detect malaria parasites in acute phases of patients. It may be useful for epidemiological surveys, but it is not sensitive or specific enough for case management.

(e) PCR (DNA detection)  
This method detects parasite DNA using PCR. It is very sensitive, and very useful to identify mixed infections and drug resistance. However, it is generally not suitable for large-scale diagnosis.

2.3.1 Challenges of RDTs  
There are several technical limitations of current RDTs. These include:

- When the patient has low-density infections (as occurs in an asymptomatic period), RDTs are not adequate enough to detect low malarial parasite counts.
- The severity of the disease and a patient’s response to treatment are less likely to be measured by RDTs because of a lack of quantification.
- Effectiveness of RDTs to *P. falciparum* malaria is well proven but there is not enough supporting data on their ability to distinguish between other *Plasmodium* species.


- HRP2-based RDTs may not differentiate between active and previous malaria episodes, and geographic variation in the expression of HRP2 antigen may lead to an increase in false negatives.
- There has been a lack of formal evaluation of RDT heat stability in actual conditions of usage, especially in excessive conditions in some malaria-endemic settings, such as higher temperature than manufacturer recommendations.

Unmet needs in malaria diagnosis include
- Detection of asymptomatic infections and low-level transmission
- Detection of malaria in pregnancy
- Detection of liver stage malaria
- Differential diagnosis of malaria fever from non-malaria fever.

2.4 Treatment

The complexity of host response to malaria makes treatment difficult. Furthermore, the plasmodia that have entered into the patient blood stream will undergo asexual maturation and another round of multiplication and a number of parasites will have transformed into sexual forms called gametocytes. Because each stage of the parasite life-cycle exhibits distinct biochemical characteristics, one medicine may kill one stage of the parasite but have little or no effect on another. Most antimalarials are inactive against gametocytes. In *P. falciparum*, gametocytes emerge after 10 days and, once ingested by a mosquito, can perpetuate transmission.

Currently available malaria medicines are broadly categorized into three types according to their chemical structure and mode of action:
- Amino-quinoline/amino-alcohol compounds: quinine (QN), quinidine, chloroquine (CQ), amodiaquine (AQ), mefloquine (MQ), halofantrine, lumefantrine, piperaquine
- Antifolate compounds: pyrimethamine, proguanil, chlorproguanil, trimethoprim
- Artemisinin compounds: artemisinin, dihydroartemisinin, artemether, artesunate

Conventional medicines (aryl aminoalcohol compounds and antifolate compound) generally attack malaria in their erythrocyte stages, while they don’t exhibit gametocytocidal effects. On the other hand, new medicines, such as artemisinin and its derivatives, have effects on gametocytes sequestered in tissues as well as malaria in their erythrocyte stages. Treatment of young gametocytes will decrease the amount of infective mature gametocytes. Along with those three classes; atovaquone and primaquine (PQ) exhibit unique modes of action. In addition to its effect on erythrocytic stages, atovaquone inhibits pre-erythrocytic development in the liver, and oocyst development in the mosquito. Primaquine is the only medicine which exhibits effects on mature gametocytes and dormant liver forms. In addition to these antimalarials, several antibacterial drugs, such as tetracycline (TC) and clindamycin (CLDM), have antiplasmodial activity, although in general their action is slow for malaria treatment. Antibacterial drugs are therefore only used in combination with other antimalarials.

There are also two new ACTs recently approved by the European Medicines Agency, dihydroartemisinin (DHA)-piperaquine (Eurartesim® from Sigma-Tau) and pyronaridine-arteresunate (Pyramax® from Shin Poong Pharmaceuticals). These two products provide
longer post-treatment protection than artemether-lumefantrine (AL).\textsuperscript{69} They are expected to provide choices of ACTs for prescribers as well as help delay the development of drug resistance to artemisinin derivatives.\textsuperscript{68} Also, arteolane/piperaquine phosphate (Ranbaxy) has been registered and marketed in India. Eurartesim® has been distributed both via the government sector and the AMFm private sector subsidy programme in Cambodia since July 2012.\textsuperscript{70} Pyramax® is under review by regulatory agencies in South-East Asian countries, such as Myanmar and Viet Nam.\textsuperscript{71} The Committee for Medicinal Products for Human Use in European Medicines Agency recommends that Pyramax® should be used for a single, three-day treatment along with liver function monitoring in areas of low malaria transmission with evidence of artemisinin-resistance.\textsuperscript{72}

Medicines used for treatment have changed since 2004. Conventional medicines, such as CQ and SP, were widely used before 2004, though they became less effective due to the increase in drug resistant strains.\textsuperscript{9} The latest treatment guideline is based on ACTs, which has been shown to have 94 - 99% efficacy.\textsuperscript{68} Guidelines also recommend a parasitological confirmation of diagnosis in all malaria suspected patients.\textsuperscript{37} However, the number of ACT treatment courses procured by the public and private sectors also increased greatly from 11 million in 2005 to 278 million in 2011.\textsuperscript{2} The number of countries which adopted ACTs as national policy for malaria treatment expanded to 79 of 88 endemic countries by the end of 2011.\textsuperscript{2} The following is the summary of the latest treatment guideline published by WHO in 2010.\textsuperscript{37,64}

\textbf{(a) Treatment of uncomplicated P. falciparum malaria}\textsuperscript{37}

(See Abbreviation page iv for drug names)

<table>
<thead>
<tr>
<th>Adult</th>
<th>First-line</th>
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|       | • ACTs (AL, AS+AQ, AS+MQ, AS+SP), depending on the level of resistance, at least for three days  
Avoid monotherapy of artemisinin and its derivatives.  
ACTs are highly recommended than SP+ AQ.  
• (DHA+PPQ)  
• Addition of a single dose PQ (0.75 mg/kg) to ACTs in pre-elimination or an elimination programmes |
|       | Second-line |
|       | • Alternative ACTs known to be effective  
• AS + TC or DOXY or CLDM (7d)  
• QN + TC or DOXY or CLDM (7d) |
| Pregnancy-First trimester | First-line |
|       | • QN + CLDM (7d) |
|       | Second-line |
|       | • ACTs is indicated only if QN + CLDM (7d) is not available or failed. |
| Pregnancy-Second and Third trimester | First-line |
|       | • ACTs  
• AS + CLDM (7d)  
• QN + CLDM (7d) |
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| Lactating women | • Standard ACT treatment excluding dapsone, PQ, and TC |
| Infants, Young children | • Standard ACT treatment |
| Travelers returning to non-endemic countries | • Atovaquone-proguanil  
• AL  
• QN + DOXY or CLDM |

#### (b) Treatment of severe malaria

Full doses of parenteral antimalarial treatment should be initiated immediately. Parenteral treatment should be continued for a minimum of 24 hours, or until the patient can tolerate oral therapy.

| Adult | First-line | • AS (IV, IM 2.4 mg/kg) on admission, 12h and 24h, followed by once per day therapy  
Follow-up therapy includes;  
• ACTs  
• AS + CLDM or DOXY  
• QN + CLDM or DOXY |
| Second-line | • artemether or quinine, if AS (IV, IM) is not available |
| Pre-referral therapy | • AS (rectal, IM)  
• QN (IM)  
• artemether (IM) |
| Children | First-line | • AS (IV, IM 2.4 mg/kg) |
| Pre-referral therapy | • AS (rectal 10 mg/kg), for children under the age of five |

#### (c) Treatment of uncomplicated P. vivax malaria

Diagnosis of P. vivax is based on microscopy. Though RDTs are available, their sensitivities become lower when parasite densities are less than 500/μl.

| Adult | First-line | • CQ+PQ, if sensitive to CQ  
PQ is contraindicated to a patient with severe G6PD deficiency.  
PQ (0.75 mg/kg) once per week for eight weeks is given to a patient with mild-to-moderate G6PD deficiency.  
• ACTs (not AS+SP) + PQ, where P. vivax is resistant to CQ  
Partner medicines with long half-lives are recommended. |
(d) Treatment of *P. ovale* / *P. malariae* malaria

There have been very few clinical studies on the effectiveness of antimalarials to *P. ovale* and *P. malariae*. Chloroquine is considered to be generally effective for these two strains. Chloroquine and primaquine are recommended as treatment for the relapsing malaria by *P. ovale*.37

(e) Treatment of mixed malaria infection37

Diagnosis of mixed malaria infection is harder, because cryptic vivax malaria are less sensitive to the RDTs. Microscopy along with HRP2 antigen test is a suggested diagnosis in a region where mixed malaria infection are common.74 ACTs are the treatment of choice. Primaquine should also be given to patients with confirmed *P. vivax* and *P. ovale* infections.

2.4.1 Challenges of case management

There are still public health demands for new malarial medicines, even though a large decrease of malaria deaths has been achieved by improved access to ACTs.68 First, there is a need for better medicines for uncomplicated malaria, such as medicines for single-dose treatment.68 Effective medicines for vulnerable population are also necessary.68 For instance, artemether is contraindicated to pregnant women in the first trimester,75 and WHO treatment guideline currently recommends quinine plus clindamycin as a first-line treatment for them.37 Furthermore, growing concerns for malaria elimination and eradication require new classes of medicines, such as medicines for transmission blocking and relapsing malaria.68

Drug resistance is a huge obstacle in the fight against malaria.76,77 Information on comprehensive and up-to-date antimalarial resistance is important to reduce the further risk of drug resistance (Worldwide Antimalarial Resistance Network has been sharing the information on malaria drug resistance).76,78 Moreover, ineffective treatment due to drug resistance can also reduce the patients’ trust in formal health care, resulting in the demand for substandard and falsified medicines, and subsequently leading to the emergence or further spread of drug resistance.76 Monitoring of drug resistance in malaria is complex.76 Molecular markers are used to identify genetic mutations related to antimalarial drug resistance in the parasite genome.76 Pharmacokinetic studies reveal metabolic resistance by measuring antimalarial drug absorption, distribution, metabolism and elimination in the body.76 However, measuring therapeutic efficacy is the gold standard for drug resistance pharmaceutical policy.76

In the studies of chloroquine (CQ) efficacy conducted in 30 countries between 2000 and 2009, the median treatment failure rates were high to extremely high (19.8 - 100%) in all the countries except Honduras, Malawi and Nicaragua (0 - 1.3%).76 According to WHO policy, over 10% of treatment failure of a 28-day follow-up indicates that countries need to change the antimalarial medicines in their treatment guidelines.76 Amodiaquine showed better effectiveness than chloroquine despite cross-resistance with chloroquine.76 However, treatment failure rates were still over 10% in many countries. In South America and the
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Middle East, the median treatment failure rate was very high, ranging from 28.8% to 53.1%.

Interestingly, it was also found that when the treatment failure rate of amodiaquine reached 22%, the failure rate of the artesunate–amodiaquine combination was likely to exceed 10%.

Also in recent years, emergence of resistance to artemisinin on the Cambodia-Thailand border has been observed. Irrational use of ACTs or inappropriate use of artemisinin monotherapy is one of the factors causing resistance to artemisinin. It has been shown that a median of 78% of patients treated for malaria in Africa may not actually have had malaria, and this proportion has increased over time. It is recommended in the Global Plan for Artemisinin Resistance Containment (GPARC) that an immediate, multifaceted response for the purpose of containing and, if feasible, eliminating the resistant parasites should be conducted in areas with evidence of artemisinin resistance.

The price of ACTs is still prohibitive to many people especially in the poorer regions, but many organizations, including The Global Fund and the President’s Malaria Initiative (PMI), are assisting in ACT procurement and distribution systems. The Affordable Medicines Facility – malaria (AMFm) is a financing mechanism to increase access to ACTs by reducing their price to the equivalence of old antimalarials.

2.5 Financial approaches to malaria diagnosis and case control

There are several organizations working on the access issues of antimalarial medicines and diagnostics. The Affordable Medicines Facility – malaria (AMFm) is a financing mechanism to expand the access to and affordability of ACTs. The intervention was hosted and managed by the Global Fund, and the largest funder was UNITAID. Increased access to ACTs also leads to ruling out of artemisinin monotherapies and traditional antimalarials, such as CQ and SP. There are three components in the AMFm. First, the Global Fund, the host and manager of the AMFm, has negotiated with pharmaceutical manufacturers for the reduction of the price of ACTs, and to set sales prices as the same between public and private sector first-line buyers. Secondly, the Global Fund has subsidized through a ‘co-payment’ for ACTs at the top of the global supply chain. It is also promoting the rational use of ACTs. As a whole, the intervention has been trying to shift the ACT market from “low-volume, high-margin” to “high-volume, low-margin.”

The first AMFm pilot intervention started in July 2010 in Ghana, Kenya, Madagascar, Niger, Nigeria, Tanzania mainland, Uganda, and Zanzibar and the first co-paid ACTs were delivered to Ghana and Kenya in August 2010. As a result, private importers pay at most 80 per cent less than they did in 2008-2009. The market price has dramatically decreased in Ghana, Kenya, Madagascar and Nigeria, resulting in a 20 fold reduction. Quality assured ACTs become available in many private stores and pharmacies in some of those countries. Consumers are currently paying between US$ 0.33 and US$ 1.32 per ACT treatment, which is a substantial decline from US$ 8 to US$ 10 a year earlier. Between 2010 and 2011, the market size for ACTs has doubled in size. Demand for paediatric formulations has also been supported by this intervention. Between August 2011 and February 2012, paediatric pack sizes and formulations accounted for 66% of all ACT treatments approved.

The AMFm pilot study was evaluated to be successful in increasing availability, decreasing retail prices, and increasing market share of quality-assured ACTs, though the effect on malaria morbidity and mortality was not assessed. The pilot phase was planned to end on
31 December 2012.\textsuperscript{82} However, in November 2012, the Global Fund Board decided to integrate the AMFm into core Global Fund grant management and financial processes after the period.\textsuperscript{81} This means that the Global Fund will continue to host the AMFm until 31 December 2013 to ensure access to quality-assured ACTs. The new, integrated AMFm model may also address RDT access.

From 2006, the President’s Malaria Initiative (PMI) has initiated the procurement and distribution of ACTs in African countries and South-East Asia. The amount of ACTs procured has dramatically increased from around one million treatments in 2006 to 40 million in 2011.\textsuperscript{11}

Funding for diagnostic test procurement is provided mainly by the Global Fund and PMI.\textsuperscript{67} PMI procured around one million RDTs in 2006 and 15 million in 2011.\textsuperscript{11} The market’s growth over the past several years has been facilitated by the availability of this funding. As a result, market price of RDTs has been declining by 11%-15% annually from 2008-2010, costing approximately on average US$ 0.51 for \textit{P. falciparum}-specific RDTs and US$ 0.69 for multispecies tests.\textsuperscript{3,83} However, funding is expected to decrease after 2011 because of the global financial crisis. Information on the price of RDTs in the private sector is limited, but estimated to be around US$ 7.51 by FIND and ACT WATCH data.\textsuperscript{67} There are/were several small pilot interventions to subsidize RDTs in the private sectors.\textsuperscript{67}

### 2.6 Approaches toward malaria elimination and eradication

Malaria control, elimination and eradication were addressed in the Global Malaria Action Plan (GMAP) in 2008, launched by the Roll Back Malaria Partnership (RBM).\textsuperscript{2} The targets are to decrease the number of preventable deaths worldwide to near zero, to reduce global incidence by 75% since 2000 and eliminate malaria in at least 8 - 10 countries currently in the elimination stages.\textsuperscript{2,13} These will be achieved by: \textsuperscript{2,42,84}

- universal access to and utilization of preventive measures
- universal access to case management
- development of high-quality surveillance and screening systems.

When the malaria incidence rate declines, countries are required to adapt different strategies (Figure 6.10.8).\textsuperscript{42,84} For instance, elimination programmes (the incidence rate declines to less than one per 1000 population at risk) requires more technical malaria expertise, such as detection of all malaria cases.\textsuperscript{42} Diagnostic methods with higher sensitivity, such as polymerase chain reaction (PCR), will be necessary when transmission levels are quite low.\textsuperscript{84} Measuring serum antibodies to malaria in a population are also important to understand malaria transmission intensity.\textsuperscript{84}

The following are examples of intervention packages for community based reduction of malaria transmission.\textsuperscript{84}

- Mass drug administration (MDA) is the administration of an antimalarial drug or drug combination to an entire population at risk, whether or not they are infected, at one or more specified times. This approach was used in the malaria eradication campaign of the 1960s. It can temporarily reduce the prevalence of infection. However, if the reduction is to be maintained, additional control activities are
required in high-transmission settings before the start of the malaria season or when malaria is prevalent.\textsuperscript{84}

- Mass screening and treatment (MSAT) becomes more cost-effective, when transmission is below a certain level. In the program, everyone is screened and only infected people receive malaria treatment. The sensitivity of the screening test used is quite important. In the study of Pailin on the Cambodia-Thailand border in 2008, it was found that MSAT requires substantial human resources. Also, involvement of mobile populations in the programme was challenging.\textsuperscript{84}

In summary, more research needs to be done to accomplish malaria elimination and eradication effectively. Frequency, scale, timing and cost-effectiveness of several interventions (mass drug administration; MDA, mass screening and treatment; MSAT and etc.) have to be assessed in different transmission settings.\textsuperscript{84} Furthermore, it was demonstrated from the past eradication approaches that \textit{P. vivax} frequently remains longer in the body than \textit{P. falciparum}, so that control measures for \textit{P. falciparum} are not adequate enough against \textit{P. vivax}.\textsuperscript{21} Therefore, the use of primaquine in the elimination programme also needs to be investigated.\textsuperscript{84}

### 3. Research and Development

#### 3.1 Pharmaceuticals

The discovery and development of antimalarial drugs registered between 1975 and 1996 was funded largely by the public sector, in particular the military. The creation of the United Nations Development Programme/World Bank/World Health Organization/ Special Programme for Research and Training in Tropical Diseases (WHO/TDR) in 1975 facilitated the establishment of a partnership approach to drug discovery and development between public sector organizations and companies for those diseases lacking the market incentive.\textsuperscript{85} Mefloquine and halofantrine were discovered, developed and registered as a result of collaboration between the Walter Reed US Army Institute of Research (WRAIR), WHO/TDR and private pharmaceutical companies.\textsuperscript{86}

This approach evolved rapidly and led to the creation of organizations such as the Medicines for Malaria Venture (MMV), which uses the product development partnership (PDP) approach to discover, develop, and deliver new antimalarials as "global public goods".\textsuperscript{87} This was made possible by a recent increase in funding opportunities through national governments, international organizations, philanthropic organizations or private industry. The establishment of the Bill & Melinda Gates Foundation with its mission of supporting such innovative approaches for product development for neglected diseases has had a tremendous impact on the capabilities of PDPs.\textsuperscript{88,89}

Since the establishment of MMV, the organization has managed the largest ever portfolio of malaria medicines.\textsuperscript{90} Importantly, the portfolio includes many completely new classes of medicines, illustrating the opportunity for innovation that PDPs have to offer. Such advances result from MMV's collaborations with public and private institutions around the world. Partnerships operate within a well-established contractual framework: pharmaceutical,
biotechnology and research institute partners contribute their know-how, staff, infrastructure and facilities to individual projects, while MMV and the Expert Scientific Advisory Committee (ESAC) manage the portfolio as a whole.\textsuperscript{80} (see also Chapter 8.1)

MMV has been working to fill the gaps between the public health needs and pharmaceutical research and development.\textsuperscript{80} Because the majority of the population most vulnerable to malaria are children and pregnant women, MMV developed a child-friendly dispersible formulation of an ACT (Coartem\textsuperscript{®} Dispersible) and is conducting clinical trials for pregnant women. Also, responding to the growing concerns for malaria elimination and eradication, it has been working on new chemical entities, such as medicines for transmission blocking and relapsing malaria.\textsuperscript{89}

Large pharmaceutical companies have been increasingly getting involved in the search for new therapeutic and preventive tools for neglected diseases. For instances, GSK, ranked top of the Access To Medicines (ATM) Index in 2012, has strengthened its policy on medicine and vaccine development for the developing countries, by establishing Developing Countries Unit in August 2012 (the ATM Index is based on efforts by pharmaceutical companies to improve access to medicines in developing countries\textsuperscript{81}). Sanofi has established the Impact Malaria program, addressing malaria treatment research including two promising antimalarials in phase II clinical trials.\textsuperscript{82}

One of the major research areas in antimalarials to date is to investigate the technology to increase the supply of artemisinin products with stable and inexpensive synthetic production, currently the active ingredient comes from extracts from plants. Enhancing the capacity of artemisinin itself is one method, achieved via the development of higher-yielding seeds of the plant Artemisia annua (the CNAP project) and yeast-based microbial fermentation for the production of artemisinic acid (the iOWH project). Another is the development of a class of new molecules with a similar chemical structure to artemisinin, called endoperoxides.\textsuperscript{84} So far, one of the new synthetic molecules (arterolane, OZ277) has been proved to be less effective than ACTs against uncomplicated \textit{P. falciparum} malaria in phase Ila study.\textsuperscript{85} Two partner compounds, used in combination with artemisinin, are also undergoing clinical trials.\textsuperscript{801}

For severe malaria, several existing and new chemical compounds have been tested in clinical trials. Rectal and injectable forms of artesunate are under registration. There are also several clinical trials for adjunctive therapy underway. Clinical trials on inhaled nitric oxide for long term neurological sequelae in cerebral malaria in children are currently in phase II. A new chemical compound, sevuparin (low anticoagulant heparin), is in phase I-II trials, and is expected to block malarial parasites from parasitizing erythrocytes.\textsuperscript{85} As for new antimalarial candidates for \textit{P. vivax}, two compounds are being tested in clinical trials. Since primaquine, a current first-line medicine for relapsing malaria has a risk for people with G6PD, safer and effective medicines for G6PD-deficient populations are desired.\textsuperscript{80} Several combinations of antibiotics are also being investigated.\textsuperscript{80}

There is much hope that efforts resulting from innovative-discovery will continue to feed the antimalarial pipeline as exciting scientific breakthroughs have occurred in our knowledge of the biology, immunology and molecular genetics of malaria. \textit{P. falciparum} genomic information can be exploited to yield new therapeutic targets, as well as antigens for potential vaccines.\textsuperscript{86, 87} The potential offered by the improved understanding of the biochemistry pathways is illustrated in Table 6.10.2.\textsuperscript{86}
Along with new antimalarials, preventive therapies are also being tested using existing medicines. One example is intermittent preventive treatment using ACTs. In a study in Mali in 2009, incidence reductions among school children aged 6-13 years, who took sulfadoxine-pyrimethamine plus artesunate (SP/AS), or amodiaquine plus artesunate (AQ/AS) were compared with a control (vitamin C) and were 66.6% and 46.5% respectively. Currently, several clinical trials on preventive therapies using ACTs are being tested in various settings, especially among children.

The current pipeline of antimalarial medicines including adjuvant therapy for severe malaria is depicted in Table 6.10.3, sorted by the mode of action.

The GMAP published in 2008 proposed that “By 2018, two IPT-specific drugs will be launched and four different types of therapeutic drugs will be developed: a next generation ACT for P. falciparum, a combination that targets P. vivax in the liver stage, and two therapeutics that separately block P. falciparum and P. vivax transmission. The transmission blocking drugs may also have the capability to treat the disease at the red blood cell stage. After launch of these drug products, it is estimated that two novel therapeutic drug combinations and one novel preventive treatment will be created every 10 years to avoid resistance buildup. In addition, new formulations for drugs will be created for pregnant women, children and infants, and different delivery modes will be created for severe malaria”.

Significant funding is required to bring all these candidate medicines to market. Also, it should be considered whether the existing funding is in fact sufficient enough to guarantee delivering the new medicines in the timeframe necessary, as well as considering the inherent risks in development of new pharmaceuticals with historically high attrition rate. In the case of MMV, expenditure on research and development has increased from US$ 10 million in 2002 to US$ 40 million in 2011. Furthermore the organization is expecting to require around US$ 66 million per year over coming years to cover research on treatments in pregnancy, P. vivax, transmission-blocking and malaria elimination and eradication products. In December 2012, UNITAID announced new grants focusing on affordable medicines for childhood HIV/AIDS, malaria and tuberculosis (TB). Out of US$ 120 million grants, up to US$ 34 million will be allocated to the MMV to support R&D on injectable artesunate.
### Table 6.10.2: Targets in Plasmodium falciparum

<table>
<thead>
<tr>
<th>Target</th>
<th>Enzyme/process</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane biosynthesis</td>
<td>Phospholipid biosynthesis</td>
<td>G25</td>
</tr>
<tr>
<td>Parasite transporters</td>
<td>Unique channels,</td>
<td>Quinolines</td>
</tr>
<tr>
<td></td>
<td>Hexose transporter</td>
<td>O-3-hexose derivatives</td>
</tr>
<tr>
<td>Parasite proteases</td>
<td>Plasmepsins, falcipains</td>
<td>Leupeptin, pepstatin</td>
</tr>
<tr>
<td>Shikimate pathway</td>
<td>5-enolpyruvyl shikimate</td>
<td>Glyphosate</td>
</tr>
<tr>
<td></td>
<td>3-phosphate synthase</td>
<td></td>
</tr>
<tr>
<td>Isoprenoid biosynthesis</td>
<td>DOXP reductoisomerase</td>
<td>Fosmidomycin</td>
</tr>
<tr>
<td>Redox system</td>
<td>Thioredoxin reductase</td>
<td>5,8-Dihydroxy-1,4-naphthoquinone</td>
</tr>
<tr>
<td></td>
<td>Gamma-GCS</td>
<td>Buthionine sulfoximine</td>
</tr>
<tr>
<td>Mitochondrial system</td>
<td>Cytochrome c oxidoreductase</td>
<td>Atovaquone</td>
</tr>
<tr>
<td>Purine metabolism</td>
<td>HGPRT</td>
<td>Immucillin-H</td>
</tr>
<tr>
<td>Pyrimidine metabolism</td>
<td>Thymidylate synthase</td>
<td>5-Fluoroorotate</td>
</tr>
<tr>
<td>Apicoplast</td>
<td>Fab H</td>
<td>Thiolactomycin</td>
</tr>
<tr>
<td></td>
<td>Fab I</td>
<td>Triclosan</td>
</tr>
<tr>
<td>Cyclin-dependent protein kinases, derivatives</td>
<td>Fab H</td>
<td>Pfmrk Oxindole</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Note: DOXP, 1-deoxy-d-xylulose-5-phosphate; GCS, glutamylcysteine synthetase; HGPRT, hypoxanthine–guanine–xanthine phosphoribosyltransferase.
<table>
<thead>
<tr>
<th>Name</th>
<th>Sponsor/Collaborators</th>
<th>Phase</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyramax® Paediatric&lt;sup&gt;90&lt;/sup&gt;</td>
<td>MMV, Shin Poong, University of Iowa</td>
<td>Phase Ib-III</td>
<td></td>
</tr>
<tr>
<td>Eurartesim® Paediatric&lt;sup&gt;90&lt;/sup&gt;</td>
<td>MMV, Sigma-Tau</td>
<td>Phase Ib-III</td>
<td>ACTs</td>
</tr>
<tr>
<td>Artemisinin-Naphthoquine (ARCO®)&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Medical University of Vienna, International Centre for Diarrhoeal Disease Research, Bangladesh Malaria Research Initiative Bandarban</td>
<td>Phase Ib-III</td>
<td></td>
</tr>
<tr>
<td>Azithromycin/Artesunate&lt;sup&gt;101&lt;/sup&gt;</td>
<td></td>
<td>Phase II</td>
<td>Artemisinin + Antibiotics</td>
</tr>
<tr>
<td>OZ439&lt;sup&gt;90&lt;/sup&gt;</td>
<td>MMV, University of Nebraska, Monash University and Swiss TPHI</td>
<td>Phase I – IIa</td>
<td>Endoperoxides</td>
</tr>
<tr>
<td>RKA182&lt;sup&gt;90&lt;/sup&gt;</td>
<td>University of Liverpool</td>
<td>Preclinical</td>
<td></td>
</tr>
<tr>
<td>Artemison&lt;sup&gt;102&lt;/sup&gt;</td>
<td>UHKST</td>
<td>Phase IIa</td>
<td></td>
</tr>
<tr>
<td>CDRI 97-78&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Central Drug Research Institute</td>
<td>Phase I</td>
<td>Endoperoxides (On Hold)</td>
</tr>
<tr>
<td>CDRI 99/411&lt;sup&gt;103&lt;/sup&gt;</td>
<td>Central Drug Research Institute, IPCA (public institution of higher education)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferroquine&lt;sup&gt;101&lt;/sup&gt;</td>
<td>Sanofi-Aventis</td>
<td>Phase Iia</td>
<td>Aminoquinoline</td>
</tr>
<tr>
<td>AQ-13&lt;sup&gt;101&lt;/sup&gt;</td>
<td>Tulane University Health Sciences Center, Donald Krogstad, University of Bamako</td>
<td>Phase II</td>
<td></td>
</tr>
<tr>
<td>Azithromycin/Chloroquine&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Pfizer, MMV, London School of Hygiene and Tropical Medicine</td>
<td>Phase IIb-III</td>
<td></td>
</tr>
<tr>
<td>Co-trimoxazole (Bactrim®)&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Institute of Tropical Medicine, Antwerp in Zimbia, UCSF in Uganda</td>
<td>Phase IIb-III</td>
<td></td>
</tr>
<tr>
<td>Fosmidomycin/ Piperaquine&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Jomaa Pharma GmbH</td>
<td>Phase I – IIa</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Fosmidomycin/ Azithromycin&lt;sup&gt;101&lt;/sup&gt;</td>
<td>Jomaa Pharma GmbH, Mahidol University, Thammasat University</td>
<td>Phase II</td>
<td></td>
</tr>
<tr>
<td>Fosmidomycin/ Clindamycin&lt;sup&gt;101&lt;/sup&gt;</td>
<td>Zentopharm GmbH, Albert Schweitzer Hospital, Centro de Investigacao em Saude de Manhica</td>
<td>Phase II</td>
<td></td>
</tr>
<tr>
<td>Nauclea pobeguinii&lt;sup&gt;90&lt;/sup&gt;</td>
<td>MMV, DRC, Antwerp</td>
<td>Phase IIb-III</td>
<td>Natural Product</td>
</tr>
<tr>
<td>ArtiMist&lt;sup&gt;TM&lt;/sup&gt;&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Proto Pharma</td>
<td>Phase IIb-III</td>
<td></td>
</tr>
<tr>
<td>Argemone mexicana&lt;sup&gt;101&lt;/sup&gt;</td>
<td>University of Bamako, University of Geneva, MMV</td>
<td>Phase IIb</td>
<td></td>
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<table>
<thead>
<tr>
<th>Compound</th>
<th>Sponsor(s)</th>
<th>Phase</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tafenoquine&lt;sup&gt;90&lt;/sup&gt;</td>
<td>GSK, MMV</td>
<td>Iib-III</td>
<td>P. vivax</td>
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<tr>
<td>NPC-1161-B&lt;sup&gt;90&lt;/sup&gt;</td>
<td>University of Mississippi</td>
<td>Preclinical</td>
<td></td>
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<tr>
<td>NITD609&lt;sup&gt;90,104&lt;/sup&gt;</td>
<td>MMV, Novartis</td>
<td>Ia</td>
<td>Spiroindolone</td>
</tr>
<tr>
<td>Sevuparin sodium&lt;sup&gt;101&lt;/sup&gt;</td>
<td>Dilaforette AB, University of Oxford</td>
<td>I-II</td>
<td>Adjuvant Therapy (Severe malaria)</td>
</tr>
<tr>
<td>SAR 97276&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Sanofi Aventis</td>
<td>Ia</td>
<td>Adjuvant Therapy (Severe malaria) (On Hold)</td>
</tr>
<tr>
<td>E6446&lt;sup&gt;105&lt;/sup&gt;</td>
<td>Eisai, Fundação Oswaldo Cruz</td>
<td></td>
<td>Adjuvant Therapy (Severe malaria)</td>
</tr>
<tr>
<td>GNF 156&lt;sup&gt;90&lt;/sup&gt;</td>
<td>MMV, Novartis</td>
<td>I</td>
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<tr>
<td>Antimalarial&lt;sup&gt;90,106&lt;/sup&gt;</td>
<td>Actelion</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>MMV390048&lt;sup&gt;90&lt;/sup&gt;</td>
<td>MMV, University of Cape Town, Swiss Tropical and Public Health Institute, Monash University</td>
<td>Preclinical</td>
<td>Cell based compounds</td>
</tr>
<tr>
<td>21A092&lt;sup&gt;90&lt;/sup&gt;</td>
<td>MMV, Drexel University College of Medicine</td>
<td>Preclinical</td>
<td></td>
</tr>
<tr>
<td>ELQ-300&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Oregon Health &amp; Science University, MMV, University of South Florida</td>
<td>Preclinical</td>
<td></td>
</tr>
<tr>
<td>BCX4945&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Biocryst, Albert Einstein College of Medicine</td>
<td>Preclinical</td>
<td>Molecular Mechanisms</td>
</tr>
<tr>
<td>DSM265&lt;sup&gt;90&lt;/sup&gt;</td>
<td>MMV, University of Texas Southwestern, Monash University</td>
<td>Preclinical</td>
<td></td>
</tr>
<tr>
<td>Aminoindole&lt;sup&gt;90&lt;/sup&gt;</td>
<td>MMV, Broad Institute and the Harvard School of Public Health</td>
<td>Preclinical</td>
<td>Others</td>
</tr>
<tr>
<td>Methylenblue&lt;sup&gt;90&lt;/sup&gt;</td>
<td>University of Heidelberg</td>
<td>Ii</td>
<td>Transmission Blocking (On Hold)</td>
</tr>
<tr>
<td>N-tert butyl isouquine&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Liverpool School of Tropical Hygiene, GSK</td>
<td>Phase I</td>
<td>(On Hold)</td>
</tr>
<tr>
<td>P218 DHFR&lt;sup&gt;90&lt;/sup&gt;</td>
<td>MMV</td>
<td>Preclinical</td>
<td>Antifolate agent (On Hold)</td>
</tr>
</tbody>
</table>

### Lead generation<sup>90</sup>
- Novartis MP
- GSK MP
- Broad & Genzyme MP
- Open source drug discovery
- Sanofi Orthologue screen
- AstraZeneca MP
- Kinases
- 18 other Projects

### Lead optimization<sup>90</sup>
- Novartis (2 projects)
- GSK (2 projects)
- Sanofi (1 project)
- St.Jude/Rutgers/USF Antimalarials
- UCT Heterocycles
- Dundee Antimalarials
- DHODH
- Oxaboroles
- Tetraoxanes
- Ferrer-GSK (1 Project)
- 21A092 back-up
3.2 Vaccines

Although vaccines have been one of the most cost effective and easily administered means of controlling infectious diseases, a safe and effective malaria vaccine is not yet commercially available. However, progress toward developing malaria vaccines has accelerated in recent years. The latest phase III clinical trial of the malaria vaccine candidate RTS,S/AS01 showed modest protection (a vaccine efficacy of about 30%) against clinical and severe malaria among infants six to 12 weeks of age, and approximately 50% reduction of episodes in children five to 17 months of age.\(^{60,61}\)

The development of a malaria vaccine is challenging because the malaria parasites have complex life cycles and distinct development stages, each of which has multiple antigens that could serve as targets of an immune response. The current approaches to malaria vaccine development can be classified into three categories.\(^{107}\)

1) Pre-erythrocytic vaccines would fight against sporozoites and/or inhibit them from developing in the liver. Furthermore, pre-erythrocytic vaccines are categorized based on the type of antigen. Whole parasite vaccination is produced by cryopreserved irradiated \(P. falciparum\) sporozoites, but the methodology of the production is not simple enough. Whole parasite vaccination is also produced by a genetic attenuation of \(P. falciparum\), where the knockout parasite cannot finish development in the liver. To date, studies show that late liver stage arresting parasites would be better than early liver stage arresting parasites and irradiated sporozoites. Subunit antigen utilizes circumsporozoite protein as an antigen. Promising candidates of subunit antigen are RTS,S and TRAP.\(^{107}\)

2) Blood stage vaccines would inhibit parasite multiplication in the red cells, thus preventing (or decreasing) severe disease during the blood infection. Because malarial parasites in the blood stage replicate rapidly and are less likely to be affected by host immune systems, this type of vaccine is expected to be less effective for malaria elimination, but effective for case management.\(^{108}\) Candidates include MSP1-3, AMA-a, EBA-175, GLURP, RESA, SERA5 and PfRh5.\(^{107}\)

3) Transmission blocking vaccines (TBV) would interrupt the cycle of transmission by inhibiting the further development of parasites ingested by the mosquito when the parasite is a gametocyte or in a sexual stage. Because this type of vaccine increases immunity in a community level rather than individual level, the population of a whole community must be vaccinated to gain the benefit from the vaccination. The promising candidates include Pfs25/Pvs25, Pfs230/Pvs230, and Pfs48/45.\(^{107}\)

The PATH Malaria Vaccine Initiative (MVI) is a public-private partnership formed in 1999 through an initial grant from the Bill & Melinda Gates Foundation, working to accelerate the development of malaria vaccines and ensure their availability and accessibility in the developing world.\(^{109}\) In addition to MVI, the European Malaria Vaccine Initiative (EMVI), the US Army Medical Research and Materiel Command (USAMRMC) via Walter Reed Army Institute of Research (WRAIR), and private pharmaceutical companies such as GSK Biologicals are contributing elaborately by providing research resources and technical knowledge for vaccine development.\(^{110}\) MVI plays an important role in partnering academic and public developers with industry because most of the early vaccine R&D was done by
non-industry academic and public developers lacking the vaccine production skills which industry often has.\textsuperscript{111}

Not only is the selection of a promising antigen important, but also the technology of delivery systems such as usage of adjuvants, recombinant viral delivery and heterologous prime boosting is important to induce the effectiveness of the vaccines.\textsuperscript{112} Vaccine candidates with multi-antigen candidates have also been increasing, accounting for over 35%. Therefore, various kinds of combinations have been tested in clinical trials. The compiled list of malaria vaccine R&D, known as \textquotedblleft the rainbow table\textquotedblright, is available from WHO\textapos;s website, which was last updated in November 2012.\textsuperscript{113}

When considering malaria vaccines as a key resource for malaria eradication, controlling malaria transmission becomes important rather than focusing on mortality and morbidity reduction alone.\textsuperscript{114} Vaccines that interrupt malaria transmission (VIMTs) include transmission-blocking vaccines as well as pre-erythrocytic and asexual stage vaccines.\textsuperscript{114} Expansion of the malaria vaccine portfolio is necessary in order to include more research on vaccines beyond those for \textit{P. falciparum}, and to develop technology of delivery systems and tools to measure and evaluate vaccines in terms of transmission rates.\textsuperscript{114}

The Global Malaria Action Plan (GMAP) published in 2008 mentioned that there would be four different vaccines available by 2028; \textit{\textquotedblleft Two vaccines will be developed for \textit{P. falciparum}, however, the second vaccine will be more efficacious than the first. In addition, one \textit{P. vivax} vaccine will be developed. One other vaccine that has the capability to target both \textit{P. vivax} and \textit{P. falciparum} simultaneously and/or block transmission and/or be used by pregnant women is anticipated.\textquotedblright\textsuperscript{99}}

### 3.3 Diagnostics

As discussed in section 2.3, high-quality RDTs have become more widely available globally, especially since the mid-2000s. Technical advancement is still required to address unmet needs in malaria diagnosis. The following figure illustrates the existing diagnostic methods and pipelines under development (Figure 6.10.11).\textsuperscript{66}

The following are the diagnostics in the pipeline and their characteristics:\textsuperscript{66}

**(a) Microscopy**\textsuperscript{66}

Computer automated slide reading is based on image processing software and algorithms to interpret information from the thin smears made and stained as they would be for traditional light microscopy. It provides an objective and reliable diagnosis as well as reduces the amount of human labor. Cell phone/mobile-based microscopy are also based on automated interpretation of microscopy images.\textsuperscript{66}
Figure 6.10.11: Technology Platforms for Malaria Diagnosis

Source: Malaria diagnostics technology landscape. UNITAID, 2011.
*predominantly in house methods, ■Multiple developers/suppliers

(b) RDTs (antigen detection) 66

Urine malaria test is a simple one-step dipstick assay that uses immune-chromatographic technology to detect malaria proteins in the urine of persons with fever. It has been developed by Fyodor Biotechnologies in collaborations with the University of Maryland, Baltimore, the Johns Hopkins University, and others. The first generation product, which detects only *P. falciparum*, is in in clinical validation phase and the second generation product, which detects both *P. falciparum* and *P. vivax* malaria, is in a pre-clinical phase.115

Fluorescent rapid diagnostic tests (by AccessBio) provide improved detection by the use of fluorescence. They are expected to be at least 100 times more sensitive than traditional RDTs. The process of testing is the same as with current RDTs: a finger-prick sample of blood is collected and transferred to the disposable RDTs. However, the cost of each kit is going to be increased and a reader is required.

New antigens and monoclonal antibodies have been sought by the Foundation for Innovative New Diagnostics (FIND) in collaboration with its partners.116 FIND is also working on developing positive control wells (PCWs) in collaboration with several institutions.117 The PCWs, consisting of a small amount of recombinant parasite antigen, are intended to be used in the health care facilities to check the performance of the RDTs.
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(c) Nucleic acid detection

A portable quantitative RT-PCR platform and a quantitative duplex assay for *P. falciparum* and *P. vivax*, MicroPCR, has been developed by the Tulip Group in collaboration with Bigtec Labs and under the banner of Molbio Diagnostics. Micronics has been developing the PanNAT™ Assay system. It is a portable, fully automated PCR system with primers, molecular beacon fluorescent probes and all other reagents in a microfluidics cartridge, using a fingerprick blood sample. Nucleic acid lateral flow immunoassay, NALFIA, has been developed by MALACTRES Consortium with the support of funding by the European Commission (EC) Seventh Framework Programme. It consists of a simplified methodology with a traditional PCR amplification instrument, designed to address the need for a molecular test of drug resistance as well as complex clinical cases.

Loop-mediated isothermal amplification (LAMP) is a simple, rapid and specific nucleic acid amplification method developed by Eiken Chemical Co., Ltd. So far LAMP methods have not been widely used routinely in the field, but are expected to be as specific and sensitive as PCR methods. Currently, a LAMP malaria diagnostic kit has been developed by Eiken Chemicals, FIND, and the Hospital for Tropical Diseases in London and the clinical evaluations are underway.

Fluorescent in-situ hybridization (FISH) is a technology to detect specific DNA/RNA sequences by fluorescent probes. A malaria FISH assay has been developed by ID-FISH Technology Inc., which is expected to differentiate species and provide quantitative results and information on morphology used for the identification of parasite stages.

(d) Haemozoin detection

Haemozoin is a byproduct of the parasites digestive pathway. Intellectual Ventures Lab has been developing a device to carry out Dark-Field Cross Polarization (DFxP), to detect haemozoin in the sample, based on the techniques of microscopy. The magneto-optical technology (MOT) has been developed by the University of Exeter in collaboration with several partners. The project began in 2005 and was funded by the European Commission. The technology is based on the magnetic properties of haemozoin. A second generation of the product is expected to be non-invasive, requiring a fingernail sample. Laser desorption mass spectrometry has been developed by Johns Hopkins University, detecting haemozoin via ultraviolet radiation.

(e) Spectroscopy

Spectroscopic approaches are based on analysis of molecules in malaria samples under a specific electromagnetic spectrum. SpectraWave and SpectraNet have been developed by Claro Scientific, which is a reagent-less point-of-care diagnostics system providing malaria diagnosis and a complete blood count.

Malaria diagnostic tests have been scaled up due to the advent of RDTs, and currently several new technologies are in the development pipeline. Several of the new diagnostic tools would fill the unmet needs and/or play an important role in surveillance activities for malaria elimination. However, there still remains a lack of knowledge about the biology of hypnozoites, which is responsible for the latent liver form of *P. vivax*. As a result, there are no effective methods to detect them and none are in the pipeline. Furthermore, there is a lack...
of funding for malaria diagnostic tools. From 2007 to 2010, approximately 1% of total malaria R&D funding was allocated to diagnostics. More funding is required to fill the research gap, especially for unmet needs and hypnozoites in *P. vivax*.

### 3.4 Vector control

As is discussed previously in section 2.1, growing resistance to pyrethroids by the mosquito vector results in a greater demand for new effective, safe and affordable insecticides with novel modes of action. However, no new public health insecticides have been introduced for over 30 years, because of a small market for public health pesticides and a decline in the agrochemical industry. The cost of developing a new insecticide is expected to be around US$ 70 million, while the overall annual public health insecticide market for all diseases and all developing countries is at most US$ 150 million.

The IVCC (Innovative Vector Control Consortium) is a product development partnership (PDP) established as a non-profit company in 2005, funded by the Bill and Melinda Gates Foundation. It has been tackling the barriers to innovation in the development of new insecticides for public health vector control. The IVCC has been elaborating on partnering industries and academics, and plays an important role in the partnership, because active involvement of industry is necessary in the early stage of the pipeline. Also, IVCC generates a balanced portfolio of projects at different stages in the development cycle, advised by External Scientific Advisory Committees. The portfolio is based on assessment each project is ranked on its merits and its ability to fulfill the criteria by IVCC and the advisory committees. The portfolio includes development of new insecticides as well as alternative active ingredients, longer-lasting formulations, and new combinations of existing insecticides for ITN and IRS applications. The following table shows the current IVCC portfolio last updated in November 2012 (Table 6.10.4). The WHO Pesticide Evaluation Scheme (WHOPES) programme tests and evaluates safety, efficacy and operational acceptability of public health pesticides, and develops specifications for quality control and international trade.

Basic biomedical research on the malaria vector is important to support the discovery and development of new insecticides. Basic research targets addressing insecticides includes malic enzyme (mitochondria), oxidative phosphorylation (mitochondria), and pathogenic fungi to adult mosquitoes.

Along with development of insecticides with novel modes of actions, better understanding of vector biology is essential for comprehensive control interventions. One of the reasons, for instance, is that vector mosquitoes can develop behavioral resistance to insecticides as well as physiological and genetic ones. Because current vector control strategies mostly address indoor female vectors, mosquitoes can bite human beings outdoors and/or in the early evening before people go to sleep protected with a mosquito net. To address those issues, development of effective systems to monitor mosquito ecology is also required. Furthermore, innovative technologies, such as genetic modification of vector mosquitoes which cannot convey malaria parasites, is another area of potential research.
Table 6.10.4: IVCC Public Health Insecticides Portfolio, November 2012

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<tr>
<th>New Active Ingredients</th>
<th>Collaborators</th>
<th>Phase</th>
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<td>Projects</td>
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<td></td>
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<tr>
<td>Discovery Platform</td>
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<td>Data mining, lead generation, screening –</td>
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<tr>
<td>(five classes)</td>
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<td>lead optimization</td>
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<tr>
<td>Active Ingredients</td>
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<td>Data mining, lead generation, screening</td>
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<tr>
<td>(three classes)</td>
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<tr>
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<tr>
<td>(one classe)</td>
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<table>
<thead>
<tr>
<th>New Formulations</th>
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<td>LLIRS Formulation</td>
<td>Dupont</td>
<td>Proof of concept</td>
</tr>
<tr>
<td>LLIN Combination</td>
<td>Dupont</td>
<td>Proof of concept</td>
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<td>Ingredient Review</td>
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<td>LLIN Combination</td>
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<td>Development</td>
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<td>Bayer</td>
<td>WHOPES PhaseII-III</td>
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<td>LLIRS Formulation</td>
<td>Syngenta</td>
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<tr>
<td>LLIN Combination</td>
<td>Vestergaard</td>
<td>WHOPES PhaseIII - Country Registration</td>
</tr>
</tbody>
</table>

Source: Innovative Vector Control Consortium

LLIN: long-lasting insecticide net. LLIRS: long-lasting indoor residual spraying.

The GMAP mentioned that three new active ingredients and 15 formulations would be required for the next 12 years to avoid pesticide resistance and integrate new mechanisms such as larviciding and consumer products. After that, one active ingredient and 10 formulations will be developed in the following decades for the same purposes.

A lack of funding is a huge obstacle in the innovation of vector control schemes. Because of funding deficiencies in basic ecological research, there are huge knowledge gaps with regard to most elements of the mosquito life cycle that occur outside of houses, including larval growth and sugar feeding, oviposition, and adult dispersal. This knowledge gap results from the fact the most of the research funding for malaria vectors in recent years has been provided based on specific biotechnological interventions rather than the need for basic ecological knowledge. Therefore, financial support to such ecological research is required to support innovative vector control strategies.
3.5 R&D under the 6th and 7th Framework Programme funded by the European Commission

The research areas in EC funded sixth Framework Programme (FP6, 2002-2006) structured European Research Areas (ERA) with three components: BiomalPar, ANTIMAL and EMVDA. BiomalPar (Biology and Pathology of Malaria Parasite) was a “Network of Excellence” coordinated by the Institut Pasteur, which targeted basic scientific research such as parasites genetics, cell biology, metabolism, pathogenesis and immunology. ANTIMAL was an “Integrated Project” coordinated by the Liverpool School of Tropical Medicine, which focused on the development of new antimalarials. The research areas include preclinical research on novel aminooquinolines and peroxides, discovery of novel compounds targeting metabolic and signaling pathways in the cytosol, and biosynthesis of plasmodial phospholipids. EMVDA (European Malaria Vaccine Development Association) is an “Integrated Project” initially coordinated by the European Vaccine Initiative, which has been dealing with development of vaccine target antigens, adjuvant research and preclinical assays. The total EU funding directly allocated to malaria under FP6 was around €65 million. In addition, €35 million went to malaria-related intervention trials and research capacities in Africa, supported by European & Developing Countries Clinical Trials Partnership (EDCTP).

The current seventh Framework Programme (FP7, 2007-2013) is following the FP6 strategic approach, “ERA structure”. The basic scientific research “BiomalPar” was transformed into EVIMalaR. It is a “Network of Excellence” coordinated by University of Glasgow, which has been aiming to further integrate the partner organizations to build up a virtual “European Malaria Research Institute”. A new ERA is taken up from FP7, targeting the mosquito vector control. AvecNet (African Vector Control: New Tools) is a collaborative project between African and European researchers to develop and evaluate new tools as well as ensuring the sustainability of existing interventions for malaria control in Africa, and is coordinated by Liverpool School of Tropical Medicine. INFRAVEC is an “Integrating Activity” project on research infrastructure to facilitate genetic modification of the malaria mosquito vector, which hinders mosquitoes from transmitting malaria parasites. In FP7, up to €80 million will be allocated to malaria related projects, with the majority of the funding going to basic research and vector control (around €30 million each).

4. Existing Resource Flows

4.1 Finance for malaria control as a whole

It was estimated by the GMAP, that US$ 5.1 billion would be required annually as full implementation costs by all 109 malarious countries to scale-up, sustain control, and eliminate malaria from 2011-2020. In later years, the amount is expected to reduce because of a projected reduction in the need for diagnostic testing and treatment due to the malaria being under control. International funding for malaria has dramatically increased in the last decade, from around 100 million US dollars in 2004 to the peak of 2 billion US dollars in 2011, but this figure is still far below the requirement. The majority of the external funding for malaria control comes from the Global Fund, which accounts for over 50% of total...
funding. Other major funders for malaria control include the United Kingdom Department for International Development (DFID), PMI, the World Bank, and AMFm.

Cost allocation depends on funding sources. National government expenditure for malaria is in general focused on human resources (36%), IRS (17%) and programme management (16%). The Global Fund resources went to ITNs (43%), antimalarial treatment (21%), programme management (12%). The PMI paid for ITNs (35%), IRS (25%), treatment (20%) and diagnostic testing (7%).

Full implementation costs consist of the costs of prevention (ITNs, IRS, and IPTp), treatment interventions (antimalarials, diagnostics, and severe case management) and control programs. Preventive tools cost nearly US$ 4 billion out of the projected US$ 5.1 billion, which comprises of 55% for IRSs, 45% for ITNs and less than 1% for IPTp. When an effective vaccine becomes available, an additional half a billion US dollars would be required. Cost of treatment is expected to peak at US$ 1.4 billion in 2011, and then decline to less than half a billion US dollars, due to the impact of scaled-up preventive interventions. The cost of malaria control program includes M&E, Operational Research, Training, Human Resources and Infrastructure, but does not include R&D costs. It is estimated to be 14 - 19% of the overall annual costs (approximately 1 billion US dollars).

4.2 Finance for research and development

According to the G-FINDER survey from 2007 to 2011, which provides global R&D funding information on basic research, diagnostics, pharmaceuticals and preventive and therapeutic vaccines for 31 neglected diseases, it is estimated that malaria research received US$ 468.4 million in 2007, and US$ 558.8 million in 2011 respectively (2011 data has been adjusted for inflation based on 2007). The decrease from 2009 to 2010 can be mostly explained by a US$ 45.5 million decrease in year-on-year funders’ investment and US$ 6.3 million lost in the follow-up. Estimates do not include funding from multi-disease organizations, such as the WHO/TDR, European & Developing Countries Clinical Trials Partnership (EDCTP) and FIND, leading to a slight underestimation of annual funds. The EDCTP has funded nine malaria projects during 2004-2010 for a total amount of €9,559,816 of which six research areas are for treatments; one is about vaccines and two are about malaria in pregnancy. An overview of the 2007-2011 malaria R&D total funding amounts is depicted in Figure 6.10.12.

The majority of malaria R&D funding went to pharmaceutical development (US$ 1004.9 million, 37.1%), basic research (US$ 716.6 million, 26.4%) and vaccine development (US$ 682.2 million, 25.2%), while just a small percentage of funding was allocated to vector control (US$ 114.0 million, 4.2%) and diagnostics (US$ 43.5 million, 1.6%). The amount of funding for vaccine research fluctuated between 2007 and 2010, mostly because of RTS,S vaccine development programme. In 2008 and 2009 more funding was needed for phase II-III clinical trials for the vaccine, whereas in 2010 the vaccine program has been winding down as products are submitted for licensing.
The GMAP estimated that malaria R&D would cost approximately US$ 750 to US$ 900 million annually from 2009 to 2018 for new tools, such as vector control, pharmaceuticals, vaccine, and diagnostic technologies.\textsuperscript{99} It means that more than US$ 8.9 billion investment is required. The breakdown highlights that approximately US$ 1.2 billion for vector control, US$ 3.5 billion for drugs, US$ 2.6 billion for vaccines, US$ 140 million for diagnostics, and US$ 1.5 billion for early research and information is necessary. Those assumptions are based on these timeframes and costs; developing a vaccine needs US$ 600 million to US$ 1 billion and approximately 13 years; a therapeutic medicine with a new active ingredient requires US$ 250 million and 10 years, and another US$ 25 million and two to six years for a reformulation; vector control tools with a new active ingredient require US$ 175 million and 12 years, and another US$ 3 million and two to six years for a reformulation; developing new microscopic and diagnostic technologies need US$ 10 to US$ 15 million annually. With current global funds, each research area is underfunded, and lack of funding for the vector control is more substantial than other areas.

The top 10 funders of malaria R&D during the period 2007 - 2010 were as follows (Table 6.10.5).\textsuperscript{139}
Table 6.10.5: top 10 funders of diarrhoea R&D during the period 2007 - 2011 (thousand US$)

<table>
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<tr>
<th>Funder name</th>
<th>Country</th>
<th>Amount of funding (million US$)</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill &amp; Melinda Gates Foundation</td>
<td>USA</td>
<td></td>
<td>124.5</td>
<td>173.7</td>
<td>182.4</td>
<td>87.3</td>
<td>144.9</td>
<td>712.8</td>
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<tr>
<td>US National Institutes of Health (NIH)</td>
<td>USA</td>
<td></td>
<td>84.4</td>
<td>104.8</td>
<td>116.0</td>
<td>132.9</td>
<td>122.2</td>
<td>560.3</td>
</tr>
<tr>
<td>Aggregate Pharmaceutical and Biotechnology Company Respondents</td>
<td></td>
<td></td>
<td>90.8</td>
<td>90.6</td>
<td>99.3</td>
<td>125.6</td>
<td>101.6</td>
<td>508.0</td>
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<tr>
<td>The Wellcome Trust</td>
<td>UK</td>
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<td>28.3</td>
<td>26.7</td>
<td>27.2</td>
<td>34.0</td>
<td>31.6</td>
<td>147.9</td>
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<tr>
<td>US Department of Defense (DOD) including DOD Defense Advanced Research Projects Agency (DARPA)</td>
<td>USA</td>
<td></td>
<td>33.1</td>
<td>30.5</td>
<td>37.6</td>
<td>22.7</td>
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<td>24.9</td>
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<td>7.1</td>
<td>9.1</td>
<td>6.3</td>
<td>43.3</td>
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<tr>
<td><strong>Grand Total</strong></td>
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<td>541.7</td>
<td>593.9</td>
<td>547.0</td>
<td>558.9</td>
<td>2,709.9</td>
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</table>

2008-2011 funding data has been adjusted for inflation and is reported in 2007 US dollars (US$).

Most funding was supplied by Bill & Melinda Gates Foundation, the US NIH, and the pharmaceutical/ biotechnological industry, which together accounted for 82.8% of global malaria R&D funding. During the same periods, the EC funded 118.9 million US dollars for malaria R&D, which accounted for 5.5% of global funding. There was a decline in the funding from the Bill & Melinda Gates Foundation in 2009 to 2010 (down 52.2%), which was due to the winding down of the RTS,S vaccine funding as it came closer to licensure. However, there was a substantial increase of funding from DFID and NIH. An overview of the global malaria R&D funding by funder type is illustrated in Figure 6.10.13.
## 5. Challenges

- Although the global malaria burden has been declining since 2004, there are still many countries whose burden has increased, especially in large endemic countries with weak health systems.
- There is an increasing awareness of an emerging fifth malaria strain, *Plasmodium knowlesi*. The new strain causes severe and sometimes fatal cases, like *P. falciparum*.
- In Europe, imported and indigenous cases have been decreasing dramatically, but indigenous cases are still reported spontaneously in countries where malaria was officially eliminated long ago, such as in Spain.
- Growing resistance to pyrethroids by the mosquito vector is a serious threat to the current vector control approaches. Durability of ITNs also needs to be researched and surveyed. New effective, safe and affordable insecticides with novel modes of action as well as innovative technology to control the malaria vector are required.
- Further research and development is vital to make effective vaccines available. The lack of scientific knowledge in areas such as usage of adjuvants, recombinant viral delivery and heterologous prime boosting needs to be addressed.
- There are several technical limitations of current RDTs, such as a lack of sensitivity in the low-density infections. There are also unmet needs against RDTs, including detection of malaria in pregnancy and detection of liver stage malaria.
The very effective malaria medicines, ACTs, have been widely administered globally, but in recent years, emergence of resistance to artemisinin has emerged on the Cambodia-Thailand border. Medicines with new modes of action as well as effective monitoring systems are necessary. New therapeutic classes include block transmission, which will provide new tools to help deliver the objective of malaria eradication as well as treatment of relapsing \textit{P. vivax} malaria.

Malaria medicines, vaccines, insecticides and diagnostic portfolios have expanded since 2004, but there is a lack of funding to facilitate research and development to make those candidates available in the field.

6. Conclusions

Malaria still remains a global threat, while there has been a decline in the number of cases and death toll since 2004. This was due to intensive vector controls, introduction of chemoprevention, better access to ACTs, and the advent of qualified RDTs. Procurement and distribution of preventive tools, RDTs and medicines have been supported by the Global Fund, PMI and AMFm. Several new ACT medicines were registered, and will be or have already been on the market. Many antimalarial candidates are in the development and discovery phases, mostly supported by MMV. No new vaccine has become available since 2004, but the vaccine development portfolio includes many promising candidates including RTS,S/AS01, which has finished phase III clinical trials.

However, the downside is that malaria parasites have been gaining resistance even to the new first-line medicines, ACTs. Vector mosquitos have also been acquiring resistance to insecticides. The resistance poses a great threat to vector control and malaria case management. Therefore, more research is needed to introduce new medicines and insecticides with novel modes of actions. Along with research on vector control, research on vaccines and chemoprevention also needs to be addressed.

Research and development of new pharmaceuticals requires a long time and long-term support. Continued and increased support from the European Commission is vital to ensure that malaria does not pose a threat to the people in Europe and the world, targeting elimination and eradication in the future.

References

Update on 2004 Background Paper, BP 6.10 Malaria


Casimiro, E., Calheiros, J., Santos, F. D., & Kovats, S. National Assessment of Human Health Impacts of Climate Change in Portugal: Approach and Key Findings. *Environmental Health Perspectives* 2006; 114.


Update on 2004 Background Paper, BP 6.10 Malaria


Update on 2004 Background Paper, BP 6.10 Malaria


81 News Release, Board Approves Integration of AMFm into Core Global Fund Grant Processes (15 November 2012). The Global Fund to Fight AIDS, Tuberculosis and Malaria. Available from:
Update on 2004 Background Paper, BP 6.10 Malaria


6.10-55

Update on 2004 Background Paper, BP 6.10 Malaria


Update on 2004 Background Paper, BP 6.10 Malaria


Annexes

Annex 6.10.1: Autochthonous malaria cases in WHO European region 2000 - 2011
Annex 6.10.2: Death due to malaria cases in WHO European region 2000 - 2011
Annex 6.10.3: Imported malaria cases in WHO European region 2000 – 2011
Annex 6.10.4: EDCTP-funded malaria projects
**Annex 6.10.1: Autochthonous malaria cases in WHO European region 2000 - 2011**


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<td>5 428</td>
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Annex 6.10.2: Death due to malaria cases in WHO European region 2000 - 2011


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## Update on 2004 Background Paper, BP 6.10 Malaria

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Blank cells indicate that data is either unavailable and/or has not yet been reported to WHO.
Annex 6.10.4: EDCTP-funded malaria projects


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<td>2009</td>
<td>Comparison of effectiveness, safety and pharmacokinetics of intravenous quinine and intravenous artesunate followed by oral artemisinin combination therapy for severe malaria treatment in Uganda.</td>
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<td>2009</td>
<td>Malaria baseline studies towards characterising and establishing a clinical trial site at Mutengene, South-West Region Cameroon.</td>
<td>treatment</td>
<td>€199 199</td>
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<tr>
<td>2008</td>
<td>A randomised placebo controlled trial of oral iron therapy for treatment of postmalaria anaemia in Malawian children comparing immediate post-discharge.</td>
<td>treatment</td>
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<td>2007</td>
<td>Optimization of the existing dose and regimen of intermittent preventive treatment with sulfadoxinepyrimethamine.</td>
<td>pregnancy</td>
<td>€3 648 811</td>
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<td>2007</td>
<td>An integrated approach to clinical trials, capacity building and networking in West Africa.</td>
<td>treatment</td>
<td>€4 699 208</td>
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<td>2007</td>
<td>Assessment of functionality of antibodies that associate with protection from clinical malaria using the in vitro \ <em>P. falciparum</em>  \ growth inhibition assay.</td>
<td>vaccines</td>
<td>€192 500</td>
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<td>2005</td>
<td>A coordinated approach to future research on malaria in pregnancy.</td>
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<td>2004</td>
<td>Public health benefit of artemisinine based combination therapies for uncomplicated malaria.</td>
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<td>2004</td>
<td>Understanding the mechanisms of piperaquine resistance.</td>
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<td><strong>Total</strong></td>
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Background Paper 6.11
Alzheimer Disease and other Dementias

By Béatrice Duthey, Ph.D
20 February 2013
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Executive Summary

Improvements in health care in the past century have contributed to people living longer and healthier lives. This has also resulted in an increase in the number of people with noncommunicable diseases, including dementia. Although dementia mainly affects older people, it is not a normal part of ageing. Dementia is a syndrome, usually of a chronic or progressive nature, caused by a variety of brain illnesses that affect memory, thinking, behaviour and ability to perform everyday activities. Dementia is overwhelming not only for the people who have it, but also for their caregivers and families. It is one of the major causes of disability and dependency among older people worldwide.

Dementia: a public health priority

In 2008, the World Health Organization (WHO) declared dementia as a priority condition through the Mental Health Gap Action Programme. 

Prevalence and incidence projections indicate that the number of people with dementia will continue to grow, particularly among the oldest old, and countries in demographic transition will experience the greatest growth. The total number of people with dementia worldwide in 2010 is estimated at 35.6 million and is projected to nearly double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050. The total number of new cases of dementia each year worldwide is nearly 7.7 million, implying one new case every four seconds.

Much of the increase will be in developing countries, the fastest growth in the elderly population taking place in China, India, and their south Asian and western Pacific neighbours. In 2010, Europe had an estimated 10 million disease cases and based on United Nation’s demographic forecast this figure will rise to 14 million in 2030. Looking at these data, it is apparent that there is an urgent need for action. Alzheimer disease (AD) has become a major public health concern as the world’s population ages. It is projected that by 2050, people aged 60 and over will account for 22% of the world’s population with four-fifths living in Asia, Latin America or Africa.

The cost of Dementia

According to the WHO, treating and caring for people with dementia currently costs the world more than US$ 604 billion per year. This includes the cost of providing health and social care as well the reduction or loss of income of people with dementia and their caregivers. Estimates of the future cost of dementia in Europe is a rise of 43% from 2008 reaching 250 billion euros in 2030. It is expected to rise by 43 % between 2008 and 2030 reaching 250 billion euros in 2030. 

In high-income countries, informal care (45%) and formal social care (40%) account for the majority of costs, while the proportionate contribution of direct medical costs (15%) is much lower. In low-income and lower-middle-income countries direct social care costs are small, and informal care costs (i.e. unpaid care provided by the family) predominate. Changing population demographics in many low- and middle-income countries (LMIC) may lead to a decline in the ready availability of extended family members in the coming decades.
A necessity to improve early risk identification, diagnosis and improve management

Alzheimer disease (AD) is the most common form of dementia. There are no available treatments that stop or reverse the progression of the disease, which worsens as it progresses, and eventually leads to death. There are currently no specific markers that can confirm with a 100% certainty AD diagnosis. A combination of brain imaging and clinical assessment checking for signs of memory impairment is used to identify patients with AD. Definitive diagnosis can only be obtained after patients autopsy by examining brain tissues. There is a clear need for tangible advances in the area of biomarkers for assessment of risk, diagnosis and monitoring disease progression. Screening of patients still remain very expensive and new research is necessary to develop non expensive and reliable tests.

Continuing efforts are still required. This includes developing medicines that would slow progression, halt, or prevent AD and other dementias from occurring. Current studies are currently underway to identify biomarkers for diagnosis and new therapeutics to prevent or slow down disease progression. Consortia of top-level European research and industrial partners will need to act in this direction and contribute to strengthen the EU’s leadership on Alzheimer disease research.
1. **Introduction**

Dementia is a syndrome characterized by disturbance of multiple brain functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation.\(^1,2\)

Alzheimer disease is the most common form of dementia and possibly contributes to 60–70% of cases. Other types of dementias include vascular dementia, dementia with Lewy bodies, and a group of diseases that contribute to frontotemporal dementia. The boundaries between subtypes are indistinct and mixed forms often co-exist.\(^3\)

Dementia can affect a person in different ways, and progression of the disease depends upon the impact of the disease itself and the person’s personality and state of health. Dementia can be divided in three stages:
- early stage – first year or two
- middle stage – second to fourth or fifth years
- late stage – fifth year and after

These periods are given as an approximate guideline and not all persons with dementia will display the same symptoms.\(^4\)

Table 6.11.1 illustrates the common symptoms of people with dementia.
Update on 2004 Background Paper, BP 6.11 Alzheimer Disease

Table 6.11.1: Common symptoms experienced by people with dementia syndrome

(from the WHO Dementia Report in reference 5.

<table>
<thead>
<tr>
<th>Early stage</th>
<th>Middle stage</th>
<th>Late stage</th>
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<tbody>
<tr>
<td>The early stage is often overlooked. Relatives and friends (and sometimes</td>
<td>As the disease progresses, limitations become clearer and more restricting.</td>
<td>The last stage is one of nearly total dependence and inactivity. Memory</td>
</tr>
<tr>
<td>professionals as well) see it as &quot;old age&quot;, just a normal part of ageing</td>
<td>➢ Become very forgetful, especially of recent events and people's names</td>
<td>disturbances are very serious and the physical side of the disease becomes</td>
</tr>
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<td>process. Because the onset of the disease is gradual, it is difficult to be</td>
<td>➢ Have difficulty comprehending time, date, place and events; may become lost</td>
<td>more obvious.</td>
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<tr>
<td>sure exactly when it begins.</td>
<td>at home as well as in the community</td>
<td>➢ Usually unaware of time and place</td>
</tr>
<tr>
<td>➢ Become forgetful, especially regarding things that just happened</td>
<td>➢ Have increasing difficulty with communication (speech and comprehension)</td>
<td>➢ Have difficulty understanding what is happening around them</td>
</tr>
<tr>
<td>➢ May have some difficulty with communication, such as difficulty in finding</td>
<td>➢ Need help with personal care (i.e. toileting, washing, dressing)</td>
<td>➢ Unable to recognize relatives, friends and familiar objects</td>
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<td>words</td>
<td>➢ Unable to successfully prepare food, cook, clean or shop</td>
<td>➢ Unable to eat without assistance, may have difficulty in swallowing</td>
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<tr>
<td>➢ Become lost in familiar places</td>
<td>➢ Unable to live alone safely without considerable support</td>
<td>➢ Increasing need for assisted self-care (bathing and toileting)</td>
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<td>➢ Lose track of the time, including time of day, month, year, season</td>
<td>➢ Behaviour changes may include wandering, repeated questioning, calling</td>
<td>➢ May have bladder and bowel incontinence</td>
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<tr>
<td>➢ Have difficulty making decisions and handling personal finances</td>
<td>out, clinging, disturbed sleeping, hallucinations (seeing or hearing things</td>
<td>➢ Change in mobility, may be unable to walk or be confined to a wheelchair</td>
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<td>➢ Have difficulty carrying out complex household tasks</td>
<td>which are not there)</td>
<td>or bed</td>
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<tr>
<td>➢ Mood and behaviour: may become less active and motivated and lose</td>
<td>➢ May display inappropriate behaviour in the home or in the community</td>
<td>➢ Behaviour changes, may escalate and include aggression towards carer,</td>
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<tr>
<td>interest in activities and hobbies may show mood changes, including</td>
<td>(e.g. disinhibition, aggression).</td>
<td>nonverbal agitation (kicking, hitting, screaming or moaning)</td>
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<td>depression or anxiety may react unusually angrily or aggressively on</td>
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<td>➢ Unable to find his or her way around in the home.</td>
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<td>occasion.</td>
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1.1 Alzheimer Disease description

Alzheimer disease (AD) is characterized by a progressive decline in cognitive function. AD is substantially increased among people aged 65 years or more, with a progressive decline in memory, thinking, language and learning capacity. AD should be differentiated from normal age-related decline in cognitive function, which is more gradual and associated with less disability. Disease often starts with mild symptoms and ends with severe brain damage. People with dementia lose their abilities at different rates.\textsuperscript{6,7,8,9,10,11}

The pathophysiology of AD is related to the injury and death of neurons, initiating in the hippocampus brain region that is involved with memory and learning, then atrophy affects the entire brain.\textsuperscript{7} Amyloid beta, also written Aβ, is a short peptide that is an abnormal proteolytic byproduct of the transmembrane protein amyloid precursor protein (APP), whose function is unclear but thought to be involved in neuronal development. Amyloid beta monomers are soluble and contain short regions of beta sheet at sufficiently high concentration, they undergo a dramatic conformational change to form a beta sheet-rich tertiary structure that aggregates to form amyloid fibrils. These fibrils deposit outside neurons in dense formations known as senile plaques or neuritic plaques, in less dense aggregates as diffuse plaques, and sometimes in the walls of small blood vessels in the brain in a process called amyloid angiopathy or congophilic angiopathie. In Alzheimer disease abnormal aggregation of the tau protein, a microtubule-associated protein expressed in neurons is also observed. Tau protein acts to stabilize microtubules in the cell cytoskeleton. Like most microtubule-associated proteins, tau is normally regulated by phosphorylation. In AD patients, hyperphosphorylated tau P-tau accumulates as paired helical filaments that in turn aggregate into masses inside nerve cell bodies known as neurofibrillary tangles and as dystrophic neurites associated with amyloid plaques.\textsuperscript{12}

Current evidence indicates changes in CSF levels of Aβ, tau, and P-tau, which are not static over the course of the disease. The mechanism that drives the formation of senile plaques and neurofibrillary tangles is still unknown at present. Senile plaques and neurofibrillary tangles prompt the injury and death of neurons, and as a consequence memory loss and behavioural symptomatic changes. As well, current hypotheses include circulating αβoligomers as potentially neurotoxic (not just the plaques). Abnormal release of neurotransmitters such as glutamate contributes to neuronal death and inflammation.\textsuperscript{9,10,11,13} Neuroinflammation is also involved in the complex cascade leading to AD pathology and symptoms. Considerable pathological and clinical evidence documents immunological changes associated with AD, including increased pro-inflammatory cytokine concentrations in the blood and cerebrospinal fluid.\textsuperscript{11} Whether these changes may be a cause or consequence of AD remains to be fully understood, but inflammation within the brain, including increased reactivity of the resident microglia towards amyloid deposits, has been implicated in the pathogenesis and progression of AD.

1.2 Risk Factors for AD

1.2.1 Age

The more individuals advance in age the higher is the risk they will develop Alzheimer disease. Most patients develop AD after the age of 65 years old. The risk of developing AD reaches 50% for individuals beyond age 85. Because more and more people live longer lives this disease is becoming a serious concern. The age-specific incidence rates for Alzheimer
disease demonstrate a doubling of incidence for about every six years of added life, which indicates an exponential increasing risk with increasing age. This exponential risk is fairly similar across studies, regardless of geographic region, even if the underlying absolute incidence rate differ (see Figure 6.11.1).

Figure 6.11.1: Incidence of AD (expressed as percent per year) as a function of age for each study.

Source: Ziegler-Graham, Alzheimer & Dementia 2008;4:316-328
Note: The studies are labeled with different numbers (in chronological order). Observed incidences marked with a “+” indicate that the age interval was open-ended. Regions are denoted by different colors. log(incidence) = -2.146 + 0.1271 (age-60); Incidence = .117 exp{.1271(age-60)}

1.2.2 Genetics of AD
The vast majority of Alzheimer disease is not genetically inherited although some genes may act as risk factors. Genetically identified forms of Alzheimer disease, which usually have an onset before the age of 65, have been identified and account for 0.1% of disease cases. The current thinking is that there are sporadic/late onset and familial/early onset cases of Alzheimer disease.

Familial/early onset
When Alzheimer disease is caused by these deterministic variations, it is called “autosomal dominant Alzheimer disease (ADAD)” or “familial Alzheimer disease”. Many family
members in multiple generations are affected. Symptoms develop before age 60, and may appear among persons between 30 and 40 years old. Most of autosomal dominant familial AD can be attributed to mutations in the amyloid precursor protein (APP) and/or presenilins 1 and 2 gene.\textsuperscript{16} Mutations in the APP and presenilin genes lead to the production of protein Aβ42 (beta amyloid 1-42) that accumulates into amyloid plaques and cause death of neurones by increasing the production of protein Aβ42.\textsuperscript{17}

**Sporadic/late onset**

Other cases, that do not exhibit autosomal-dominant inheritance are termed sporadic AD. Genetic risk factors have been identified such as the inheritance of the α4 allele of the apolipoprotein (APOE).\textsuperscript{18} Risk genes increase the likelihood of developing a disease, but do not guarantee it will happen. Individual carrying a mutation in the APOE α4 allele have a three to 15 times increase risk of developing Alzheimer disease. Table 6.11.2 shows the main genetic mutations associated with Alzheimer disease.

### Table 6.11.2: Main genetic mutations associated with Alzheimer disease.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Main alteration</th>
<th>Presumed mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid precursor protein (APP)</td>
<td>Mutation</td>
<td>Autosomal dominant, mostly early onset</td>
</tr>
<tr>
<td>Presenilin 1 (PSEN1)</td>
<td>Mutation</td>
<td>Autosomal dominant, mostly early onset</td>
</tr>
<tr>
<td>Presenilin 2 (PSEN2)</td>
<td>Mutation</td>
<td>Autosomal dominant, mostly early onset</td>
</tr>
<tr>
<td>Apolipoprotein-E (APOE)</td>
<td>Common variant</td>
<td>Familial and sporadic, late onset</td>
</tr>
<tr>
<td>Sortilin-related receptor, L(DLR class) A repeats-containing (SORL1)</td>
<td>Common variant</td>
<td>Familial and sporadic, late onset</td>
</tr>
<tr>
<td>Clusterin (CLU)</td>
<td>Common variant</td>
<td>Sporadic, late onset</td>
</tr>
<tr>
<td>Phosphatidylinositol binding clathrin assembly protein (PICALM)</td>
<td>Common variant</td>
<td>Sporadic, late onset</td>
</tr>
<tr>
<td>Complement component (3b/4b) receptor 1 (CRI)</td>
<td>Common variant</td>
<td>Sporadic, late onset</td>
</tr>
<tr>
<td>Bridging integrator 1 (BIN1)</td>
<td>Common variant</td>
<td>Sporadic, late onset</td>
</tr>
</tbody>
</table>

Source: Alzheimer Europe. Available at http://www.alzheimer-europe.org/?lm1=D8105B21BD2C

Alzheimer disease is a complex multi-factorial and multi-mechanism disease merging genetics and epistasis that can unravel novel pathways.

### 1.2.3 Role of environment for AD

Several studies indicate a role for environmental effects on AD development. In a recent review Richard Mayeux and Yaakov Stern summarized the role of diet, activities, or diseases that potentially play a role in the onset of Alzheimer disease.

Diabetes, hypertension, smoking, obesity, and dyslipidemia have all been found to increase risk as well a history of brain trauma, cerebrovascular disease, and vasculopathies. A higher level of education, as well as Mediterranean diet were shown to decrease the risk of developing AD. Table 6.11.3 shows identified risks factors for AD.
Table 6.11.3: Factors that modify the risk of Alzheimer disease.

<table>
<thead>
<tr>
<th>Antecedent</th>
<th>Direction</th>
<th>Possible mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>Increased</td>
<td>Parenchymal destruction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Strategic location</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Aβ deposition</td>
</tr>
<tr>
<td>Smoking</td>
<td>Increased</td>
<td>Cerebrovascular effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Increased and decreased</td>
<td>Microvascular disease</td>
</tr>
<tr>
<td>Type II diabetes</td>
<td>Increased</td>
<td>Cerebrovascular effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin and Aβ compete for clearance</td>
</tr>
<tr>
<td>Obesity</td>
<td>Increased</td>
<td>Increased risk of type II diabetes inflammatory</td>
</tr>
<tr>
<td>Traumatic head injury</td>
<td>Increased</td>
<td>↑ Aβ and amyloid precursor protein deposition</td>
</tr>
<tr>
<td>Education</td>
<td>Decreased</td>
<td>Provides cognitive reserve</td>
</tr>
<tr>
<td>Leisure activity</td>
<td>Decreased</td>
<td>Improves lipid metabolism, mental stimulation</td>
</tr>
<tr>
<td>Mediterranean diet</td>
<td>Decreased</td>
<td>Antioxidant, anti-inflammatory</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Decreased</td>
<td>Activates brain plasticity, promotes brain vascularization</td>
</tr>
</tbody>
</table>


2. Size and Nature of Disease Burden

Dementia mainly affects older people, although there is growing awareness of cases that start before the age of 65. Population ageing is having a profound impact on the emergence of the global dementia epidemic, influencing awareness and driving demand for services.

2.1 Incidence and prevalence

Exact estimates of the prevalence of dementia depend on the definition and specific threshold used. The syndrome affects approximately 5%-8% of individuals over age 65, 15%-20% of individuals over age 75, and 25%-50% of individuals over age 85. Alzheimer disease is the most common dementia, accounting for 50%-75% of the total, with a greater proportion in the higher age ranges. Vascular dementia is probably next most common, but its prevalence is unknown. The remaining types of dementia account for a much smaller fraction of the total.

Dementia Worldwide

The WHO 2012 Report “Dementia: a public health priority” estimates there are at present 35.6 million people living in dementia worldwide. Alzheimer disease is the most frequent cause of dementia in Western societies.

As the world population ages, the frequency is expected to double by 2030 and triple by 2050. Neither healthcare nor financial systems are prepared to face the magnitude of the situation.
Late onset dementia (from the WHO Dementia Report)

In 2005, Alzheimer’s Disease International (ADI) commissioned a panel of experts to review all available epidemiological data and reach a consensus estimate of prevalence in each of 14 world regions. The panel estimated 24.3 million people aged 60 years and over with dementia in 2001, 60% living in LMIC. Each year, 4.6 million new cases were predicted, with numbers affected nearly doubling every 20 years to reach 81.1 million by 2040. Incidence was estimated from prevalence and mortality. The estimates were provisional, due to limited data. Coverage was good in Europe, North America, and in developed Asia-Pacific countries. Studies from China and India were too few and estimates too variable to provide a consistent overview. There was a dearth of studies from Latin America, Africa, Eastern Europe, Russia and the Middle East, and a consequent reliance on the consensus judgment of the international expert panel. This supported a tendency, noted in the few LMIC studies available at that time, for the age-specific prevalence of dementia to be lower in developing countries than in developed ones.

Global prevalence is being reappraised for the revision of the Global Burden of Disease (GBD) study 2010 (http://www.globalburden.org/), with findings summarized in ADI’s 2009 World Alzheimer Report. The evidence base was expanded considerably with more studies from LMIC and from other regions and groups previously underrepresented in the literature. Enhancements included a fully systematic review of the world literature on the prevalence of dementia (1980–2009) in 21 GBD regions, a critical appraisal of study quality, and an attempt, where possible, to generate regional estimates from quantitative meta-analysis.

Meta-analysis of dementia prevalence within GBD regions

There were sufficient studies of good quality to conduct meta-analyses for 11 of the 21 GBD regions; Western Europe, North America, Latin America (combining Andean, Central, Southern and Tropical regions), Asia Pacific high-income, Australasia, East Asia, South-East Asia and South Asia. For Latin America, we considered it pragmatic and appropriate to pool studies from across the four GBD regions to conduct a single continent-wide meta-analysis. Given that the North American region comprised just Canada and the USA, and that Canada was represented by a large and well-conducted survey on a nationally representative sample, the national prevalence figures for Canada were applied to Canada and the USA studies were meta-analysed to generate estimates for that country.

Modelling the prevalence of dementia

Age-specific and age- and sex-specific meta-analysed dementia prevalence estimates are described for each region in Annex 6.11.1. Prevalence increased exponentially with age in each region, doubling with every 5.5 year increment in age in Asia Pacific, Latin America and North America, with every 5.6 year increment in East Asia, every 6.3 years in South Asia and Western Europe, and every 6.7 years in Australasia and South-East Asia. In all regions other than Asia Pacific and North America, the predicted prevalence for men was lower (by 19–29%) than that for women. There was a tendency in all regions for the divergence in prevalence between men and women to increase with increasing age; however, this was statistically significant only for the Asia Pacific region. There was statistically significant heterogeneity (variation in prevalence between studies within regions) for all regions other than South-East Asia; it was most marked for South Asia (alpha=0.39), Western Europe (alpha=0.19) and Asia Pacific (alpha=0.18).
Generation of prevalence estimates for other GBD regions

Where it was impractical to conduct a meta-analysis due to insufficient data, the default option was to apply relevant estimates from the Delphi consensus of 2005, representing the best available estimates of likely dementia prevalence in those regions.  

Estimated prevalence of dementia

Estimated prevalence of dementia for all those aged 60 years and over, age-standardized to the Western Europe population structure, can be compared directly between the 21 GBD regions (Annex 6.11.1, 6.11.2 and Figure 2-2 in Annex 1). There is a four-fold variation, from 2.07% (West sub-Saharan Africa) to 8.50% (Latin America). However, most of the estimated age-standardized prevalence figures lie in a band between 5% and 7%. The major source of variation is the very low estimated prevalence for the four regions of sub-Saharan Africa.

Figure 6.11.2: Estimated prevalence of dementia for persons aged 60 and over, standardized to Western Europe population, by Global Burden of Disease region

Estimated numbers of people with dementia

Having applied the age-specific, or age- and sex-specific, prevalence estimates to UN population projections, it was estimated that 35.6 million people worldwide were living with dementia in 2010 (Annex 6.11.3). Western Europe is the GBD region with the highest number of people with dementia (7.0 million), closely followed by East Asia with 5.5 million, South Asia with 4.5 million and North
America with 4.4 million. The nine countries with the largest number of people with dementia in 2010 (1 million or more) were China (5.4 million), USA (3.9 million), India (3.7 million), Japan (2.5 million), Germany (1.5 million), Russia (1.2 million), France (1.1 million) Italy (1.1 million) and Brazil (1.0 million).

The total number of people with dementia is projected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050. Much of the increase is attributable to increases in the numbers of people with dementia in LMIC (Figure 6.11.3); in 2010, 57.7% of all people with dementia lived in LMIC, and this proportion is expected to rise to 63.4% in 2030 and 70.5% in 2050. The projections are driven mainly by population growth and demographic ageing (Annex6.11.3). World regions fall into three broad groups. High-income countries start from a high base, but will experience only a moderate proportionate increase – a 40% increase in Europe, 63% in North America, 77% in the southern Latin American cone and 89% in the developed Asia Pacific countries. Other parts of Latin America and North Africa and the Middle East start from a low base but will experience a particularly rapid increase – 134–146% in the rest of Latin America, and 125% in North Africa and the Middle East. China, India and their neighbours in South Asia and Western Pacific start from a high base and will also experience rapid growth – 107% in South Asia and 117% in East Asia. Projected increases for sub-Saharan Africa (70–94%) are modest and are consistent with limited demographic ageing in view of persistently high child mortality and the effects of the HIV epidemic.

**Young onset dementia (early onset dementia)**

Young onset dementia (YOD), defined typically as onset before the age of 65 years, is a rare condition. Few population-based surveys have been carried out, since large sample sizes are needed to estimate prevalence with precision. Instead, researchers typically conduct registry-based studies, reporting prevalence calculated as the number of cases known to local service providers divided by the total local population from the census. The assumption is that all of those with YOD seek help early in the disease course. This is not always the case, and therefore such studies will underestimate the true prevalence of dementia.

**Review**

The European Collaboration on Dementia group (EuroCoDe) carried out a systematic review of prevalence of YOD. In addition to two registry-based studies from the United Kingdom, the group identified a registry-based study from the USA, and a population-based survey of late-onset dementia from Rotterdam, Netherlands, in which the youngest age group was 55–59 years. The reviewers commented on the scarcity of data and variability of estimates, and did not attempt a meta-analysis. A Delphi consensus had previously been attempted for the Dementia UK report, using the two United Kingdom studies, one carried out in Cambridgeshire, and the other in four London boroughs. The prevalence of persons aged 45–64 was, for males, 120/100 000 in London and 101/100 000 in Cambridgeshire; and for females 77/100 000 in London and 61/100 000 in Cambridgeshire. For YOD, as with late onset dementia, the expert consensus was that prevalence increased exponentially with increasing age, roughly doubling every five years from 9/100 000 at age 30 to 156/100 000 at age 60–64 years. Two-thirds (68%) of all young onset cases were aged 55 and over. Among this larger, middle-aged group of people with YOD, males predominated over females with a gender ratio of 1.7 to 1.

The consensus group’s estimate for 60–64 years (156/100 000, or 0.16%) is one-ninth rather than, as expected, one half of the late-onset prevalence for the next five-year age band (1.3% for those aged
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65–69). This discrepancy is likely to be artefactual, arising from an underestimation of population prevalence in the YOD studies, which ascertained cases from service contact only. This explanation is supported by the Rotterdam population-based survey prevalence of 423/100 000 for those aged 55–59 and 418/100 000 for those aged 60–64.22 Thus, there may be an underestimation by registry-based studies of the true prevalence of YOD by a factor of 2.5 to fourfold. While it was estimated that YOD accounts for only 2.2% of all people with dementia in the United Kingdom, the true proportion may be closer to 6–9%.23

It is sometimes suggested, chiefly on the grounds of lower life expectancies at birth, that ageing begins earlier in LMIC. These differences are mainly accounted for by early life mortality and there is little evidence that YOD is more common in LMIC. Three prevalence studies from India included participants aged less than 65 years, and prevalences of YOD were as low as those seen in high-income population-based surveys: 328/100 000 (60–64 years) in Kerala,21 249/100 000 in Ballabgarh (55–64 years), and 63/100 000 (50–59 years) and 280/100 000 (60–64 years) in Mumbai.8 26 27 However, this statement must be qualified given the likely impact of the HIV epidemic which is concentrated among younger people in low-income countries, particularly in southern and eastern Africa. HIV-associated dementia is an AIDS-defining illness, with a prevalence of 15–30% in untreated populations, presenting with neurocognitive impairments (forgetfulness, poor concentration and slowed mental processing), emotional disturbances (agitation, apathy), and motor dysfunction. The condition is also seen among those receiving Highly Active Antiretroviral Therapy (HAART) with a prevalence of 10% and an annual incidence of 1%.28 29

Figures 6.11.2.4a and 2.4b: Dementia UK report: consensus estimates of the proportion of all dementia cases accounted for by different dementia subtypes, by age and gender

a) Women
2.2 Discussion - prevalence of dementia

The current estimates provide an indication of the numbers of people aged 60 years and over with dementia worldwide and in different world regions. There is much more uncertainty as to the prevalence of YOD but, if such cases were to be included, the total numbers affected might be up to 6–9% higher. The current estimates for the prevalence of dementia among those aged 60 years and over are approximately 10% higher than those from the earlier ADI Delphi consensus, accounted for by a higher age-standardized prevalence for South Asia (5.7% versus 3.4%), Western Europe (7.3% versus 5.9%) and the Latin American regions (8.5% versus 7.3%). These increases were partly offset by the lower estimated prevalence for East Asia (5.0% versus 6.5%). The new estimates are likely to be an improvement on those provided earlier, given the extension in the evidence base from LMIC. It was possible to include seven studies from South Asia, 52 from Western Europe, 34 from East Asia and 11 from Latin America in the regional meta-analyses. There was previously just one prevalence study available from Latin America. The decision to pool the data across the four GBD regions in Latin America was supported by the relatively low level of heterogeneity in estimates between sites. The evidence base from China was considerably extended by a recent systematic review that included data from publications previously available only in Chinese journals. The previous estimates for South Asia were perhaps disproportionately influenced by one large study, from rural Ballabgarh in northern India, which recorded an unusually low prevalence. Earlier estimates for Europe were strongly influenced by two previous reviews by the European Community Concerted Action on the Epidemiology and Prevention of Dementia Group (EURODEM). The current systematic review is much more comprehensive, and the new estimates coincide with the 7.1% prevalence derived from a recent systematic review by the EuroCoDe group.

Data was insufficient for certain regions, particularly Eastern Europe, North Africa, the Middle East, Russia, and sub-Saharan Africa. As such, the estimates must still be considered provisional. The current estimates have drawn on previous Delphi consensus estimates for these regions. A limitation of this review could be using two methodologies to quantify prevalence estimates for different GBD regions, i.e. meta-analysis for 11 out of 21 regions where sufficient studies were available and for

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others (due to insufficient data), use of relevant estimates from the Delphi consensus. Meta-analysis methods that allow estimates for regions without data by borrowing strength from those with data would allow updated estimates for all regions. This also emphasizes the need of more data of good quality for the GBD regions where sufficient studies were not available.

The low prevalences for sub-Saharan Africa are mainly determined by the one good-quality study (Ibadan, Nigeria) that was available when the review was conducted in 2009.\textsuperscript{15} Subsequent studies from francophone countries in western and central Africa, and one further study from northern Nigeria suggest a more variable prevalence, higher in urban than in rural sites, and higher in central compared with western Africa.\textsuperscript{36,37,38,39} The Nigerian study recorded a low prevalence that is consistent with findings from the earlier USA/Nigeria study (2.4% for those aged 65 and over, age-standardized to Western Europe, with an age-standardized prevalence of 1.9% for those aged 60 and over assuming that the prevalence for those aged 60–64, which was not assessed, was half that of those aged 65–74).\textsuperscript{39} Prevalence was similarly low in rural Benin (2.4% age-standardized for age 65+ and 2.0% for age 60+ similarly estimated).\textsuperscript{36} The prevalence in urban Benin was higher (4.3% and 3.5%) and that recorded in cities in the Central African Republic (10.1% and 8.2%) and the Republic of the Congo (7.2% and 6.0%) was substantially higher.\textsuperscript{38,39}

Current evidence therefore challenges the previous consensus that the prevalence of dementia was lower in LMIC, and strikingly so in some studies.\textsuperscript{9,11} Methodological factors may be implicated.\textsuperscript{6,7,8} In the 10/66 Dementia Research Group studies, the group’s 10/66 dementia diagnosis – developed, calibrated and validated in a 26-site pilot study – was both more prevalent than that according to DSM-IV criteria, and more consistent between sites.\textsuperscript{40} The prevalence of DSM-IV dementia was particularly low in rural and less developed sites.\textsuperscript{41} It may be that milder dementia is under-detected in LMIC because of low awareness, high levels of support routinely provided to older people, and reluctance to report failings to outsiders, which could all contribute to difficulties in establishing the DSM-IV criterion of social and occupational impairment.\textsuperscript{8} In Cuba, the criterion validity of the 10/66 diagnosis was superior to that of DSM-IV which selectively missed mild and moderate cases.\textsuperscript{42} In India, the predictive validity of the 10/66 diagnosis was supported by high mortality after three years of follow-up, with survivors showing expected progression of cognitive impairment, disability and needs for care;\textsuperscript{43} this suggested that the true prevalence at baseline was likely to be much closer to the 7.5% recorded for 10/66 dementia than the 0.9% prevalence according to DSM-IV criteria.\textsuperscript{41}

Extracted from the WHO dementia Report 5.

Recent epidemiological surveys report that “North America and Western Europe have at age 60, the highest prevalence of dementia (6.4 and 5.4% of the population at age 60), followed by Latin America (4.9%) and China and its developing western-Pacific neighbors (4.0%). The annual incidence rates (per 1000) for these countries were estimated at 10.5 for North America, 8.8 for Western Europe, 9.2 for Latin America and 8.0 for China and its developing western-Pacific neighbors, increasing exponentially with age in all countries, especially through the seventh and eighth decades of life”\textsuperscript{14}
Figure 6.11.3: Growth in numbers of people with dementia in high-income and low- and middle-income countries.

![Graph showing growth in numbers of people with dementia](image)


Figure 6.11.4: Estimated age-specific annual incidence of dementia, derived from mixed-effects Poisson meta-regression, for world regions for which meta-analytical synthesis was feasible.

![Graph showing estimated age-specific annual incidence of dementia](image)

2.3 Dementia in Europe

According to Alzheimer Europe Association and following UN’s demographic forecast number of demented patients in Europe will rise substantially in the following years. There are over six million people with dementia in the EU. Currently, 40% of those with late-stage Alzheimer disease live at home, while 60% live in healthcare establishments. Families have often to take care of a relative with Alzheimer disease, which is a challenging experience. With the ageing of the baby boomer generation, managing dementia in elderly is one of the greatest challenges that Europe will have to face in the next 50 years.

From The WHO dementia Report:

The most sophisticated analysis of dementia subtype was that carried out for the Dementia UK report. Authors estimated the proportion of dementia cases accounted for by different subtypes according to age and sex, using a Delphi consensus of United Kingdom and other European evidence. Three of six United Kingdom population-based studies of late-onset dementia included information on subtype diagnoses (Alzheimer disease, VaD or mixed dementia and “other”). A more recent community-based study provided information on the relative frequency of a wider range of subtypes; Alzheimer disease (41%), VaD (32%), dementia in Parkinson Disease (3%), FTD (3%) and DLB (8%); Only the EURODEM meta-analysis of studies in the 1990s provided gender- as well as age-specific proportions with Alzheimer disease and VaD. In that study, while the proportion with Alzheimer disease among females remained constant at around 70%, among men the proportion increased progressively from 38% among those aged 65–69 years to 80% in those over 90 years of age. Two YOD studies included detailed information on the full range of dementia subtypes, based on specialist dementia clinic assessments. Two further YOD studies provided limited information on the relative frequency of Alzheimer disease, VaD and mixed dementia.

The results indicate that the FTD is a common subtype in YOD, particularly among men among whom it is the commonest subtype up to age 55 (Figures 6.11.2-4a and 2-4b). Vascular dementia is also relatively more common among men aged 45–75 years of age. While the proportion of dementia cases attributable to Alzheimer disease, the commonest subtype overall, is relatively constant among women varying between 40–60% across the age range from 30 years and over, among men the proportion increases steadily with age from around 20% at age 30 to around 70% at ages 95 and over.

Studies in developed countries have consistently reported Alzheimer disease to be more prevalent than VaD. Early surveys from South-East Asia were an exception, though more recent studies suggest that the pattern may now have reversed. This may be due to increasing longevity and better physical health. Alzheimer disease, with typically a later age of onset than VaD, increases as the number of very old people increases. Better physical health reduces cerebrovascular disease and hence the numbers with VaD. These changes also tend to shift the sex ratio towards a preponderance of female cases.

Detailed graphs regarding DALYs and mortality caused by Alzheimer disease and other dementias by regions and sex are in Annex 6.11.7 and 6.11.8.

Global incidence of dementia

Studies of the incidence of the Alzheimer disease subtype were recently systematically reviewed. Twenty-seven studies were identified, of which only seven were conducted outside of North America and Europe – three from Japan, and one each from China (Province of Taiwan), India, Nigeria and
Brazil. Hence, only three studies were performed in LMIC. Incidence at age 80 was higher in North America (20.6/1000 person years) and Europe (15.1) than in other countries (8.3). However, the doubling time was shorter in other countries (5.0 years) than in North America (6.0) or Europe (5.8). Incidence was slightly higher among women (13.7 per 1000 person years) than in men (10.6/1000 person years). The last review of the incidence of dementia was conducted in 1998, in which 23 studies were identified, with only one from LMIC. Incidence in Europe increased from 9 per 1000 person years at ages 60–64 to 180 per 1000 person years at ages 90–94. A new review was conducted to estimate annual incidence rates and expected annual numbers of new cases in 21 GBD regions.

Search results

The search yielded 1718 abstracts, from which we identified 34 fully eligible studies. Of these, 16 had been conducted in Western Europe, five in North America (four in the USA and one in Canada), four in East Asia (four in China, including one in the Province of Taiwan), six in Latin America or the Caribbean (Brazil, Cuba, Dominican Republic, Mexico, Peru and Venezuela), one in Australasia (Australia), one in the Asia Pacific region (Republic of Korea), and one in West sub-Saharan Africa (Nigeria). Collectively, the studies included 72,224 older people “at risk” and accumulated 214,756 person years of follow-up. The median cohort at risk was 1,769 (interquartile range 937–3,208) and the median person years was 4,679 (interquartile range 2,795–9,101). Most studies applied DSM-III-R (n=14), DSM-IV (n=14) or ICD-10 (n=3) criteria. The six 10/66 Dementia Research Group studies applied both DSM-IV and 10/66 dementia criteria.

Coverage

While the evidence base from Europe and North America dominated, 13 of the 34 studies were from outside these regions, and 10 studies were conducted in countries with low or middle income regions. There was no coverage for nine GBD regions: Oceania, South-East Asia, Central Asia, Central Europe, Eastern Europe, North Africa/Middle East, Southern sub-Saharan Africa, Central sub-Saharan Africa and Eastern sub-Saharan Africa. Five studies (four in Europe and one in the USA) focused on persons aged 80 years or over. The Western European studies contributed 52% of the total person years, the North American studies 21% and the Latin American studies 15%, with just 12% contributed by studies from other regions.

Modelling the incidence of dementia

The incidence of dementia increases exponentially with increasing age. For all studies combined, the incidence of dementia doubles with every 5.9 year increase in age, from 3.1 per 1000 person years at age 60–64 to 175.0 per 1000 person years at age 95+ (see Figure 6.11.4). The incidence of dementia appears to be higher in countries with high incomes (doubling every 5.8 years from 3.4 per 1000 person years to 202.2 per 1000 person years) than in LMIC (doubling every 6.7 years from 2.9 per 1000 person years to 99.4 per 1000 person years). Overall the incidence of dementia in LMIC was 36% lower (RR 0.64, 95% CI 0.48–0.85) than in high-income countries. However, if the 10/66 Dementia Research Group’s cross-culturally validated 10/66 dementia criteria were applied rather than DSM-IV criteria, then this difference was no longer apparent (RR 0.99, 95% CI 0.74–1.33). There was significant heterogeneity in the incidence estimates when all studies were combined (alpha = 0.16). Heterogeneity was greater for studies in countries with high incomes (0.17) than in countries with low or middle incomes (0.02).
Estimation of annual numbers of incident cases of dementia

Numbers of new cases increase and then decline with increasing age in each region; in Europe and the Americas peak incidence is among those aged 80–89 years, in Asia it is among those aged 75–84 years, and in Africa among those aged 70–79 years (Table 6.11.4). The researchers estimated nearly 7.7 million new cases of dementia each year worldwide, implying one new case every 4 seconds. Some 3.6 million (46%) would impact in Asia, 2.3 million (31%) in Europe, 1.2 million (16%) in the Americas, and 0.5 million (7%) in Africa.

Discussion - the incidence of dementia

Incidence rates and numbers of new cases are particularly relevant to efforts to develop, initiate and monitor prevention strategies. Prevalence differences between populations and trends in prevalence over time are difficult to interpret since they may arise from differences in underlying incidence or duration (survival with dementia). The current estimate of 7.7 million new cases per year is an important benchmark, globally and regionally, particularly given the relatively low levels of heterogeneity between studies.

Various explanations have been advanced for previous observations of very low prevalences of dementia in some LMIC sites. Estimates of the incidence of dementia were also exceptionally low in the US-Nigeria and US-India studies, suggesting that differences in survival could have been only part of the explanation for the low prevalence recorded in those sites. Differences in levels of exposure to environmental risk factors may also have contributed (e.g. the healthy cardiovascular status of older Nigerians). Differing patterns of mortality in early life might also be implicated; older people in very poor countries are exceptional survivors, and some of the factors that confer survival advantage may also protect against dementia onset in late life. However, the evidence from our meta-analysis suggests that differences in dementia incidence between developed and developing countries may not be as large as had previously been suggested, and that methodological factors, particularly the use of DSM-IV diagnostic criteria, may have contributed. For the 10/66 Dementia Research Group studies, as with prevalence, the incidence of 10/66 dementia is higher than that of DSM-IV dementia, and when that criterion is applied in this meta-analysis the developed/developing country incidence rates converge. Clearly more research is required into the incidence of dementia in order to provide more evidence on the extent of the problem in different world regions.

Mortality associated with dementia

Dementia shortens the lives of those who develop the condition. One of the best studies in the field estimated median survival with Alzheimer disease at 7.1 years (95% CI 6.7–7.5 years) and for VaD 3.9 years (3.5–4.2 years). There is much individual variability around these median estimates. The independent contribution of dementia to mortality is difficult to assess. Death certificates are unreliable, since dementia is rarely considered as a direct or underlying cause of death. People with dementia often have comorbid health conditions that may or may not be related to the dementia process and which themselves may hasten death. Hence deaths of people with dementia cannot automatically be considered to be deaths attributable to dementia.

Review

A meta-analysis of studies principally from high-income countries estimated a two-and-a-half-fold increased mortality risk for people with dementia (RR 2.63, 95% CI 2.17–3.21). The EURODEM incidence studies reported a constant relative risk of 2.38 up to age 89 years, declining to 1.80 in...
females and 1.60 in males over the age of 90 years. Estimates from LMIC suggest a slightly higher relative mortality hazard: in the 10/66 Dementia Research Group studies, the pooled HR was 2.77 (95% CI 2.47–3.10), with a modest degree of heterogeneity, while even larger relative risks have been recorded in studies in Nigeria (HR 2.83, 95% CI 1.10–7.27) and Brazil (HR 5.16, 95% CI 3.74–7.12). In the three studies published to date that have compared dementia with other health and sociodemographic factors influencing mortality in countries with low or middle incomes, dementia emerged as the leading contributor among health conditions. 59, 60

In the Dementia UK report, the EURODEM mortality relative risks were used to calculate the proportion of deaths at different ages independently attributable to dementia. This proportion increased steadily from 2% at age 65 years to a peak of 18% at age 85–89 years in men, and from 1% at age 65 to a peak of 23% at age 85–89 in women. Overall, 10% of deaths in men over 65 years, and 15% of deaths in women are attributable to dementia, the majority occurring among those aged 80–95 years.

Estimates of deaths attributable to dementia from the GBD Report are much more conservative – 4.0% of deaths (275 000) among those aged 60 and over in high-income countries, 0.6% (19 000) in upper-middle-income countries, 0.6% (72 000) in lower-middle-income countries and 1.3% (111 000) in lower-income countries, amounting to 477 000 annual deaths worldwide, just 1.6% of the global total for this age group.

Extracted from the WHO dementia Report.

2.4 Economic impact: the global societal cost of dementia

Dementia is expensive. The financial costs of managing AD are enormous. The cost of illness is high in terms of both public and private resources. Families and caregivers who are required to provide care and patients affected by dementia also pay a high price in terms of their quality of life. “In high-income countries, informal care (45%) and formal social care (40%) account for the majority of costs, while the proportionate contribution of direct medical costs (15%) is much lower. In low-income and lower-middle-income countries direct social care costs are small, and informal care costs (i.e. unpaid care provided by the family) predominate. Changing population demographics in many LMIC may lead to a decline in the ready availability of extended family members in the coming decades” states the 2012 WHO report “Dementia: a health priority”.

Most European countries are spending about 1% of their gross domestic product (GDP) on dementia. Sweden spends over 2.5%. The biggest driver of costs is nursing homes or residential care.

From the WHO dementia Report:

A proper understanding of the societal costs of dementia, and how these impact upon families, governments and their health and social care systems, is fundamental to raising awareness, achieving proper prioritization, and focusing efforts to improve the lives of people with dementia and their caregivers. Cost-of-illness studies for dementia have been carried out for some, mainly high-income, countries such as Australia, Canada, Sweden, United Kingdom and the USA, as well as the European Union.23, 62, 63, 64, 65, 66 The consensus is that dementia is already imposing huge economic burdens, both through direct (medical and social care) and indirect costs (unpaid caregiving by families and friends). Evidence is also emerging of the extent of the economic burden in middle-income countries. 67, 68, 69, 70
Cost-of-illness studies are descriptive, quantifying the total societal economic burden of a health condition and highlighting its impact on different health and social care sectors. The distribution of costs between countries and regions can also be estimated and compared, and trends over time can be monitored or, tentatively, projected into the future. Comparison of costs of illness across health conditions is more challenging; it has also been argued that prioritization for investment should be determined more by the relative cost-effectiveness of available interventions than by the economic burden of the disease.\(^7^1\)

Three previous reports of the global economic burden of dementia were each based on the best available data for the prevalence of dementia and care inputs.\(^7^2\),\(^7^3\),\(^7^4\) The most recent of these estimated global costs at US$ 422 billion in 2009, 74% contributed by high-income countries. The aim of this recent cost-of-illness study was to generate evidence-based estimates of resource utilization for each country. Thus, country-specific annual per capita costs (direct medical and social care costs, and informal care) were applied to estimated numbers of people with dementia in each country, and aggregated up to the level of WHO regions, and World Bank country income-level groupings. The costs (as well as the prevalence of dementia) reflect estimates for 2010. Cost estimates based on previous years are inflated appropriately. Costs are expressed as US dollars, converted from local currencies based on current exchange rates. Where no estimates were available for a country, estimates from other similar countries within the same region or adjacent regions were used. For direct costs, the strong relationship between the direct costs per person with dementia and per capita Gross Domestic Product (GDP) was used to predict total direct costs for countries within regions with no data. The split between medical and social care costs was estimated by applying data from China, the one LMIC with available data.

Figure 6.11.5: Distribution of total societal costs (%) by World Bank Income level

Table 6.11.4: Per capita (US$) and aggregated costs (billions US$) by Global Burden of Disease region and World Bank income classification

<table>
<thead>
<tr>
<th>GBD world region</th>
<th>Per capita costs (US$)</th>
<th>Number of people with dementia</th>
<th>Aggregated costs (US$ billion)</th>
<th>Total costs as % of GDP</th>
<th>Direct costs as % of GDP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Informal care (all ADLs)</td>
<td>Direct medical costs</td>
<td>Direct social costs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.30</td>
<td>0.70</td>
<td>5.07</td>
</tr>
<tr>
<td>Australasia</td>
<td>32 370</td>
<td>311 327</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia Pacific, High Income</td>
<td>29 057</td>
<td>2 826 388</td>
<td>34.60</td>
<td>5.23</td>
<td>42.29</td>
</tr>
<tr>
<td>Oceania</td>
<td>6 059</td>
<td>16 553</td>
<td>0.07</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Asia, Central</td>
<td>2 862</td>
<td>33 0125</td>
<td>0.43</td>
<td>0.28</td>
<td>0.24</td>
</tr>
<tr>
<td>Asia, East</td>
<td>4 078</td>
<td>5 494 387</td>
<td>15.24</td>
<td>4.33</td>
<td>2.84</td>
</tr>
<tr>
<td>Asia, South</td>
<td>903</td>
<td>4 475 324</td>
<td>2.31</td>
<td>1.16</td>
<td>0.57</td>
</tr>
<tr>
<td>Asia, South-East</td>
<td>1 601</td>
<td>2 482 076</td>
<td>1.77</td>
<td>1.48</td>
<td>0.73</td>
</tr>
<tr>
<td>Europe, Western</td>
<td>30 122</td>
<td>6 975 540</td>
<td>87.05</td>
<td>30.19</td>
<td>92.88</td>
</tr>
<tr>
<td>Europe, Central</td>
<td>12 891</td>
<td>1 100 759</td>
<td>8.59</td>
<td>2.67</td>
<td>2.94</td>
</tr>
<tr>
<td>Europe, Eastern</td>
<td>7 667</td>
<td>1 869 242</td>
<td>7.96</td>
<td>3.42</td>
<td>2.94</td>
</tr>
<tr>
<td>North America, High Income</td>
<td>48 605</td>
<td>4 383 057</td>
<td>78.76</td>
<td>36.83</td>
<td>97.45</td>
</tr>
<tr>
<td>Caribbean</td>
<td>9 092</td>
<td>327 825</td>
<td>1.50</td>
<td>0.78</td>
<td>0.71</td>
</tr>
<tr>
<td>Latin America, Andean</td>
<td>3 663</td>
<td>254 925</td>
<td>0.35</td>
<td>0.31</td>
<td>0.28</td>
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<tr>
<td>Latin America, Central</td>
<td>5 536</td>
<td>1 185 559</td>
<td>1.58</td>
<td>2.61</td>
<td>2.37</td>
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<tr>
<td>Latin America, Southern</td>
<td>8 243</td>
<td>61 4523</td>
<td>2.36</td>
<td>1.42</td>
<td>1.29</td>
</tr>
<tr>
<td>Latin America, Tropical</td>
<td>6 881</td>
<td>1 054 560</td>
<td>2.17</td>
<td>2.67</td>
<td>2.42</td>
</tr>
<tr>
<td>North Africa/Middle East</td>
<td>3 296</td>
<td>1 145 633</td>
<td>1.90</td>
<td>2.05</td>
<td>0.54</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Central</td>
<td>1 081</td>
<td>67 775</td>
<td>0.04</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Sub-Saharan Africa, East</td>
<td>1 122</td>
<td>360 602</td>
<td>0.28</td>
<td>0.08</td>
<td>0.04</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Southern</td>
<td>6 834</td>
<td>100 733</td>
<td>0.52</td>
<td>0.11</td>
<td>0.06</td>
</tr>
<tr>
<td>Sub-Saharan Africa, West</td>
<td>969</td>
<td>181 803</td>
<td>0.11</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>World Bank classification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low income</td>
<td>868</td>
<td>5 036 979</td>
<td>2.52</td>
<td>1.23</td>
<td>0.62</td>
</tr>
<tr>
<td>Lower middle income</td>
<td>3 109</td>
<td>9 395 204</td>
<td>18.90</td>
<td>6.74</td>
<td>3.57</td>
</tr>
<tr>
<td>Upper middle income</td>
<td>6 827</td>
<td>4 759 025</td>
<td>13.70</td>
<td>10.44</td>
<td>8.35</td>
</tr>
<tr>
<td>High income</td>
<td>32 865</td>
<td>16 367 508</td>
<td>216.77</td>
<td>78.00</td>
<td>243.14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16 986</td>
<td>35 558 717</td>
<td>251.89</td>
<td>96.41</td>
<td>255.69</td>
</tr>
</tbody>
</table>


The major limitation was the sparse data on health and social care from LMIC, with cost models relying largely on extrapolation of economic conditions from higher-income to lower-income countries, adjusted for per capita GDP. Also, it was not possible to distinguish between direct medical costs (within the health care sector) and direct social care costs (within the community and care-home
The global costs of dementia (base case option)

The total global societal costs of dementia were US$ 604 billion in 2010 (Annex6.11.5). This corresponds to 1.0% of the aggregated worldwide GDP, or 0.6% if only direct costs are considered. The total cost as a proportion of GDP varied from 0.24% in low-income countries to 1.24% in high-income countries, with the highest proportions in North America (1.30%) and Western Europe (1.29%). The per capita costs of dementia varied considerably by World Bank income classification, from US$ 868 in low-income countries, to US$ 3 109 in lower-middle-income countries, to US$ 6 827 in upper-middle-income countries, to US$ 32 865 in high-income countries. When multiplied by the estimated numbers of people with dementia, this generated aggregated costs of US$ 4.37 billion in low-income countries, US$ 29.21 billion in lower-middle-income countries, US$ 32.39 billion in upper-middle-income countries, and US$ 537.91 billion in high-income countries. Therefore, the costs of dementia are unevenly distributed. About 70% of the global societal costs of dementia occur in just two WHO GBD regions (North America and Western Europe) and 89% of the total costs are incurred in high-income countries. However, the minority (46%) of people with dementia live in high-income countries, 39% of people with dementia live in middle-income countries (where 10% of costs are incurred) and 14% in low-income countries (accounting for less than 1% of the total costs).

The distribution of total costs between sectors also varies markedly by country income level. In high-income countries, the costs of informal care (45%) and the direct costs of social care (40%) contribute similar proportions to total costs, while the proportionate contribution of direct medical costs (15%) are much lower (Figure 6.11.7). However, in low-income countries and lower-middle-income countries direct social care costs are small and informal care costs predominate. Thus, while the total cost per person with dementia is 38 times higher in high-income countries than in low-income countries, the direct costs of social care are 120 times higher. In the ADI worldwide survey of care home utilization, the proportion of people with dementia living in care homes was significantly higher in high-income countries (30%, 95% CI 23–37%) than in LMIC (11%, 95% CI 5–17%).

Sensitivity analyses

If only basic ADLs are used for the costs of informal care instead of combining basic ADLs and IADLs, the total costs are 22% lower. They are 30% higher if combined ADLs/IADLs and supervision are included. Compared with US$ 604 billion in the base case, these sensitivity analyses provide a lower bound of US$ 470 billion (only basic ADLs) and an upper bound of US$ 783 billion (all informal care including assistance with basic ADL and IADL and supervision).

Since a substantial proportion of caregivers are spouses and most, but not all, could be assumed to be beyond the usual working age, the informal care and total costs were recalculated by applying a reduced wage to the estimated proportion of caregivers in each country who were spouses. This leads to a 9% reduction in the total worldwide cost estimate from US$ 604 billion to US$ 548 billion when costed at 50% of the average wage and a 14% reduction to US$ 520 billion when costed at 25% of the average wage. With the replacement costs approach, based on the average wage of a social care professional in that country, the total costs were slightly higher.

Under the base case option, low-income countries accounted for just 0.7% of total worldwide costs, middle-income countries for 10.2% and high-income countries for 89.1%. Using PPP rather than
exchange rates to translate costs in local currencies to the common US dollar metric, the proportions increased for low-income countries (2.1%) and middle-income countries (20.0%) and fell for high-income countries (77.9%).

Discussion - the economic cost of dementia

The estimated annual worldwide cost to society of dementia, US$ 604 billion, highlights the enormous impact that dementia has on socioeconomic conditions worldwide. If dementia care were a country, it would be the world’s twenty-first largest economy, ranking between Poland and Saudi Arabia. The scale of these costs is understandable given that:

- the 35.6 million people worldwide comprise 0.5% of the world’s total population;
- a high proportion of people with dementia need some care, ranging from support with IADL, to full personal care and round-the-clock supervision;
- in some high-income countries, one third to one half of people with dementia live in resource- and cost-intensive residential or nursing homes.23,76

The marked imbalance in the global distribution of prevalence and costs arises, in part, because of the imbalance of costs between sectors. In LMIC, the formal social care sector (accounting for the direct costs of care in the community by paid social care professionals, and of care homes) is practically nonexistent. Therefore, responsibility falls largely on unpaid informal carers, and informal care costs predominate. In high-income countries the direct costs of social care account for nearly half of all costs. Since average wages (used to estimate informal care costs) are much lower in LMIC, this has an important impact on comparative total costs.

It is difficult to compare our estimates of the global societal costs for dementia with those for other conditions because few such estimates exist and there are problems with comparability. In the United Kingdom, a recent report commissioned by the Alzheimer Research Trust focused on the economic burden of dementia and other chronic diseases, and sought to compare like-for-like disease costs with national expenditure on research.77 The societal costs of dementia (£23 billion) almost matched those of cancer (£12 billion), heart disease (£8 billion) and stroke (£5 billion) combined. However, for every £1 million in costs arising from the disease, £129 269 was spent on cancer research, £73 153 on heart disease research and £4 882 on dementia research. In a paper from Sweden the costs of dementia were compared with other estimates for chronic disorders.78 The annual costs of dementia (50 billion SEK) was higher than for depression (32.5 billion SEK), stroke (12.5 billion SEK), alcohol abuse (21–30 billion SEK) and osteoporosis (4.6 billion SEK).

Future trends

The reported projections for future growth in numbers of people with dementia should be treated with caution. First, these rely on demographic projections which may not be accurate for many parts of the world, especially for older age groups. Second, it was assumed that age-specific prevalence in each region would remain constant over time. However, changes in risk exposure may increase or decrease incidence. Conversely specific therapies and better social and medical care may reduce case mortality and increase prevalence. Disease-modifying therapies that delay onset, even to a modest extent, would have considerable potential for reducing age-specific prevalence.

It is particularly difficult to make confident projections of future economic costs. If we assume that all potential background factors remain unchanged, and we factor in only the forecast increases in the number of people with dementia, then by 2030 worldwide societal costs will have increased by 85%.
The reality is more complicated. Future costs could be influenced by macroeconomic factors (e.g. the pace of economic development) and by dementia-specific factors. These would include changes in the prevalence of dementia, in patterns of help-seeking and trends towards earlier diagnosis, in the availability of health and social care services, changes in care systems and care conditions and the availability of new and more effective treatments. There are very few estimates of the extent of the “treatment gap” for dementia in LMIC, but it is likely to be much greater than in better-resourced settings. The current inequitable distribution in dementia costs between world regions will also have implications for future trends, which are likely to tend towards more rapidly increasing per capita and population costs in LMIC, with the result that the global distribution of costs will come to resemble that of morbidity. These cost increases will be driven by several underlying factors. First, increases in numbers of people with dementia will occur much more rapidly in LMIC because of the more rapid demographic ageing in those regions. Second, with economic development, wages will rise rather rapidly in LMIC. Third, resources for dementia care, particularly formal medical and social care, are unequally distributed worldwide. With increased awareness will come increased demand for care. Residential and community social care systems are well developed in many high-income countries but are scarce in LMIC where there is a reliance on traditional, informal family care arrangements. In many LMIC the traditional family and kinship structures are under threat from the demographic, social and economic changes that accompany economic development and globalization. Therefore, the need for community and residential care is likely to grow in LMIC, and with it direct costs.

3. Control Strategy

Dementia is a complex disease and its management is often challenging. Personality and behavioural changes, and the eventual inability to perform activities of daily living lead to dependence. As functional impairment deteriorates, health care utilization increases until patients are forced to become institutionalized. Patients can remain in severe stages of AD for several years. From The WHO dementia Report 5:

3.1 Etiology and potential for prevention

The US National Institutes of Health (NIH) conducted a state-of-the-science conference review in 2010 to provide health-care providers, patients and the public with an assessment of currently available data on prevention of Alzheimer disease and cognitive decline. Their report states that “firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or Alzheimer disease”. However, the evidence base is still incomplete and further research is required. Very few primary prevention randomized controlled trials have been conducted, and the results do not support potential for risk reduction. Nevertheless, many of these trials recruited older people, and follow-up periods were relatively short. Given that neurodegeneration may precede the onset of dementia by several decades, this may have been a case of too little too late. There is, however, a strong evidence base from population-based cohort studies attesting to the potential risk reduction benefits of better cardiovascular health, more education, and higher levels of physical activity.
Dementia, cardiovascular risk factors and cardiovascular disease

Research suggests that vascular disease predisposes to Alzheimer disease as well as to vascular dementia.\textsuperscript{84} In short and longer latency incidence studies, smoking increases the risk for Alzheimer disease.\textsuperscript{85,86,87,88,89} Diabetes is also a risk factor and, in longer-term cohort studies, midlife hypertension and raised cholesterol are associated with the onset of Alzheimer disease in later life.\textsuperscript{90,91,92} Aggregated cardiovascular risk indices incorporating hypertension, diabetes, hypercholesterolemia and smoking increase risk for dementia incidence incrementally whether exposure is measured in midlife or a few years before onset of dementia.\textsuperscript{87,89}

Despite occasional negative findings from large prospective studies, the accumulated evidence for a causal role for cardiovascular risk factors and cardiovascular disease in the etiology of dementia and Alzheimer disease is very strong.\textsuperscript{93,94} This has led to speculation that atherosclerosis and Alzheimer disease are linked disease processes, with common pathophysiological and etiologic underpinnings (ApoE ε4 polymorphism, hypercholesterolemia, hypertension, hyperhomocysteinemia, diabetes, metabolic syndrome, smoking, systemic inflammation, increased fat intake and obesity).\textsuperscript{95}

One of the complicating factors for interventions in this area is that evidence suggests that while hypertension, raised cholesterol and obesity in midlife increase the risk for later onset of dementia, blood pressure levels, cholesterol and body mass index fall progressively before the onset of the disease.\textsuperscript{91,96,97} Hence people with dementia have lower blood pressure levels, cholesterol and body mass than others. Therefore, early primary prevention may be the most effective intervention. Preventive trials indicate that statins and antihypertensive treatment do not seem to lower the incidence of dementia when initiated in older people, but there have been no long-term trials from midlife onwards.\textsuperscript{98,99}

### 3.2 Diagnosis of Alzheimer disease

Alzheimer disease is usually diagnosed on physical and neurological exams, and checking for signs of intellectual impairment through standard tests of mental function. For a diagnosis of AD, new criteria were published in 2011.\textsuperscript{100}

McKhan et al. define the initial and most prominent cognitive deficits based on history and examination in one of the following categories:\textsuperscript{100}

- **Amnestic presentation**: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.

- **Nonamnestic presentations**: Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.

- **Executive dysfunction**: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

Diagnostics tests such as MRI and CT and laboratory testing are also done to rule out medical causes of decreased brain function. Definitive changes found in the brain of affected
AD patients are microscopic and can be seen only when a sample of brain tissue is removed and examined, usually on autopsy.\textsuperscript{11,13} To appropriately diagnose for AD, other forms of dementia or diseases need to be ruled out. This includes the following:

- **Medication-induced dementia.** Medication-induced dementia is the most frequent cause of “reversible” dementia. To rule out a medication-induced dementia, a thorough drug history and a review of all current medication (both prescription and over-the-counter) needs be undertaken.

- **Metabolic/endocrine/nutritional/systemic disorders.** Metabolic/endocrine/nutritional/systemic disorders (e.g., hypothyroidism, B12 deficiency, and systemic diseases and heavy metal metal poising) are additional causes of “reversible” dementias and can be diagnosed with routine laboratory tests. Tests recommended include blood count, sedimentation rate (if indicated), electrolytes (including calcium), liver and renal function tests, urinalysis, syphilis serology, B12 levels, thyroid function tests, and a toxicity screen (if medical history and the physical exam so indicate).

- **Vascular dementia/hydrocephalus/tumors/hematoma.** Vascular dementia (VaD) may result as a sequel to any form of cerebrovascular disease and blood hyperviscosity. VaD is responsible for approximately 20 per cent of dementia cases including Alzheimer disease.

- **Normal pressure hydrocephalus, brain tumors, and subdural hematoma,** the most common of the structural brain lesions, and stroke can also present with dementia. Confirmation or exclusion of their presence usually requires a CT or MRI scan.

- **Depression** is another common cause of dementia in the elderly population. The following symptoms cognitive impairment symptoms may be present: confusion, memory disturbance, and attention deficits, all of which can be mistaken for dementia. Depression may also coexist with dementia and exacerbate the problem, causing “excess disability.” A good history and thorough mental-status is required as part of the treatment plan. The DSM-IV criterion for diagnosis of depression is often referred to confirm or rule out depression. As the patients affected by Alzheimer disease are advanced in age they are likely to have other chronic illnesses. Most patients with chronic illnesses do not have a single, predominant condition. Rather, most have comorbidity, the simultaneous presence of multiple chronic conditions.

The clinical criteria and diagnosis of dementias, including AD, has not changed since the 1990’s. Given the advantages of early diagnosis and early intervention, there is an urgent need to revise the criteria for diagnosis so that the disease may be identified in the earlier stages. There is much research in identifying the shift between **EARLY** cognitive changes associated with dementia and that associated with normal aging, an area known as mild cognitive impairment (MCI). The current consensus is that mild cognitive impairment is not synonymous with early dementia, one in three regress, one in three stay the same and one in three progress to dementia.\textsuperscript{14} This remains a challenge for both clinicians and researchers since the Mini Mental State Examination (MMSE), Dementia Rating Scale and other evaluating tools are relatively insensitive to early cognitive symptoms.\textsuperscript{13}

### 3.3 Management of Alzheimer disease

The primary goals of treatment are to maximize the patient’s ability to function in daily life, maintain quality of life, slow the progression of symptoms, and treat depression or disruptive behaviors.
Treatment of AD takes on a systematic approach. First, if there are medical conditions that make Alzheimer symptoms worse that illness needs to be managed. There are several medications such as alcohol, sedatives and antihistamines, that can also aggravate AD, and these must be identified and removed, or switched to alternative medicines. If non-pharmacological methods fail, medications may also be administered to treat depression, while antipsychotics medicines can be used to treat aggressive or violent behavior. Finally, “caring for the caregiver” is another vital part of any treatment strategy for AD. Experts within this field recognize that caregivers are at a high risk for depression and medical illness. As a result, recommendations and guidance about community resources and support is integrated into the overall management of the disease.

3.3.1 Pharmacological therapy review for AD

The current pharmacologic therapy for AD only provides short-term improvement for a short period of time, six to eighteen months. The only medicines approved in the US and several parts of Europe for short term alleviation of symptoms are cholinesterase inhibitors and memantine. These drugs do not affect the pathology of AD, but allows the brain to compensate for the loss of neurones that communicate via acetylcholine, a neurotransmitter. This section reviews the clinical efficacy of approved and possible pharmacological therapies for AD.

Cholinesterase inhibitors

Cholinesterase inhibitors are a class of medicines that block cholinesterase—an enzyme that breaks down the neurotransmitter acetylcholine. AD is linked with low levels of acetylcholine, hence inhibiting or blocking the breakdown of acetylcholine through cholinesterase inhibitors may help to improve brain function.

Treatment effects have been demonstrated with several different cholinesterase inhibitors, indicating that the class of agents is consistently better than placebo. However, the disease eventually continues to progress despite treatment and the average effect is often modest. However, global changes in cognition, behavior and functioning have been detected by both physicians and caregivers, indicating that even small measurable differences may be clinically significant. These drugs are similar yet have distinct pharmacology profiles such as onset of action, side effect profile, potential drug interactions, ease of administration (e.g. twice a day versus three times a day), and route of metabolism. Donepezil is indicated for treatment of AD in the USA. However, no published results are available for severe dementia, though open-label follow up from trials suggests that these drugs continue working as the cholinergic deficit increases. Benefits reported for these medications tend to occur at higher doses. However, the higher the dose, the more likely the side effects.

Given the increase in AD prevalence, more studies are needed to determine the role of cholinergic medicines in patients with severe AD and to provide comparative data on therapeutic options for this subset of patients. Efficacy is always likely to be limited by the nature of the stage of the disease. The more severe the dementia, the more neuronal damage and the less the number of surviving cholinergic neurons hence the limitation of the effectiveness of an AChEI – once all receptors are saturated there is no more effect that can be produced – there is a ceiling.
Cochrane Reviews of the cholinesterase inhibitors suggest that treatment effects have been demonstrated with several agents, and that this class is generally more efficacious than placebo. Positive changes in cognition, behavior and function were demonstrated, however, the disease continues to progress and the treatment effect is modest and short lived.\textsuperscript{102}

While none of these (cholinesterase inhibitors and NMDA) are FDA approved for vascular dementia (VaD); the growing body of evidence indicates that these may be equally effective in VaD. The implication is that for clinical trials of these therapies may be less susceptible to misclassification (AD v VaD) than putative therapies that intervene is AD specific pathology.

The cholinesterase inhibitors (donepezil and rivastigime) may not be cost effective for the management of AD but the study that reached this conclusion has been challenged by the industry which has asserted that it was under powered. Results of this study were asserted to "… incompatible with many drug company-sponsored observational studies and advertisements claiming remarkable effects of cholinesterase inhibitors".\textsuperscript{104} In addition, previous claims that donepezil can stabilize cognitive deterioration and delay nursing home placement by two to three years have not been validated by this study. The study also showed that the long-term use of donepezil cost the UK National Health Service more than placebo.\textsuperscript{104} The more general understanding is that these drugs do not work in the more severe states of the disease.

Improvements in cognitive functions for the first two years were significantly better than placebo. However, no benefits were seen in the long term endpoints of institutionalization, and the experts state that improvements in cognition does not reduce institutionalization as reported by pharmaceutical companies.\textsuperscript{105}

The National Institute of Health and Clinical Excellence recommend donepezil and rivastigmine as options for managing mild as well as moderate Alzheimer disease. Guidance from NICE technology appraisal guidance 111 issued in November 2006 was amended on September 2007, August 2009).\textsuperscript{108} The criteria is based on QALYs (quality adjusted life years) in the UK. Also, a therapy that is beneficial but results in longer life expectancy may actually increase health care costs compared to not treating due to the longer life expectancy.

Glutamatergic agents

One of the pathological hypotheses suggested to cause AD is neurotoxic mechanisms resulting is excessive amounts of amino acids being released. AD patients have a loss of glutamatergic pyramidal neurons, while the glutamatergic receptors NMDA (N-methyl-D-aspartate) are preserved. An over stimulation of these receptors could lead to neuronal loss which could affect the pathophysiology of Alzheimer disease. A glutamatergic NMDA receptor blocker, called memantine is effective in treating severe AD. The drug has been approved in Germany since 1970's, but clinical trial data to support its use have been limited. Data from recent clinical trials investigating the safety and clinical efficacy of memantine show that it is effective for moderate to severe AD. The medication is still being studied and is approved in the United States and several European countries.\textsuperscript{106}

3.3.2 Psychiatric management of non-cognitive symptoms

While an important aspect of AD, there a numerous therapies many with issues and challenges in the AD patient.
Non-cognitive symptoms of dementia tend to evolve over time, so regular monitoring allows adaptation of treatment strategies to current individual needs. For example, among the behavioural disturbances common in Alzheimer disease, depression is more common early in the illness, while delusions and hallucinations are more common in the middle and later stages. Behavioural issues to be addressed include major depression and other depressive syndromes, suicidal ideation or behaviour, hallucinations, delusions, agitation, aggressive behaviour, disinhibition, anxiety, apathy, and sleep disturbances.\textsuperscript{107}

Early intervention is important since psychiatric symptoms can respond to treatment more readily than cognitive and functional deficits.\textsuperscript{107} Table 6.11.5 shows the behavioural clusters manifested in AD and relevant classes of medications for intervention.\textsuperscript{107}

**Table 6.11.5: Behavioural Clusters Matched with Potentially Relevant Classes of Medications.**

<table>
<thead>
<tr>
<th>Behaviour</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation/aggression</td>
<td>Antipsychotics, anticonvulsants, antidepressants, anxiolytics</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Antidepressants, anxiolytics, anticonvulsants</td>
</tr>
<tr>
<td>Apathy</td>
<td>Antidepressants, stimulants</td>
</tr>
<tr>
<td>Disturbed effect/mood</td>
<td>Antidepressants, anticonvulsants</td>
</tr>
<tr>
<td>Altered ideation/perception</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Vegetative features</td>
<td>Antidepressants, anxiolytics, stimulants</td>
</tr>
</tbody>
</table>

Source: American Psychiatric Association. Practice guidelines for the Treatment of Alzheimer Disease and Other Dementias of Late Life.

- There is sufficient evidence from randomized controlled trials to support the use of both traditional and atypical antipsychotics for the management of agitation and psychosis in dementia. Of the two classes atypical antipsychotics appear to be better tolerated compared to traditional antipsychotics.\textsuperscript{107}
- There is evidence that SSRIs (selective serotonin reuptake inhibitors) antidepressants may be administered and are better tolerated than other antidepressants.

The American Academy of Neurology practice guidelines conducted an in-depth review of pharmacological therapies for non-cognitive symptoms in dementia. The expert panel conclude that most studies in this area focus on mixed populations with dementia. Therefore, it is not entirely possible to assess the efficacy of specific medications for patients with specific form of dementias such as AD.
4. Major Problem and Challenges for Disease Control: Why Does the Disease Burden Persist?

While a cure is desirable, the likely first step may be an intervention that reduces the risk of future disease, similar to the approach to cardiovascular disease. Clinicians and caregivers are challenged with caring for an increasing aging population affected by dementia. Increased life expectancy has seen a rise in chronic medical disease and associated illnesses, including dementia. For example, there will be an estimated 400% increase in population of North Americans aged 85 and older by 2050, 40% of whom will develop dementia. Clinicians providing care for patients with dementia are confronted with numerous challenges in managing AD and other dementias. Psychiatric and behavioural problems are present in up to 90% of patients with dementia. Behavioral issues tends to wax and wane, peaking during the middle stages of AD. Aggression, is significant predictor of nursing home admission in the USA. Some of these treatment options include employing unique social and environmental interventions; knowledge and use of increasingly sophisticated medications, and providing individualized therapy to patients, working with care givers or varying systems providing care. The burden for the general practitioner is the lack of specific medicines for AD and other dementias - the physician has a limited range of therapeutic options. Management of dementia is also complex since it requires differentiating and managing various changing neuropsychiatric and behavioural problems. A balance also has to be reached between aggressive intervention and palliative care continued treatment versus withdrawal of medicines, and patient benefit versus caregiver burden. Managing dementia is complex and presents a major public health concern for the today and the future.

4.1 Country preparedness for dementia

From the WHO dementia Report 5:

The challenges to governments to respond to the growing numbers of people with dementia are substantial. A broad public health approach is needed to improve the care and quality of life of people with dementia and family caregivers. The aims and objectives of the approach should either be articulated in a stand-alone dementia policy or plan or be integrated into existing health, mental health or old-age policies and plans. Some high-income countries have launched policies, plans, strategies or frameworks to respond to the impact of dementia.

There are several key issues that are common to many national dementia policies and plans, and these may be necessary to ensure that needs are addressed in an effective and sustainable manner. These include: scoping the problem; involving all the relevant stakeholders, including civil society groups; identifying priority areas for action; implementing the policy and plan; committing resources; having intersectoral collaboration; developing a time frame and monitoring and evaluation.

The priority areas of action that need to be addressed within the policy and plan include raising awareness, timely diagnosis, commitment to good quality continuing care and services, caregiver support, workforce training, prevention and research.
People with dementia and their families face significant financial impact from the cost of providing health and social care and from reduction or loss of income. Universal social support through pensions and insurance schemes could provide protection to this vulnerable group.

Formal recognition of the rights of people with dementia and their caregivers through legislation and regulatory processes will help reduce discriminatory practices. Fundamental to upholding a person’s rights is the recognition of capacity in persons with dementia. Where capacity is impaired due to dementia, legal provisions should recognize and protect the right to appropriate autonomy and self-determination including substitute or supported decision-making and procedures for implementing advance directives. Education and support relating to ethical decision-making and human rights should be an essential part of capacity-building for all involved in providing dementia care, including policy-makers, professionals and families.

4.2 Health and social systems development

The health and social care needs of the large and rapidly growing numbers of frail dependent older persons should be a matter of great concern for policy-makers in all countries. This is particularly so for LMIC which will experience the greatest increase in ageing in the coming decades.

This challenges governments to develop and improve services for people with dementia, focusing on earlier diagnosis, provision of support in the community, and a responsive health and social care sector. Integrated and coordinated health and social pathways and services will be needed to cater for the changing needs of people with dementia and their caregivers. Such pathways should ensure that the needs of specific or minority population groups are taken into account.

Improved community support will assist families to provide care for longer and to delay or reduce reliance on high-cost residential care. Where resources are finite, especially in LMIC, a focus on community outreach could be an efficient use of scarce resources to improve the quality of life of people with dementia and their caregivers. The effectiveness of task shifting (with appropriate guidelines and training) in LMIC should be further evaluated as a solution to the under-supply of a professional workforce.

Capacity-building of the workforce is essential to improve knowledge and awareness of the benefits of a coordinated response to care. Dementia care, long-term care and chronic disease management incorporating a multidisciplinary team should form part of professional education and should be supported by the development of appropriate practice guidelines. The effectiveness of task shifting (with appropriate guidelines and training) in LMIC should be further evaluated as a solution to the under-supply of a professional workforce. In a world with an increasingly mobile population, the migrant workforce brings its own set of challenges that need to be understood and addressed.

4.3 Support for informal care and caregivers

Dementia has an immense impact on the lives of the family, and particularly the person who takes the primary role in providing care. Most care is provided by family and other informal support systems in the community and most caregivers are women. However, changing population demographics may reduce the availability of informal caregivers in the future.

The provision of care to a person with dementia can result in significant strain for those who provide most of that care. The stressors are physical, emotional and economic. A range of programmes and
services have been developed in high-income countries to assist family carers and to reduce strain. The beneficial effects of caregiver interventions in decreasing the institutionalization of the care recipient have been clearly demonstrated.

Evidence from LMIC also suggests that home-based support for caregivers of persons with dementia, emphasizing the use of locally-available low-cost human resources, is feasible, acceptable and leads to significant improvements in caregiver mental health and in the burden of caring. Despite evidence of effectiveness, there have been no successful examples of scale-up in any of the health systems in which the evaluative research has been conducted. Further research should focus on implementation in order to inform the process of scale-up.

Despite the availability of services in some countries or parts of countries, there are barriers to uptake. Lack of understanding of services, lack of understanding or stigma attached to the syndrome, previous poor experience with services, and cultural, language and financial barriers creates obstacles to service utilization. Information and education campaigns for the public - including people with dementia, their caregivers and families – can improve service utilization by raising awareness, improving understanding and decreasing stigmatizing attitudes.

Support is needed to enable informal caregivers to be able to continue in their role for as long as possible. Support includes information to aid understanding, skills to assist in caring, respite to enable engagement in other activities, and financial support.

4.4 Awareness-raising and advocacy

Despite the growing impact globally, a lack of understanding of dementia contributes to fears and to stigmatization. For those who are living with dementia (both the person and their family), the stigma contributes to social isolation and to delays in seeking diagnosis and help. There is an urgent need to improve the awareness and understanding of dementia across all levels of society as a step towards improving the quality of life of people with dementia and their caregivers. Governments have a role to play in resourcing public awareness campaigns and in ensuring that key stakeholders are involved in such campaigns. Awareness-raising campaigns should be relevant to the context and audience. They should be accurate, effective and informative and should be developed in consultation with people with dementia, their families and other stakeholders, including civil society.

4.5 The way forward

The findings of this report demonstrate that dementia is a global public health challenge. A range of actions is required to improve care and services for people with dementia and their caregivers. These actions include advocacy and awareness-raising, developing and implementing dementia policies and plans, health system strengthening, capacity-building, supporting caregivers and research. The actions need to be context-specific and culturally relevant.
5. Current Pharmaceutical Product “Pipeline” for AD Treatment

Currently there are numerous medicines under investigation in the pharmaceutical pipeline using different approaches than the currently approved medicines. According experts from industry more than 100 compounds are in development. On Alzheimer disease these proposed therapies target a variety of proteins such as circulating Aβ protein, Aβ plaques, protein tau, P-tau. More detailed information on clinical trials can be obtained on the Evaluation of Medicinal Products (EMEA) and the US Food and Drug Administration (FDA) websites. Table 6.11.6 mentions some of the new compounds currently under development for Alzheimer disease.

Table 6.11.6: New Medicines in Development for Alzheimer disease

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Indication</th>
<th>Company</th>
<th>Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-126 acetylcholinesterase inhibitors</td>
<td>Alzheimer disease</td>
<td>Abbott</td>
<td>Phase 2</td>
</tr>
<tr>
<td>ABT-126</td>
<td>Alzheimer disease</td>
<td>Abbott</td>
<td>Phase 2</td>
</tr>
<tr>
<td>LY2886721</td>
<td>Alzheimer disease</td>
<td>Eli Lilly and Company</td>
<td>Phase 1</td>
</tr>
<tr>
<td>AZD3480</td>
<td>Alzheimer disease</td>
<td>Targacept Inc.</td>
<td>Phase 2</td>
</tr>
<tr>
<td>AVP-923 (dextromethorphan/quinidine)</td>
<td>Alzheimer disease, mild cognitive impairment</td>
<td>Avanir Pharmaceuticals</td>
<td>Phase 2</td>
</tr>
<tr>
<td>MABT5102A</td>
<td>Alzheimer disease</td>
<td>Genentech</td>
<td>Phase 2</td>
</tr>
<tr>
<td>AZD5213</td>
<td>Alzheimer disease</td>
<td>AstraZeneca</td>
<td>Phase 2</td>
</tr>
<tr>
<td>gantenerumab</td>
<td>Alzheimer disease</td>
<td>Hoffmann-La Roche</td>
<td>Phase 3</td>
</tr>
<tr>
<td>AAB-003 (PF-05236812)</td>
<td>Alzheimer disease</td>
<td>Pfizer</td>
<td>Phase 1</td>
</tr>
<tr>
<td>BMS-241027</td>
<td>Alzheimer disease</td>
<td>Bristol-Myers Squibb</td>
<td>Phase 1</td>
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<tr>
<td>MABT5102A</td>
<td>Alzheimer disease</td>
<td>Genentech</td>
<td>Phase 2</td>
</tr>
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<td>BIIB037</td>
<td>Alzheimer disease, prodromal or mild AD</td>
<td>Biogen Idec</td>
<td>Phase 1</td>
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<tr>
<td>GSK2647544</td>
<td>Alzheimer disease, GlaxoSmithKline</td>
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<td>Phase 1</td>
</tr>
</tbody>
</table>

6. Past/Current Research into New Therapeutic for AD

There are a lot of clinical trials going on at present, research into possible interventions is moving fast. This section provides some information on some of the areas of ongoing research for AD. The past five years has seen a growth in the number of drugs being developed for AD. Future compounds under research are aimed at delaying progression of the illness.\textsuperscript{110}

6.1 Immunotherapy

The exact mechanisms leading to Alzheimer disease (AD) are largely unknown which limits possible sources of target for effective immunization. During the last decade, much efforts have been done from pharma industries on targeting clearance of Aβ from the brain of AD patients via the administration of Aβ antigens (active vaccination) or anti-Aβ antibodies (passive vaccination).\textsuperscript{111}

Active immunotherapy

Based on promising results from animal models, the first phase I human clinical trial using active vaccine with multiple doses of Aβ42 in adjuvant (AN1792 and QS-21) was performed on 80 patients with mild to moderate dementia. A significant percentage of patients developed antibodies to Aβ, although at different titers, and no adverse events were reported.\textsuperscript{112}

Following the success of this trial, a phase II trial was designed and performed in 2001 with a cohort of 372 patients to evaluate vaccine efficacy. This trial was stopped after the report of serious adverse events from 18/298 patients (6%), who developed meningoencephalitis.\textsuperscript{112} Although the trial was stopped prematurely, results from post mortem biopsies of AD patients enrolled in the trial showed promising results. Indeed, there was a marked reduction in Aβ deposition in some patients, as well as significant reduction of plaques deposition in different cortical regions. Residual plaques showed a particular appearance suggesting phagocytosis from microglia.\textsuperscript{113} Long term follow-up of immunized patients showed no signs of cognitive improvement or survival although Aβ42 immunization titers lasted for years in several immunized patients.\textsuperscript{114} They also showed greater reductions in brain volume which has never been explained.

Passive immunotherapy

Passive immunization has also been investigated ultimately, in two major clinical trials.\textsuperscript{72, 73} The first two trials were performed in individuals with mild to moderate Alzheimer dementia. In this large phase III trial, patients were administered intravenously a humanized recombinant Aβ monoclonal antibody directed against the N terminus of Aβ (AAB-001 or Bapineuzumab).\textsuperscript{115}

The AAB-001 antibody is a humanized version of mouse monoclonal antibody m3D6 directed against the first 8 amino acids at the N-terminus of Aβ that has been shown to be able to decrease amyloid plaques in mouse models of AD.\textsuperscript{116}
The clinical results with bapineuzumab were equivocal in terms of cognitive benefit. The occurrence of ARIA-E (amyloid-related imaging abnormalities)-effusion or edema after bapineuzumab, and more rarely ARIA-H (hemosiderin deposits), which may not actually be hemorrhages (especially in ApoE ε4 carriers), has raised concerns on the safety of these antibodies directed against the N-terminus of the Aβ peptide. The North American studies 301 and 302 completed as planned; the two complementary studies in Europe were early terminated in August 2012.115

One possible explanation for the ARIA-E or ARIA-H induced by bapineuzumab is that it targets the non-soluble forms of the Aβ protein. Other trials, targeting the midregion of the Aβ peptide have been performed sequentially. Solanezumab, a humanized anti-Aβ monoclonal antibody directed against the midregion of the Aβ peptide, was shown to neutralize soluble Aβ species, prone to be toxic. Solanezumab Phase II study showed a good safety profile as well as indications of a possible clearance of the Aβ peptides in brain of AD patients. Antibody administration was well tolerated with doses up to 400 mg weekly.

These promising results gave rise to two Phase III trials on AD patients with solanezumab.117 This study, led by Eli Lilly & Co.’s recently provided its results. Although it missed its primary outcome, the trials showed some signs of slowing cognitive decline perhaps more evident in milder subjects. Statistics found a 34% less mental decline in mild Alzheimer patients compared to those on a placebo treatment for 18 months according the Eli Lilly & Co.’s analyses.71 According experts in the field, the results are not as clear as stated by Eli Lilly & Co.’s in particular results on the cognitive endpoints.

Further studies need to be performed. Researchers and medical doctors have suggested that treatment must be given earlier on, at the prodromal stage, or even earlier.

A clinical trial, targeting healthy asymptomatic individuals with a genetic mutation leading to early onset (generally aged less than 50 years) AD dementia is now being launched by Genentech & Co.’s.72 Subjects will be injected with crenezumab, a humanized Aβ monoclonal antibody. The study will involve about 300 participants from Colombia and the United States. The participants come from the same family in Medellin and can be traced. They all share a rare genetic dominant mutation that typically triggers Alzheimer symptoms around the age of 45. This trial is unique and has great expectations from the scientific and medical communities as it will help determine if the amyloid hypothesis is correct. Results are expected by 2015.118 The generalizability of the results of this particular study for sporadic or late onset cases of Alzheimer disease will have to be investigated further.

### 6.2 Drugs for Disease Modification and Disease Prevention

#### 6.2.1 Drugs for Disease Modification

_Therapies targeting tau protein._ Clinical trials of medicines targeting tau protein are in their initial phases. By targeting tau, the medicine aims to stabilize microtubules, which help support and transport of essential nutrients and information between cells. When tau malfunctions, microtubules break and tau accumulates into tangles. The medicine, identified through Penn’s Center for Neurodegenerative Disease Research (CNDR) Drug Discovery Program, was previously shown to prevent further neurological damage and improve cognitive performance in animal models. Bristol-Myers Squibb, who developed and owns
the rights to the drug, has started enrolling patients into a phase I clinical trial in people with mild Alzheimer disease.

Secretase inhibitors. One of the features of AD pathophysiology is the accumulation of senile plaques at the end of degenerating brain neurons. β amyloid, a major constituent of these plaques, is toxic to neurons in vitro and is considered to be responsible for the neuronal cell loss in AD. β and γ secretases are the two enzymes critically responsible for forming β amyloid. This discovery has prompted new therapies directed at blocking these enzymes, thus preventing or slowing the progression of the disease. Result of significant clinical trial data demonstrated that the use of secretase inhibitors is non-specific, worsens cognitive decline and is associated with serious safety issues.

Metal chelation. As mentioned above, brain damage in Alzheimer disease is caused by β amyloid, but metal ions, such as zinc and copper, both of which accumulate in the brain with old age, are also neurotoxic. Research has shown that these metals cause β amyloid aggregation, and the mixture of the two (i.e. β amyloid and metal ions) results in the production of hydrogen peroxide, which in turn causes oxidative damage. Clioquinol, an antibiotic, which acts as a chelating agent, facilitates the removal of metal ions, and has the potential to slow progression of AD and modify disease pathology.

Neurotransmitter targets. Cholinesterase inhibitors, are currently the only widely approved class for the treatment of AD and other dementias (See Role of Acetylcholinesterase inhibitors and antidepressants in people with dementia). This therapeutic class inhibits the enzyme acetylcholinesterase, which breaks down acetylcholine in the synaptic cleft and therefore they increase acetylcholine levels in the brain. These drugs, do not attack the underlying disease pathology, instead they compensate for the loss of neurons that communicate via this enzyme. Cholinesterase inhibitors appear to slow down cognitive decline, however the improvements are very modest. Memantine, which works to inhibit the action of neurotransmitter glutamate, has been launched in the US and some European countries.

6.2.2 Drugs for Prevention and Disease Modification

AD is an insidious disease; sometime years go by before symptoms become noticeable. Disease prevention, therefore may be beneficial, and may decrease the prevalence of AD. Studies assessing prevention are underway.

- **NSAIDS**: One such prevention study is evaluating the use of NSAIDS (non steroidal anti-inflammatory drugs) on AD. Preliminary results were promising, however AD researchers are reluctant to recommend NSAIDS given the toxicities (gastrointestinal ulcers, renal toxicity, hypertension) associated with taking these medicines.

- **Antioxidants**: Pathological data indicates that oxidative stress and the accumulation of free radicals results in neuronal damage in AD. There are several studies evaluating the effects of antioxidative compounds on AD. Vitamin E and selegeline appear to delay progression. Research continues on the use of antioxidative vitamins and large studies in the USA are underway to clarify the role of vitamin E in AD prevention. A number of studies have evaluated selegeline for the treatment of AD. Most of these studies show some improvement in cognition, however there is very little evidence to support global improvements in cognition, functional ability and behavior. In a metanalysis of 15
selegiline trials, authors concluded that there was insufficient evidence to recommend its use for AD. A cochrane review of selegeline for AD concluded that there may be some benefit in cognition and its use may be promising. However, at present there is insufficient evidence to recommend its use in practice.¹²⁰

- **Hormones.** The attention and potential uses of hormone replacement therapy to treat AD is derived from epidemiological, clinical, and neuropathological observations and are still ongoing. Women are at a higher risk of developing AD than men since women are estrogen deficient post menopause whereas men benefit from estrogen as testosterone undergoes aromatization to estradiol. Estrogen is considered to have numerous beneficial properties some of which were thought to be antioxidant and anti-inflammatory properties, interactions with neurotransmitters such as acetylcholine and its ability to alter apolipoprotein which could lower the risk of developing AD. Unfortunately, no studies to date have demonstrated a positive impact on improving the biological course of AD. Studies are still ongoing and need to assess the type of HRT administered, timing of HRT in AD, effect of HRT with cholinergics. Currently, there is insufficient evidence for HRT in AD management.¹²¹ The largest study to date, Women’s Health Initiative Memory Study did not demonstrate any benefit of HRT on AD, and actually had a slightly increased risk among those actively treated.

- **Other Agents.** Various other pharmacological agents to treat AD are being studied. *Gingko biloba*, a plant extract that contains numerous pharmacological properties, some of which are thought to be antioxidative, anti-inflammatory or neurotransmitter modulators. Current research suggests that the use of gingko biloba provides smaller effects that that of cholinergics. Also, it is currently unknown which of the active components of this alternative compound contributes to cognitive enhancing effects. Furthermore, the compound is a non-regulated supplement in several countries and standardized preparations are not available.¹²²

### 6.3 Biomarkers

A Biomarker is a biological signature that can be used as an indicator of a pathological situation. According to the 1998 Consensus Report of the Working Group on Molecular and Biochemical Markers of Alzheimer Disease, ideal biomarkers for AD should be: 1) reflective or indicative of AD pathology; 2) reliable; 3) easy to perform/analyze; and 4) relatively inexpensive.

Biomarker may have different roles, which have different standards. One is a surrogate for the disease, which demands nearly perfect sensitivity and specificity. The other is a supporting measure in the diagnosis, which again, requires a fairly high sensitivity and specificity. Another is as risk factor for future event, cardiovascular disease has many examples, such as the ratio of LDL to HDL, while not deterministic of a MI, predictive and used to intervene, at least to lower one marker (LDL), while there are essentially no effective pharmacological therapies that substantially raise HDL. (Sensitivity & specific require a standard on which to validate, which is another problem in AD).
There is currently a lack of specific and non-invasive biomarkers for Alzheimer disease. Still, as of 2013 a definite diagnostic is only possible after death of the patient with brain histopathology.

AD is a challenging disease for the development of biomarkers because a clinical diagnosis has substantial misclassification and a standard does not exist.

Identification of AD specific biomarkers is complicated because it can take 10 to 20 years between disease onset and symptomatic stage, difficulty of accurate clinical diagnostic, and complex genetic polymorphism. Identification of specific biomarkers for AD will have a considerable impact in the understanding of the disease itself. New biomarkers will allow the identification of individuals at risks and help in characterizing subpopulations for disease onset, progression and outcome. These specific markers could potentially facilitate the development of personalized treatments for each stage of the disease. Again most promising expectations of these new biomarkers would be to target molecules that researchers will use to develop medicines vaccines for individuals at risks. Biomarkers are also important monitoring tools for high throughput screening of candidate molecules such as active compounds, antibodies or genes which can modulate a particular biomolecular pathway involved in Alzheimer disease. However, recent data suggest extremely limited utility of biomarkers for Go/NoGo decisions in early stages of clinical development as there are still have no evidence linking them to clinical outcome.

6.3.1 Imaging and radiological markers

Magnetic resonance imaging (MRI) and computer aided tomography (CAT) scans can be used to visualize brain structure and help in AD diagnostic. In AD patients, a considerable reduction of hippocampus region, involved in memory processes, is observed. This anatomical measurement is useful in predicting the transition from normal to MCI and from MCI to AD. However, there are concerns that this approach may lack the specificity needed to clearly diagnose AD. While some individuals have hippocampal atrophy without substantial AD pathology, one of the challenges to volumetric measures, particularly sub-regions, is the accuracy, i.e. variability around the measure.

Brain metabolism is another important neurological parameter measured in AD diagnostic. As a result of brain atrophy and neuronal loss, patients in early stages of AD demonstrate reduced levels of brain metabolism. Functional magnetic resonance imaging (fMRI) and PET scans with flurodeoxy glucose (FDG-PET) as secondary measures of metabolic activity in various parts of the brain are key markers of brain metabolism. (fMRI) measures changes in oxygen concentrations related to regional cortical blood flow, while FDG-PET measures glucose metabolism in neuronal populations.

Development of positron emission tomography (PET) imaging and compounds such as 11C labeled Pittsburgh compound B (11C-PIB) ligand has revolutionized imaging in dementia and opened new avenues for advanced diagnostic tools in AD. 11C-PIB binds with high affinity and high specificity to neuritic Aβ plaques.

Studies from Klunk et al. have shown that 11C-PIB binds in several brain regions in cases of AD, with a significant 1.5–2 fold increase of 11C-PIB binding compared to controls. Other studies have suggested that 11C-PIB load is indicative of disease progression in the next 2
Since amyloid is known to start accumulating several years before clinical signs of disease, imaging techniques may allow detection at the prodromal stage of AD. There are numerous technical issues and challenges to measuring brain amyloid: 1) limit of detection, 2) not possible to distinguish vascular deposition from cerebral deposition, 3) the measure is continuous but often treated as a binary, positive or negative, 4) the amyloid burden is reported relative to a reference region, the cerebellum.

Further research that will identify new imaging markers and tracers will definitely help making a more accurate diagnostic for AD and monitor therapeutic effects. These imaging techniques remain extremely costly and therefore cannot be used in routine in all countries to monitor disease progression. Moreover as has happened in other areas of imaging and diagnostics modified and cheaper could potentially be developed and may be worth researching.

### 6.3.2 Biomarkers in cerebrospinal fluid

Cerebrospinal fluid (CSF) is a fluid surrounding the brain and the spinal cord. It is produced by the choroid plexus and serves as a protection for shocks and transport waste from the central nervous system. Because AD is a neurodegenerative disease, cerebrospinal fluid (CSF) has evolved as prime target for biomarker investigation. Samples of CSF can be obtained after lumbar puncture, which is invasive and potentially painful and stressful for elderly patients.

Several biomarkers in CSF have been identified so far for AD disorders such as such as decreased Aβ42, increased total tau (T-tau), and increased phosphorylated tau (P-tau).

The identification and characterization of amyloid-β (Aβ) and tau as the main pathological components of Alzheimer disease (AD) has driven many efforts in search for suitable biomarkers for AD. While these two proteins represent the two key pathological mediators of disease, other aspects of this multifaceted disease such as oxidative stress, calcium-mediated toxicity, and neuroinflammation are being unraveled, giving rise to possible new biomarkers for diagnostic or disease progression. As with amyloid imaging, measuring Aβ in the CSF has technical challenges, as to what is being measure, total versus free Aβ.

There are different assays that provide different results, which while correlated, are not directly interpretable. Also, the techniques and materials are a particular issue. The key issue is that a clinical standard has yet to be developed, which make comparison of results across studies a challenge. Also, the ability to identify what is an optimal cutpoint is a challenge given the variation in assays and assay results.

### CSF markers and conversion from MCI to AD

Combinations of P-tau and Aβ42 protein levels in CSF were successful in discriminating AD patients from normal cases with a sensitivity of 86% and 80% sensitivity between AD individuals and other non-AD related dementias in a study reported by Maddalena et al.
Further research is needed to clarify if the ratio of Aβ 42 to P-tau can be a diagnostic criteria for AD, in particular to discriminate patients with possible AD (NINCDA-ADRSA criteria) or the more recent NIA-AA criteria.

**CSF markers and conversion from normal to MCI/AD**

More interestingly, while dementia patients can be identified through neuropsychological tests and clinical evaluation, a gap remains in diagnosing asymptomatic patients at risk of developing AD. Moreover, MCI is a heterogeneous category of all prodromal dementia, some of which are AD some of which are not which makes the study difficult to interpret. Many studies have focused on identifying biomarkers of the prodromal stage, before MCI/AD onset. Results from Fagan et al. show that an increased ratio of tau/Aβ42 and P-tau/Aβ42 in asymptomatic individuals is associated with an increased risk for conversion to mild cognitive impairment and very mild dementia (CDR-0.5).135

In the Fagan et al. study about 70% of patients with a high tau/Aβ42 ratio converted from normal to very mild dementia over a 3 year period while only 10% of those with a normal ratio converted to very mild dementia. After a five year follow-up period, less than 10% patients with MCI with a normal tau/Aβ42 ratio progressed to AD whereas more than 90% progressed to mild to moderate AD if there was a high tau/Aβ42 ratio. These promising results should be replicated in larger cohort of patients, and could possibly be used to design clinical trials for immunization or preventive treatment of individuals at high risk to convert from normal to MCI/AD. CSF markers of amyloid beta 42, P-tau or a ratio appear predictive of individuals likely to progress to frank AD dementia and may provide a mechanism to improve the diagnosis of AD or prodromal AD.136

**CSF Markers of inflammation**

As a result of amyloid plaque deposition in the brain, markers of inflammation such as cytokine IL-6, C-reactive protein, interleukin (IL)-1β, tumor necrosis factor-α, IL-6, IL-6 receptor complex, α-antichymotrypsin and transforming growth factor- β, have been described in the CSF of patients with AD although levels of these CSF components were not able to discriminate between AD patients and other non-AD demented patients.137

Therefore experts question if they can be viable biomarker candidates. As CSF closely reflects the composition of the brain extracellular space it remains a target of choice for identifying new biomarkers for diagnostic and disease progression.138 However, because of its invasive collection procedure, it is not routinely used for the evaluation of AD patients.

**6.3.3 Biomarkers in blood and plasma**

There are many challenges to blood & plasma markers, some technical, some relate to issues of the blood-brain barrier. Blood-based biomarkers represent a considerable challenge because blood is not in direct contact with brain. Therefore brain derived proteins and metabolites that passes through the blood-brain barrier become markedly diluted into blood and plasma which are other complex mediums. Also the size of the particles may affect the rate of exchange across the blood brain barrier. There are at the moment high expectations for the search of new biomarkers for AD in blood and plasma. The advantages of using markers in blood and plasma are obvious as they can easily be collected from patients at an
affordable price and would allow large screenings to identify trial participants for early interventions and monitoring the effectiveness of new therapies.

Blood is a complex fluid, composed of proteins, lipids and metabolites as well as different cell types eg red cells, platelets and lymphocytes, which composition can fluctuate depending on internal and external environment. This makes it more challenging to target specific assay for disease but also offers a large palette of possible targets.

Search for a protein assay

Measuring proteins in blood is complex due to the wide dynamic range of proteins, isoforms, complexes as well as activities, and post-translational modifications. Despite these challenges, developments in both bioinformatics and mass spectrometry have led to substantial advances in proteomic analysis in blood and plasma. So far, using several protein identification techniques such as MALDI-qTOF and ion-trap MS, 2D electrophoresis, researchers have identified several proteins which were significantly increased in AD patients serum versus controls. These include inflammatory response mediators, such as CFH, complement components C3 and C4 and A2M.139

Studies performed in transgenic mice overexpressing APP and PS1 mutations also allowed identification of eight proteins to be differentially expressed in AD relative to controls in the original cohort of subjects. These include clusterin, complement component C1r, α1-antitrypsin and EGF receptor. Moreover plasma concentrations of complement-related proteins were shown to be associated with brain atrophy in AD.140 A two- to six fold increase in oxidative damage markers such as oxidized forms of fibrinogen and α1-antitrypsin have been identified using proteomics.141,142,143

Recent studies using samples of AD patients have identified a panel of 18 proteins that effectively discriminate individuals with high and low brain Aβ. Among these proteins are the apolipoprotein-E (ApoE) and several proteins with established roles in Aβ clearance. These promising results may to accelerate the development of new biomarkers for AD and AD drug monitoring.

Search for mRNA and miRNA signature

Search for RNA/DNA biomarkers in blood in currently underway. The difficulty lies in the complexity single nucleotide polymorphisms, copy number variants and other ‘static’ variation of epigenetic changes, which may be more responsive to the internal and external environment. Isolating RNA from blood is also technically challenging but feasible. There is at present relatively little evidence of a transcript signature in blood of AD that might act as a biomarker. Exciting results on this direction are coming from research on miRNA which act as regulators of gene expression with BACE1 as a possible AD marker.144,145 With the help of genome-wide technologies and bioinformatic approaches it is possible that research in this area will come to findings of blood based transcripts disease assay.

The latest research have clearly shown that proteins, transcripts and probably other constituents in CSF and blood, are different in people with AD. Although at present progress is being made, there are no proteins, transcripts or metabolites in blood that have been sufficiently replicated to be established as AD biomarkers. If the progress that has been made
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to date is to be sustained and even accelerated, efforts should be made in facilitating design and collection of larger cohort of patient samples from different regions of the world and facilitate collaborations between academic research, clinic and pharmaceuticals.

Public–private partnerships have established large longitudinal cohorts with extensive sample collection, neuroimaging and clinical data in the USA through the Alzheimer Disease Neuroimaging Initiative (ADNI) study and in Europe through the AddNeuroMed study joined by others in Europe and ADNI-like studies in Japan, Australia and China. These collaborations are essential as they provide larger and cross validation between studies. Considerable expectations are been made in finding biomarkers in blood that would definitively ease sample collection procedures. With technical improvements of the proteome analysis, it is very likely that specific and reproducible markers will become available in the near future. Most likely, several researchers are convinced that there will not be just one single marker for AD but rather different sets of markers to predict conversion to MCI and AD disease onset. These markers are essential for the design and monitoring of effects of new AD therapies. We can also envisage that these markers could be used to help differentiate different sets of patients with distinct disease progression rates and adapt treatment in consequence. Several EU funded projects are currently being developed to identify such markers. One example is PredictAD, a project partially funded under the seventh Framework Programme by the European Commission. This project aims at developing a standardised and objective approach to diagnose AD. PredictAD is composed of a consortium of of top-level European research from VTT Technical Research Centre of Finland, GE Healthcare (UK), Nexstim Ltd. (Finland), University of Kuopio (Finland), Imperial College of London (UK), Karolinska Institutet (Sweden), University of Milan (Italy) and Copenhagen University Hospital, Rigshospitalet (Denmark).

The European Union is also involved to find new therapies for neurodegenerative diseases and enable early diagnosis for early targeted treatment. In this regard, a EU Joint Programmes - Neurodegenerative Disease Research (JPND) initiative, led by Philippe Amouyel, is working actively to promote translational and collaborative research for AD. Funding calls for Centres of Excellence in Neurodegeneration (COEN) and harmonisation of the use of biomarkers were initiated under the umbrella of JPND.

Pharmacog for “Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development” is a partnership of 32 academic and industry actors from seven countries, coordinated by GlaxoSmithKline R&D and the Université de la Méditerranée. Pharmacog started its activities on January 1, 2010 thanks to significant funding (EUR 20.2 million) from the Innovative Medicines Initiative. This ambitious European project aims at providing the tools needed to define more precisely the potential of a drug candidate, reduce the development time of new medicines and thus accelerate the approvals of promising new medicines.
7. Opportunities for Research into New Pharmaceutical Interventions

A great deal more is known about AD and other dementias than in 2004, but new found knowledge and new drugs currently being studied also pose new questions. The following sections describe some opportunities of research for AD.

Cholinergic therapies only bring about a temporary relief in AD symptoms, and it is not possible to predict who will respond. It is also unclear whether patients who do not respond to one anticholinesterase inhibitor will respond to another. Systematic clinical research is needed to answer these clinical questions. Furthermore, ways of measuring, determining response, and assessing when medications need to be stopped remain unclear and need to be addressed.

There may also be a need for more comparative clinical trials of these agents to determine which agent offers the greatest benefit and causes least resistance. The effective and appropriate administration of cholinergic and other medicines requires good baseline assessment with validated scales for objective measurement. Further work is required and practice guidelines are needed to assist clinicians in effectively diagnosing patients suspected with AD. There is also a need for better scales for the non-cognitive symptoms.

Cholinesterase inhibitors such as donepezil are licensed for use in mild to severe AD in the USA at present. More comparative trials evaluating multiple cholinergic medicines, as well as combination therapy with different classes for drugs, also remains unanswered and well-designed RCTs, with clear indications for appropriate doses for various stages of AD are needed.

AD is a complex disease overlaid with neuro-psychotic and behavioural symptoms, and management rarely responds to medicines alone. Important factors other than cognitive functions and activities of daily living need to be studied. Behavioural modification and education combined with drug therapies as well as caregiver’s interventions require systematic clinical research with outcome variables related. These data are extremely difficult to capture as Alzheimer disease is also prone to external environmental and social factors.

Gaps Between Current Research and Potential Research Issues that Could Make a Difference

A review of currently available treatments suggests a number of areas for further study. Some of these recommendations are within the realm of improved evaluation and assessment.

- Improved detection and evaluation of Alzheimer disease, especially in the prodromal and early stages, when treatment that slows progression would be more likely to be beneficial. This implies the development of a reliable diagnostic tool.
- There is a clear need for validated biomarkers for measuring and monitoring disease progression – the lack of these means that trials of disease modifying therapies will not move ahead as rapidly as possible. The use of surrogate endpoints e.g. imaging also needs more investigation. Expert say what is needed is to characterize the relationship
between specific measure of cognitive function (such as episodic memory) and biomarkers to improve our understanding the progression of early cognitive of the AD type and how this predicts progression to a formal diagnosis of AD. To understand the relationship and timing of the various measures of pathology (CSF amyloid beta, tau, P-tau, amyloid burden), perhaps volume/atrophy, cognition and function. There are many hypotheses but limited data.

- Work on standardization of the current biomarkers into the research criteria for a diagnosis of either early disease or advanced AD dementia is necessary.
- Development of consensus on clinically meaningful outcome measures and further characterization of the cognitive measures for early cognitive impairment.
- Within the field of pharmacologic therapy, there is a critical need for medicines with greater ability to improve cognition or at least slow the progression of dementia. Despite the progression in the areas mentioned above, research and development needs to further identify and test new cognition-enhancing medicines based on the pathophysiology and information learned about the disease from neuroscience and molecular genetics. For example, pharmacologic agents that prevent or slow amyloid deposition or remove precipitated amyloid might serve to slow down disease progression.
- Other research directions that could affect management of AD, is the optimal pharmacologic treatment of non-cognitive symptoms, including psychosis, agitation, depressions and sleep disturbances. Many current recommendations are based on small-uncontrolled studies or agents no longer in common use and/or at doses well above those used in current practice. There is, therefore, a critical need for randomized controlled studies and guidelines on up-to-date treatments for non-cognitive symptoms present in AD.
- Clinical questions that need to be further evaluated and studied include what to treat? There is a problem surrounding the terminology, and diagnosis associated with dementia and AD. Confusion remains about when to initiate treatment; how to treat i.e. which agents to start, how to switch drugs in the case of decreased efficacy, intolerance, adverse effects or drug interactions and how long to treat AD.
- In addition to symptomatic or palliative options, increased knowledge of the anatomical, cellular and molecular basis of AD, together with the identification of new drug targets, which may prevent, slow or delay its onset are needed. These possibilities may be expedited by the further progress in research and development of improved animal models; introduction of more efficient and effective clinical trials, and the use of non-invasive imaging to monitor the progression of the disease. Combination therapies may to offer maximum benefit in longer term disease modification but their use would need to be evaluated particularly in regard to safety.
8. Barriers to Closing the Alzheimer Pharmaceutical Gap

- **Access to human tissue** and developing a large biobank that could allow the finding of novel pathways for Alzheimer disease from genetics to gene expression and methylation
- **Lack of validated targets.** AD requires a clinical diagnosis, and at present, there are no reliable tests to confirm a diagnosis. Definitive diagnosis can only be made postmortem from brain tissue. Despite years of research, there is still an unclear understanding on the pathogenesis of AD. Further research is still needed at the basic neuroscientific level. Companies are already investing large amounts of money in AD, but the high risk and cost coupled with long clinical trials in disease modification, mean that at most a company could only take one or two approaches forward in disease modification trials at present. The problem is the high risk and the lack of markers to increase confidence in moving from Phase II to large Phase III trials.
- **Lack of animal models.** There are no good animal models that reflect the disease state. Those models that do exist model only aspects of pathology e.g. amyloid over-expression. Equally as important is the issue of access to animal models and the need to couple to functional endpoints such as for behaviour, neuroimaging, electrophysiology. Current animal models are not readily accessible for research and drug screening at the preclinical level because of intellectual property and licensing issues. Many of these models belong to academia (not industry) and institutes and the costs of the models are prohibitive to academic scientists and small biotech companies. Public Private Partnerships such as Pharmacog, a partnership of 32 academic and industry actors from 7 countries exist and aim at reducing the development time of new medicines and thus accelerate the approvals of promising new medicines.
- **Barriers in the design and implementation of clinical trials.** Experts from industry say “Adaptive clinical designs, along with ‘adaptive development programs’ use the concept of adaptive clinical trial design and apply that to program development. Using both will result in reaching the goal, earlier and with less resources, overall, although the upfront cost is higher than the ‘traditional’ approach.” Clinical trials are needed to determine the efficacy and safety of AD medicines. In an effort to control AD at the early stages, clinical studies are evaluating the effectiveness of therapies at mild cognitive impairment (MCI) stages, which is considered the prodromal stage to AD. Guideline’s for MCI studies have not been established. Another area that requires further work is the design and outcomes measures to slow down AD progression. Scientific evidence has determined that neuropathology processes resulting in AD occurs several years prior to the onset of AD symptoms. However, conducting long-term clinical studies to monitor a patient’s progression or decline in function is costly and requires substantial resources. Morever the earlier a patient moves into disease course the less exact the diagnosis is going to be. As well, the more patients are included in a clinical trial, the larger the study is, the more it costs, the harder it is to detect a change of parameter and the higher risk of safety issues will occur.
- **Lack of biomarkers for therapeutic endpoints** remains a major barrier in the clinical development of efficacious AD drugs. The availability of such markers would benefit and hasten AD drug development. Any reliable predictor of clinical outcome will accelerate the development of effective AD medicines. Much work in this area is already ongoing, however continued efforts are still required. Commonly accepted markers in cerebrospinal fluid (CSF) or blood such as alpha -amyloid and tau are still not adequately validated and may not be sensitive for longitudinal progression and treatment effects on
AD. Additionally, neuroimaging markers, as determined by MRI are reasonably validated and sensitive for use in long-term trials but are not suitable for short-term duration, proof-of-concept trials. Recent evidence suggests the CSF biomarkers may also not change much over a short timeframe. There is also a need to develop an infrastructure to speed up validation studies, such as large-scale biologic sample collection from ongoing aging populations. The availability and development of specific imaging technology such as positron emission tomography (PET) is also needed to determine whether changes in the brain or its function can be identified before the person develops symptoms of the disease.

- **Barriers in academia.** Academic drug discovery and development programs are usually underfunded and lack infrastructure, in terms of staff and equipment especially at the preclinical level. Furthermore, the lack of communication, interaction and collaboration between necessary research groups can limit drug discovery and research. Today, science and medicine requires an interdisciplinary approach to solving medical conditions. Several partnerships of public-private partnerships (PPP) launched by EU and have been discussed previously.

- **Barriers in biotechnology.** AD drug discovery and development is considered high risk and attracting capital for early high-risk projects is very difficult, especially when the return on investment is questionable or long-term. The cost of conducting clinical trials is also another major barrier to small companies: risks are high and the probabilities of scientific success low. Therefore, external funding is important. Experts from industry say risk sharing plays an important role as well (discussed in chapter 8.4). EUROPA, the European commission group to improve innovation proposes that a small business innovation research programme (SBIR) mechanism like that employed in public funding in the USA, be introduced into the FP7-through integrated projects. This programme will speed up the creation of new companies and provide capital for small-to-medium sized enterprises. In the United States, SBIR mechanisms amounts to 1.3 billion US dollars.¹⁴

- **Regulatory barriers.** Another barrier that affects both the pharmaceutical and biotech industry is the lack of international harmonization of clinical trials and regulatory requirements. Designing trials that meet individual requirements is costly and timely. A further barrier to drug development is the definition of therapeutic effectiveness of AD medicines. The FDA requires that medicines show superiority to placebo on a performance-based test and a measure of global clinical function. Outcome measures are still nonspecific and need to be established by the medical community. Other outcome efficacy measures that affect AD function are needed to guide drug development, novel delivery methods, and registration. Biotech industry is the lack of international harmonization of clinical trials and regulatory requirements. Designing trials that meet individual requirements is costly and timely. A further barrier to drug development is the definition of therapeutic effectiveness of AD medicines. The FDA and EMEA require that medicines show superiority to placebo on a performance-based test and a measure of global clinical function. Outcome measures are still nonspecific and need to be established by the medical community. Other outcome efficacy measures that affect AD function are needed to guide drug development, novel delivery methods, and registration.
9. European Union Funding Opportunities for AD

Europe and the Seventh Framework Program for Alzheimer disease

Alzheimer disease is an important topic of the key action on “the aging population and disabilities” of the European Union’s Seventh Framework Programme. The European commission recognizes the impact of AD on individuals and society and the urgent need for treatments that can prevent, arrest and reverse degeneration and death of neurons. The multidisciplinary projects launched with EU support set a prerequisite in the understanding of the fundamental molecular and cellular mechanisms of AD and the development of diagnostic tools that may identify patients at an early pre-symptomatic stage. Furthermore a consortium of 21 of the most experienced AD laboratories from Europe and beyond are to conduct our research projects integrating data from studies with tissue cultures and genetically modified animals into a clinical investigations of demented patients. A broad array of bio-technological methods is also to be used. Results of these studies will lead to diagnostic screening strategies combing genetic, pathophysiological and biomarker information.

Giving advice on research

The European Research Advisory Board is a high-level independent advisory committee, made up of 45 top experts from EU countries, which provides advice on the design and implementation of EU research policy. It focuses on realizing the European Research Area, and on using policy instruments such as the Community Research and Development Framework Programme.

10. Conclusion

In 2012, dementia was declared a public health priority by the World Health Organization (WHO). Due to the ageing of the world population the number of patients with Alzheimer disease will rise significantly. If no treatment is available, this will be a major health issue with enormous financial burdens to health care systems.

Thus, there is an urgent need for both early diagnosis with specific markers as well as effective therapies that could be taken at the different stage of the disease. Currently only short term symptomatic treatment is available. While there is research and development already in this area, much work still is required. This includes:

- basic research in the pathophysiology of the disease and its risk factors;
- noninvasive and clinically effective diagnostics tools;
- wider scale outcome efficacy measures for the disease function;
- progress and developing medicines that slow progression, halt, or prevent AD from occurring;
- Additionally, challenges for clinical services include early diagnosis, and intervening early with the most appropriate and effective medicine.
There are several barriers to closing the obvious pharmaceutical "gaps" with regard to AD. Specific recommendations include the following:

The EU and EU-based philanthropic organizations need to recognize and help overcome the various scientific and systemic barriers to improving pharmaceutical R&D for Alzheimer disease and provide funding for making animal models more accessible and affordable. Also new grant agreements should be implemented that compensate investigators and institutions while making the models more widely available. There is a need for improved AD assessment tools, with increased sensitivity and efficiency for patient evaluation for AD primary prevention. More specifically, curtailing time requirements for clinical staff, data monitoring and data entry could decrease costs for trials.

An important research goal should also be the development and evaluation of new instruments in relevant domains that are sensitive, reliable, and valid for detecting changes in normal aging and early AD and before disease onset. Furthermore, it would be helpful if these can be self-administered and not require significant professional involvement. New uses of technology, such as computerized assessments and telephonic methods are some options and may be desirable in this field.

There needs to be more collaboration and a multidisciplinary approach in the areas of research and development for AD. Grant review should be by government and industry to facilitate bench to bedside Neurobiologists, clinicians, chemists need to work together. Funding resources and guidelines that can assist scientists in preclinical drug development is required.

New funding models should be explored which can support core research facilities and non-tenured staff in academic institutions, such as the creation of endowments for facilities and pharmaceutical and biotech consortia. Innovation is needed to encourage diversity of approaches to fight AD.

References


5 WHO dementia report. World Health Organization. (forthcoming)


Knapp M, Prince M. Dementia UK - A report into the prevalence and cost of dementia prepared by the Personal Social Services Research Unit (PSSRU) at the London School of Economics and the Institute of Psychiatry at King’s College London, for the Alzheimer Society. London, Alzheimer Society, 2007.
Update on 2004 Background Paper, BP 6.11 Alzheimer Disease


Alzheimer’s association. Diagnostic procedures http://www.alz.org/professionals_and_researchers_diagnostic_procedures.asp


Update on 2004 Background Paper, BP 6.11 Alzheimer Disease


Update on 2004 Background Paper, BP 6.11 Alzheimer Disease


Sultana R, Mecocci P, Mangialasche F, Cecchetti R, Baglioni M, Butterfield DA. Increased protein and lipid oxidative damage in mitochondria isolated from lymphocytes from patients with Alzheimer disease: insights into the role of oxidative stress in Alzheimer disease and initial investigations into a potential biomarker for this dementing disorder. J Alzheimers Dis. 2011;24(1):77-84.


Predictad EU funded project. http://www.predictad.eu/

EU joint Programm initiative website: http://www.neurodegenerationresearch.eu/initiatives/strategic-research-agenda/


Annex 6.11.1: Meta-analysed estimates of dementia prevalence, generated from Poisson random effects models, by Global Burden of Disease region

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1. Standardized for age, or for age and sex (*)
Annex 6.11.2: Estimates of dementia prevalence (%) for Global Burden of Disease regions where it was not possible to carry out a quantitative meta-analysis

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<tr>
<th>GBD world region</th>
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<th>60–64 years (%)</th>
<th>65–69 years (%)</th>
<th>70–74 years (%)</th>
<th>75–79 years (%)</th>
<th>80–84 years (%)</th>
<th>85+ years (%)</th>
<th>Age-standardized prevalence for those aged 60 years and over (%)</th>
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Note: AFR D, WHO African Region with high child and high adult mortality; AFR E, WHO African Region with high child and very high adult mortality; AMR B, WHO Region of the Americas with low child and low adult mortality; AMR D, WHO Region of the Americas with high child and high adult mortality; EMR B, WHO Eastern Mediterranean Region with low child and low adult mortality; EMR D, WHO Eastern Mediterranean Region with high child and high adult mortality; EUR A, WHO European Region with very low child and very low adult mortality; EUR B, WHO European Region with low child and low adult mortality; EUR C, WHO European Region with low child and high adult mortality; WPR, WHO Western Pacific Region with low child and low adult mortality.
Annex 6.11.3: Total population over 60, crude estimated prevalence of dementia (2010), estimated number of people with dementia (2010, 2030 and 2050) and proportionate increases (2010–2030 and 2010–2050) by Global Burden of Disease - region

<table>
<thead>
<tr>
<th>GBD world region</th>
<th>Population over 60 years (millions, 2010)</th>
<th>Crude estimated prevalence (%), 2010</th>
<th>Number of people with dementia (millions)</th>
<th>Proportionate increases (%)</th>
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Annex 6.11.4: Estimated annual numbers of incident cases of dementia, by age group and world region and Global Burden of Disease region

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<th>GBD world region</th>
<th>60–64 years</th>
<th>65–69 years</th>
<th>70–74 years</th>
<th>75–79 years</th>
<th>80–84 years</th>
<th>85–89 years</th>
<th>90+ years</th>
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<td>11 999</td>
<td>74 300</td>
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<td>Asia Pacific, High Income</td>
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<td>60 232</td>
<td>90 569</td>
<td>130 732</td>
<td>156 054</td>
<td>135 777</td>
<td>111 191</td>
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Annex 6.11.5: Per capita (US dollars) and aggregated costs (billions US dollars) by Global Burden of Disease region and World Bank income classification

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<th>GBD world region</th>
<th>Per capita costs (US$)</th>
<th>Number of people with dementia</th>
<th>Aggregated costs (US$ billion)</th>
<th>Total costs as % of GDP</th>
<th>Direct costs as % of GDP</th>
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<td>Informal care (all ADLs)</td>
<td>Direct medical costs</td>
<td>Direct social costs</td>
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<td>7 667</td>
<td>1 869 242</td>
<td>7.96</td>
<td>3.42</td>
<td>2.94</td>
</tr>
<tr>
<td>North America, High Income</td>
<td>48 605</td>
<td>4 383 057</td>
<td>78.76</td>
<td>36.83</td>
<td>97.45</td>
</tr>
<tr>
<td>Caribbean</td>
<td>9 092</td>
<td>327 825</td>
<td>1.50</td>
<td>0.78</td>
<td>0.71</td>
</tr>
<tr>
<td>Latin America, Andean</td>
<td>3 663</td>
<td>254 925</td>
<td>0.35</td>
<td>0.31</td>
<td>0.28</td>
</tr>
<tr>
<td>Latin America, Central</td>
<td>5 536</td>
<td>1 185 559</td>
<td>1.58</td>
<td>2.61</td>
<td>2.37</td>
</tr>
<tr>
<td>Latin America, Southern</td>
<td>8 243</td>
<td>61 4523</td>
<td>2.36</td>
<td>1.42</td>
<td>1.29</td>
</tr>
<tr>
<td>Latin America, Tropical</td>
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<td>1 054 560</td>
<td>2.17</td>
<td>2.67</td>
<td>2.42</td>
</tr>
<tr>
<td>North Africa/Middle East</td>
<td>3 296</td>
<td>1 145 633</td>
<td>1.90</td>
<td>2.05</td>
<td>0.54</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Central</td>
<td>1 081</td>
<td>67 775</td>
<td>0.04</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Sub-Saharan Africa, East</td>
<td>1 122</td>
<td>360 602</td>
<td>0.28</td>
<td>0.08</td>
<td>0.04</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Southern</td>
<td>6 834</td>
<td>100 733</td>
<td>0.52</td>
<td>0.11</td>
<td>0.06</td>
</tr>
<tr>
<td>Sub-Saharan Africa, West</td>
<td>969</td>
<td>181 803</td>
<td>0.11</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>World Bank classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low income</td>
<td>868</td>
<td>5 036 979</td>
<td>2.52</td>
<td>1.23</td>
<td>0.62</td>
</tr>
<tr>
<td>Lower middle income</td>
<td>3 109</td>
<td>9 395 204</td>
<td>18.90</td>
<td>6.74</td>
<td>3.57</td>
</tr>
<tr>
<td>Upper middle income</td>
<td>6 827</td>
<td>4 759 025</td>
<td>13.70</td>
<td>10.44</td>
<td>8.35</td>
</tr>
<tr>
<td>High income</td>
<td>32 865</td>
<td>16 367 508</td>
<td>216.77</td>
<td>78.00</td>
<td>243.14</td>
</tr>
</tbody>
</table>
Annex 6.11.6: Numbers of prevalence studies, by year of data collection and income level of the country where the research was carried out
ANNEX 6.11.7: DALYs and death rates caused by Alzheimer disease and other dementia by age group and regions

*By Faraz Chavoushi, World Health Organization, Department of Essential Medicines and Health Products, Geneva Switzerland.

Data from the Global Burden of Disease 2010, Lancet Dec 2012.


Update on 2004 Background Paper, BP 6.11 Alzheimer Disease

Absolute DALYs caused by Alzheimer’s and dementia by age group in the world

DALY rates caused by Alzheimer’s and dementia by age group in the world
Update on 2004 Background Paper, BP 6.11 Alzheimer Disease

Death rates caused by Alzheimer’s and dementia by age group and region

- Central Europe
- Eastern Europe
- Western Europe
- Global

Age groups include:
- 50-54 years
- 55-59 years
- 60-64 years
- 65-69 years
- 70-74 years
- 75-79 years
- 80+ years

The chart illustrates the death rates per 100,000 for each age group across different regions.
ANNEX 6.11.8: Mortality caused by Alzheimer disease and other dementias by region and sex


Appendices


Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper
Written by Saloni Tanna, Pharm.D. MPH

Background Paper 6.12
Osteoarthritis

By Rachel Wittenauer, Lily Smith, and Kamal Aden

January 28th 2013
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Executive Summary

Osteoarthritis (OA), the most common musculoskeletal condition, is a long-term chronic disease involving the thinning of cartilage in joints which results in bones rubbing together, creating stiffness, pain, and impaired movement. OA is related with age, but is associated with a variety of both modifiable and non-modifiable risk factors, including obesity, lack of exercise, genetic predisposition, bone density, occupational injury, trauma, and gender.

Osteoarthritis is a major cause of disability in elderly populations around the globe, especially in developed countries. The prevalence of OA is increasing and will continue to do so as the population increases, ages, and is subject to risk factors such as the obesity epidemic. As OA causes pain and impairs functionality of the patient, it places a major burden on individuals, communities, health systems, and social care systems.

The current control strategy mainly consists of palliative pain treatment, as there are several medicines on the market that alleviate pain and improve function in OA patients. In severe cases, joint replacement surgery has been proven effective in relieving the painful and debilitating effects of the disease, though the high cost and use of advanced resources mean these procedures are not available in many countries around the world. There are currently no therapies available that can reverse or halt the progression of osteoarthritis; larger studies are needed to evaluate the clinical and cost effectiveness of the few therapies that have shown promise in animal trials.

Another principal aspect of osteoarthritis care that requires further research is diagnostic techniques. The current methods of clinical diagnosis and X-rays are not precise enough to effectively measure status and progression of the condition, which presents serious difficulties in evaluating both the impact of risk factors and the effectiveness of potential therapies. The lack of valid biomarkers limits pharmaceutical development and clinical monitoring.

The issues presented by the lack of both reliable diagnostics and medicines that can reverse the progression of osteoarthritis must be addressed through further research in order to effectively reduce the large health and economic burden of osteoarthritis.
Key Updates Since 2004

- As the global population continues to age, the burden of osteoarthritis will increase dramatically.
- Some progress has been made in biomarkers for osteoarthritis diagnosis, but much more research still needs to be done before they can be used in a clinical setting.
- Meta-analyses of clinical trials show that avocado-soybean unsaponifiables significantly reduce pain associated with osteoarthritis and may be an effective complementary treatment that could be used in conjunction with traditional pharmaceuticals.
- While they are expensive operations, total hip and knee replacement surgeries have been shown to be cost effective in the long term. More research should be conducted on how to introduce low cost joint replacement surgeries into hospitals in low and middle income countries.
1. Introduction

In 2004, a report *Priority Medicines for Europe and the World* was written by Warren Kaplan and Richard Laing and published by the World Health Organization (WHO). A chapter (6.12) and background paper on osteoarthritis were written for this publication by Saloni Tanna.

Osteoarthritis is characterized by the breakdown of cartilage in joints.\(^1\) As cartilage deteriorates, the bones of the joint begin to run against one another, causing stiffness and pain, which often impairs movement. Osteoarthritis also can damage ligaments, menisci, and muscles. Bone or cartilage fragments may float in the joint space, causing irritation and pain. Bone spurs, or osteophytes, may also develop, causing additional pain and potentially damaging surrounding tissues.\(^1\) Around the world, an estimated 10%-15% of adults over 60 have some degree of osteoarthritis.\(^1\) It most commonly affects the joints in the knee, hands, feet, and spine, and is also relatively common in other joints such as the shoulder and hip joints.\(^1\)

There are two types of osteoarthritis: primary and secondary.

Primary osteoarthritis is a chronic degenerative disease that is related to, but not caused by, aging. As a person ages, the water content of their cartilage decreases, thus weakening it and making it less resilient and more susceptible to degradation. There are strong indications that genetic inheritance is a factor, as up to 60% of all OA cases are thought to result from genetic factors.\(^2\)

Secondary arthritis tends to show up earlier in life, often due to a specific cause such as an injury, a job that requires kneeling or squatting for extended amounts of time, diabetes, or obesity. But though the aetiology is different than that of primary OA, the resulting symptoms and pathology are the same.\(^2\)

The main symptoms are pain, loss of ability, and “joint stiffness after exercise or use.” These symptoms are often aggravated by activity or rigorous exercise and relieved during rest, though the disease may eventually progress to the point where the patient even feels pain when resting, and some people report pain so intense that it wakes them up when they are sleeping.\(^2\)

Osteoarthritis, at present, cannot be cured, and will likely get worse over time, but the symptoms can be controlled. Treatments vary widely, from alternative medicine, to lifestyle changes such as exercise and diet, to physical aids such as canes or braces, to medications such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDS), corticosteroids, and more. This range of treatments is elaborated on in section 6.12.3 of this OA chapter.\(^2\)
2. Size and Nature of the Disease Burden

Osteoarthritis primarily affects the elderly population and is present worldwide. Because of its function-impairing nature, its burden on society is quite substantial both in terms of its epidemiology and its economic impact.

2.1 Epidemiology

Osteoarthritis is the single most common cause of disability in older adults. It ranks as the fifth highest cause of years lost to disability in the whole population in high-income countries, and the ninth highest cause in low- and middle-income countries (See Figure 6.12.1). It accounts for 50% of the entire musculoskeletal disease burden, and thus is considered the highest-burden condition within the musculoskeletal group of diseases, which also includes rheumatoid arthritis and osteoporosis. Radiographic evidence of knee osteoarthritis is present in approximately 30% of men and women over the age of 65. Worldwide estimates are that 9.6% of men and 18.0% of women over the age of 60 years have symptomatic osteoarthritis. Approximately 80% of those with OA will have limitations in movement, and 25% cannot perform their major activities of daily life.

Figure 6.12.1: Leading global causes of years lost to disability by income group (2004)

The 2010 Global Burden of Disease Study published in the Lancet in December of 2012 reports that the burden of musculoskeletal disorders is actually much larger than in previous assessments of the global burden of disease. Previous reports estimated this group of disorders to account for approximately 2.0% of DALYs, while this report estimates it to be closer to 6.8%. These data show that osteoarthritis and other musculoskeletal disorders are extremely common in all populations.
Altogether 10%-15% of adults over 60 have some degree of osteoarthritis. Across the EU Member States, diagnosed OA prevalence varies from 2.8% in Romania to 18.3% in Hungary. Figure 6.12.2 illustrates the health resource use burden of osteoarthritis across Europe.

As the elderly population increases around the world, there is a consequent rise in the prevalence of non-communicable and chronic diseases (see Chapter 5). One of the major disabling conditions among the elderly population is musculoskeletal (MSK) diseases, such as osteoarthritis. According to the United Nations, the proportion of people over the age of 60 will triple over the next 40 years, meaning this demographic will account for more than 20% of the world's population by 2050. Of that 20%, a conservative estimate of 15% will have symptomatic osteoarthritis, and one third of these people will be severely disabled. This translates to 130 million people who will suffer from osteoarthritis and 40 million people who will be severely disabled by OA by 2050.
Osteoarthritis is the most common form of arthritis in both developed and developing countries. However, the majority of patients in developing countries do not have access to joint replacement surgery, and as a result will have to endure severe disability for a substantial part of their lives, placing an enormous burden on their communities.13

2.2 Economic Burden

In terms of health resource use, 82.9% of patients with osteoarthritis had at least one investigative test over the previous six-month investigative period, and 7.9% of OA patients had purchased adaptive aids and devices over the same six-month period in a 2004 study.11 Total six-month costs related to OA were US$ 2456, with direct costs accounting for just over 80% of these costs. Almost half of all direct costs were attributable to drug costs, especially prescription drug costs. Of the patients surveyed, 30.7% were unable to do chores, and 3.6% of the patients had taken time off work in the past six months because of their condition.11 See Annex 1 for further breakdown of healthcare resource use, and Annex 2 for elaboration of the cost of illness for patients with OA. Figure 6.12.3 below depicts the burden of musculoskeletal diseases on primary care in the United Kingdom.11

Figure 6.12.3: GP consultation rates for non-infectious diseases per 100,000 people

2.3 Burden of Specific OA Treatments

Treatment of Pain

Data from a large claims database of a private insurer from 2003 to 2004 found that 15% of annual drug costs went to pain and pain-related medications. More than half (54%) of the patients in the study took a COX-2 inhibitor, 46% used non-selective NSAIDS, 34% were prescribed antidepressants, and 9% took tramadol.12

Viscosupplementation

Little data is available regarding the effect of viscosupplementation, also known as intraarticular hyaluronate (IAH,) on total OA costs. A 2007 study in the U.S. estimated the actual cost of IAH to range from US$ 852 to US$ 1840 (including injections, arthrocentesis, and office visits) depending on the specific regimen.13 IAH’s purpose is often to delay joint replacement surgery.

Joint Replacement Surgery

The average age of a patient who receives a total hip replacement (THR) in the United States is just under 68 years of age, and the likelihood of having the surgery increases with age.12 The same trend is apparent for total knee replacements (TKR). The number of hip and knee replacement surgeries performed is projected to continue increasing at a rapid rate: between 2005 and 2030, hip arthroplasties are expected to increase by 174%, and the number of knee arthroplasties is expected to increase even more rapidly: increasing by 673% by 2030.12 Though joint replacement surgeries are expensive procedures, their high effectiveness may justify their prevalence, especially in high-income countries that have adequate resources for such treatments. The inpatient costs for primary THR are estimated to be around US$ 30 000; secondary or revision hip replacement costs are estimated to be around US$ 38,000. Similarly, primary TKR costs are estimated to be around US$ 21 000 and TKR revisions to cost approximately US$ 25 000.12 Figures 6.12.4 and 6.12.5 depict the number of knee and hip replacement surgeries per 100 000 people in various European countries.

In summary, OA has widespread prevalence and sizeable economic costs (both direct and indirect) which causes it to have a substantial burden both in terms of health and economics around the globe.
3. Control Strategy

Patients with OA suffer from pain and loss of function. Objectives of OA management are to reduce the level of pain, reduce inflammation, slow cartilage degradation, improve function and reduce disability. This section reviews the overall control strategy for osteoarthritis, and is specifically divided into Prevention, Diagnosis, and Medical Management. Medical Management is further subdivided by nonpharmacological and pharmacological treatments.
3.1 Prevention

Because no highly effective pharmaceutical treatments exist and surgical options are expensive and not widely available, prevention is a major strategy in addressing the disease burden of osteoarthritis.

Primary prevention

Only a limited number of primary interventions have been identified for osteoarthritis, including:

- Weight control: Obesity is considered a risk factor for OA. Thus, maintaining or reducing weight through altered diet and increased physical exercise can lower the risk of developing OA.\(^{14}\)
- Occupational injury prevention: Avoidance of repetitive joint use and proper management of related injuries can help prevent arthritis.\(^ {14}\)
- Sports injury prevention: Taking the necessary precautions to prevent injury such as warming up and using proper equipment can help reduce joint injuries.\(^ {14}\)
- Misalignment: Improper alignment of the knee or hip can contribute to osteoarthritis and proper treatment such as orthotics or bracing can help reduce the risk of developing the disease.\(^ {15}\)

Secondary prevention

The aim of secondary prevention is early diagnosis which allows for effective and appropriate interventions that will minimize the health consequences of the disease. Recently, research into bone and cartilage degradation has identified biochemical markers that may be used to identify OA early in the progression of the disease.\(^ {16}\) However, not enough is known about these biochemical markers to implement them in clinical practice. Currently, identification of arthritis is primarily done with X-rays or other imaging methods. But access to well-equipped health care facilities with X-ray technology is limited in many parts of the world.\(^ {17}\)

Tertiary prevention

Tertiary prevention focuses on minimizing the complications of disease once it has been diagnosed. Such strategies for osteoarthritis are aimed at reducing pain and disability, and improving quality of life. Tertiary prevention strategies for OA include self-management (weight control, physical activity, and education), home help programs, cognitive behavioural interventions, rehabilitation services, and medical or surgical treatments.\(^ {14}\) See further elaboration in the section on Medical Management.

3.2 Diagnosis

As of 2004, biochemical markers of the disease were not available. However, more recent research has indicated that it may be possible to assess bone and cartilage using biochemical markers. Two processes that contribute to the development of osteoarthritis are bone degradation and cartilage degradation, and research has indicated that both of these two processes have potential biomarkers.
Bone Degradation

An osteoclast is a type of bone cell that degrades bone tissue by removing minerals and breaking up the organic bone; this process is called bone resorption. The majority of bone resorption by osteoclasts is mediated by the protease cathepsin K, which specifically results in the fragmentation of collagen type I (CTX-I). The presence of CTX-I fragments has been used as a surrogate measure of bone resorption for in vitro, preclinical and clinical studies.\(^1\)

Cartilage Degradation

An investigation of urinary concentrations of type-II collagen (CTX-II) fragments has revealed an association between these concentrations and the prevalence and progression of osteoarthritis of the knee and hip. Furthermore, these concentrations seem higher in patients with joint pain. Baseline CTX-II concentration was higher in subjects with baseline OA (see Table 6.12.1), and there were also associations between CTX-II and progression of OA (see Table 6.12.2).\(^2\) It has been proposed that an assessment of collagen degradation be used as a quantitative measure of cartilage damage in assessing OA.\(^3\)

Currently, the most common strategy to diagnose OA is a physical examination, which can show many of the symptoms of OA including crepitation (grating sound during joint movement), joint swelling, limited range of motion, tenderness where the joint is pressed, and pain during normal movements. Additionally, an X-ray of affected joints will show a loss of the joint space. In more advanced cases, there may be bone spurs or evidence of worn-down ends of the bones in the affected joint.\(^4\) An MRI scan may be helpful in distinguishing OA from other kinds of injuries.\(^5\) Arthroscopy is a common method of diagnosis and monitoring of progression. It also combines an opportunity for therapeutic joint surgery at the same time. However, all these diagnostic tools have low sensitivity and specificity.

Given properly trained doctors, physical examinations are an inexpensive way to diagnose osteoarthritis around the world, though access to treatment may not be adequate. However, X-rays and similar imaging technologies are not available in many parts of the world.

### Table 6.12.1: Cross-sectional association between baseline CTX-II concentration and baseline radiographic OA of the knee and/or hip

<table>
<thead>
<tr>
<th>Quartile (range of CTX-II values)‡</th>
<th>Radiographic knee OA (n = 237)</th>
<th>Radiographic hip OA (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR (95% CI)†</td>
</tr>
<tr>
<td>First (1.19–2.10)</td>
<td>1</td>
<td>I</td>
</tr>
<tr>
<td>Second (2.11–2.25)</td>
<td>1.7 (1.0–2.9)</td>
<td>1.7 (1.0–2.9)</td>
</tr>
<tr>
<td>Third (2.26–2.39)</td>
<td>3.2 (2.0–5.2)</td>
<td>2.8 (1.6–4.6)</td>
</tr>
<tr>
<td>Fourth (2.40–3.11)</td>
<td>5.2 (3.3–8.4)</td>
<td>4.2 (2.5–7.0)</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change in risk per SD§</td>
<td>1.9 (1.6–2.2)</td>
<td>1.7 (1.4–2.0)</td>
</tr>
</tbody>
</table>

* Associations are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs) for risk of radiographic OA according to CTX-II levels. Knee and hip radiographic OA is defined as a Kellgren/Lawrence score ≥2 in at least 1 joint. See Table 1 for other definitions.

† For age, sex, body mass index, and lower limb disability index.
‡ Log transformed.
§ SD of mean log-transformed value.

Update on 2004 Background Paper, BP 6.12 Osteoarthritis

Table 6.12.2: Associations between baseline CTX-II concentration and radiographic progression of knee OA

<table>
<thead>
<tr>
<th>Quartile (range of CTX-II values):</th>
<th>JSN ≥1.0 mm (n = 233)</th>
<th>JSN ≥1.5 mm (n = 73)</th>
<th>JSN ≥2.0 mm (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First (1.49–2.10)</td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
<td>Crude OR (95% CI)</td>
</tr>
<tr>
<td>Second (2.11–2.25)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Third (2.26–2.39)</td>
<td>1.0 (0.7–1.5)</td>
<td>0.9 (0.6–1.5)</td>
<td>1.5 (0.7–3.3)</td>
</tr>
<tr>
<td>Fourth (2.40–3.11)</td>
<td>1.2 (0.8–1.8)</td>
<td>1.1 (0.7–1.7)</td>
<td>1.9 (0.9–4.1)</td>
</tr>
<tr>
<td></td>
<td>p for trend</td>
<td>0.219</td>
<td>0.730</td>
</tr>
<tr>
<td></td>
<td>Change in risk per SD$</td>
<td>1.1 (1.0–1.2)</td>
<td>1.1 (0.9–1.3)</td>
</tr>
</tbody>
</table>

* Associations are presented as ORs and 95% CIs for risk of radiographic OA according to CTX-II levels. Joint space narrowing (JSN) is defined as the joint space width at baseline minus the joint space width at followup (medial and lateral compartments), using different cutoff points. See Tables 1 and 2 for other definitions.
† For age, sex, body mass index, lower limb disability index, baseline radiographic OA of the knee, and followup time.
‡ Log transformed.
§ SD of mean log-transformed value.


3.3 Medical Management

Persons affected by OA have a wide range of ages, demographics, disease impairment, comorbidities, and goals. Therefore management of the patient with OA should be comprehensive and individualized, taking into account the anatomical distribution, the phase and the progression rate of the disease. Comorbid conditions such as cardiac disease, hypertension, peptic ulcer disease or renal disease must be taken into account, as well as the patient’s needs and expectations. The management plan of OA patients also needs to be regularly reviewed and adjusted in light of their response and adherence. This will vary between patients and location. The management of OA is broadly divided into non-pharmacological, pharmacological, and surgical treatments. The recommended hierarchy of treatment should be non-pharmacological treatments first, followed by pharmacological treatment and then surgery if the first two are unsuccessful (see Figure 6.12.6). Examples of the different classes of therapies are outlined in Table 6.12.3.

Figure 6.12.6: recommended hierarchy of treatment options for OA.

![Figure 6.12.6](image_url)

Table 6.12.3: Summary of therapeutic options in osteoarthritis

<table>
<thead>
<tr>
<th>Non-pharmacological treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education (patient and spouse or family)</td>
</tr>
<tr>
<td>Social support</td>
</tr>
<tr>
<td>Physical therapy</td>
</tr>
<tr>
<td>Occupational therapy</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Exercise</td>
</tr>
<tr>
<td>Orthotic devises</td>
</tr>
<tr>
<td>Pulsed EMF (Electromagnetic field therapy)</td>
</tr>
<tr>
<td>Transcutaneous electrical nerve stimulation (TENS)</td>
</tr>
<tr>
<td>Acupuncture</td>
</tr>
<tr>
<td>Herbal remedies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacological treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol/Acetaminophen</td>
</tr>
<tr>
<td>NSAIDS (Non-steroidal anti-inflammatory drugs) [plus misoprostol or a proton pump inhibitor]*</td>
</tr>
<tr>
<td>COX-2 inhibitors (cyclo-oxygenase-2 selective non-steroidal anti-inflammatory drugs)*</td>
</tr>
<tr>
<td>Opioid analgesics</td>
</tr>
<tr>
<td>Psychotropic drugs</td>
</tr>
<tr>
<td>SYSADOA (Symptomatic Slow Acting Drugs for OA (avocado/soybean unsaponifiables (ASU), chondroitin, diacerein and glucosamine)</td>
</tr>
<tr>
<td>Topical NSAIDS</td>
</tr>
<tr>
<td>Topical capsaicin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intra-articular treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Hyaluronans</td>
</tr>
<tr>
<td>Tidal irrigation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthroscopy</td>
</tr>
<tr>
<td>Osteomy</td>
</tr>
<tr>
<td>UKR (unicompartmental knee replacement)</td>
</tr>
<tr>
<td>Total joint arthroplasty (knee or hip)</td>
</tr>
</tbody>
</table>


*Note: many COX-2 inhibitors were withdrawn due to side effects

3.3.1 Non-pharmacological Management

The first step of non-pharmacological management should be patient education. Patients should be counseled on coping skills, given resources for support, and encouraged to join self-management programs. Patients who are overweight or obese should be encouraged to
lose weight and increase their physical activity. Moreover, exercise is beneficial even to those patients who are at a healthy weight because increased muscle strength can reduce some of the complications of OA. Doctors should properly advise patients on low impact activities that will not increase their chance of exacerbating their OA symptoms. Non-pharmacological therapy also can include a referral to a physical therapist. Knee braces, orthotics, and appropriate footwear can reduce pain and improve function in people with poor alignment.\textsuperscript{17}

Apart from the traditional non-pharmacological approaches, there has been recent research into other therapeutic options to treat OA. Of the newer therapies, pulsed ultrasound appears to be one of the most promising. A 2012 meta-analysis of 341 patients found that treatment had a significant effect on pain when compared to a placebo (mean difference on a visual analog scale from 0-10, -1.2 [95% CI -1.9 to -0.6]). No patients in any of the trials withdrew due to adverse effects, indicating that ultrasound is a very safe therapy.\textsuperscript{20} In a 2010 Cochrane Review, acupuncture showed small but significant short term effects on pain (standardized mean difference of multiple scales -0.28, [95% CI -0.45 to -0.11]). However, many of these trials suffered from incomplete blinding.\textsuperscript{21} A Cochrane Review completed in 2009 found potentially promising results of treatment with electromagnetic fields. Several of the individual trials conducted showed significant results but their clinical importance was questionable.\textsuperscript{22} Transcutaneous electrical nerve stimulation, electro-acupuncture, and low level laser therapy all demonstrated clinically relevant pain relief in a 2007 systematic review (visual analog scale 0-100, 18.8 mm [95% CI 9.6 to 28.1], 21.9 mm [95% CI 17.3 to 26.5] and 17.7 mm [95% CI: 8.1 to 27.3]).\textsuperscript{23}

3.3.2 Pharmacological Management

At present, there is no cure for OA. The primary strategy for pharmacological management of OA is to control pain and improve function and quality of life for the patient, while limiting drug toxicity. When OA pharmaceuticals are prescribed, the trade-offs between the risks and the benefits must be assessed because side effects are common and the long-term efficacy of these drugs is often variable or is yet to be determined.\textsuperscript{17}

There are many pharmacological products on the market for the management of symptoms associated with OA. A review of the most common treatments is listed below.

Paracetamol (Acetaminophen)

Paracetamol (acetaminophen) is a commonly prescribed oral analgesic to treat mild to moderate OA pain. It has a relatively low level of short and long term side effects and can be taken up to four times daily.\textsuperscript{20} However, a 2006 Cochrane Review found that acetaminophen is less effective than NSAIDs at treating moderate to severe OA pain (Table 6.12.4). But because adverse effects in some patients limit the wider use of NSAIDs, acetaminophen should still be an option.\textsuperscript{24}
Table 6.12.4: Cochrane Review of Paracetamol Outcomes as measured by Standard Mean Differences on a variety of scales.

<table>
<thead>
<tr>
<th></th>
<th>Studies</th>
<th>SMD</th>
<th>Lower CI</th>
<th>Higher CI</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>6</td>
<td>-1.64</td>
<td>-1.22</td>
<td>-0.94</td>
<td>yes</td>
</tr>
<tr>
<td>Adverse GI events</td>
<td>RR = -1.47</td>
<td>-1.08</td>
<td>-2.0</td>
<td>yes</td>
<td></td>
</tr>
</tbody>
</table>


Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are a large class of drugs which have analgesic and anti-inflammatory. Common oral NSAIDs include ibuprofen, aspirin, and naproxen. A Cochrane Review found NSAIDs to be more effective than placebo at treating OA pain. However, treatment with NSAIDs is associated with gastrointestinal effects and potential toxicity, especially in the elderly. It has been recommended that the use of a gastrointestinal protectant in conjunction with NSAID treatment can reduce the risk of adverse effects.

A new class of NSAIDS called COX-2 inhibitors was introduced in 1999 with the aim of relieving pain and reducing gastrointestinal side effects. However one of the class, rofecoxib was found to increase the risk of cardiovascular events and was withdrawn in 2004. Celecoxib and etoricoxib remain on the market though with substantially reduced usage.

Topical NSAIDs

Topical NSAIDs, in the form of cream, patches, gels, solutions, have been found to be effective compared to placebo at reducing pain associated with musculoskeletal conditions, including OA. According to a Cochrane analysis, the most promising and effective topical NSAID drug appears to be diclofenac (Table 6.12.5). When compared to a placebo, patients who took diclofenac had significant reduction in pain (50% reduction in pain, RR 2.0 [95% CI 1.5 to 2.6]). The benefit of topical NSAIDs is that they eliminate the gastrointestinal side effects of oral treatment. However, they have been associated with certain local adverse effects and the current research indicates that they may be less efficacious than oral NSAIDs.

Table 6.12.5: Cochrane Review of Pain Reduction with topical diclofenac

<table>
<thead>
<tr>
<th></th>
<th>Studies</th>
<th>Patients</th>
<th>RR</th>
<th>Lower CI</th>
<th>Higher CI</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful Treatment</td>
<td>4</td>
<td>569</td>
<td>2.0</td>
<td>1.5</td>
<td>2.6</td>
<td>yes</td>
</tr>
</tbody>
</table>

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Opioids

Opioids have the ability to be used as alternatives for pain relief in patients who cannot use either NSAIDs or acetaminophen.24 A large review of 11 clinical trials suggests that the small to moderate pain relieving effects of opioid treatment were outweighed by their adverse effects. The meta-analysis of 10 trials involving 2268 participants found that 4 times as many patients on opioid treatment dropped out due to negative side effects compared to those taking a placebo (RR 4.05 [95% CI 3.06 to 5.38]) (Table 6.12.6). The most serious adverse effect from opioid treatment is respiratory depression and overdosage while more mild side effects often include constipation, nausea, and itching.27 Abuse potential is high with opioids.

Table 6.12.6: Cochrane Review of treatment outcomes with opioids.

<table>
<thead>
<tr>
<th></th>
<th>Studies</th>
<th>Patients</th>
<th>SMD</th>
<th>Lower CI</th>
<th>Higher CI</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>10</td>
<td>2268</td>
<td>-0.36</td>
<td>-0.47</td>
<td>-0.26</td>
<td>yes</td>
</tr>
<tr>
<td>Function</td>
<td>10</td>
<td>2268</td>
<td>-0.33</td>
<td>-0.45</td>
<td>-0.21</td>
<td>yes</td>
</tr>
<tr>
<td>Drop outs due to adverse events</td>
<td>10</td>
<td>2268</td>
<td>RR = 4.05</td>
<td>3.06</td>
<td>5.38</td>
<td>yes</td>
</tr>
</tbody>
</table>


Diacerein

Diacerein is another pharmaceutical that can be used to control pain resulting from OA. A review of seven clinical trials found a small but consistent reduction in pain (weighted mean difference, -5.16 [95% CI -9.75, -0.57]) (Table 6.12.7). The authors concluded that more research should be done into the side effects of diacerein treatment given that the analysis found that 42% of patients in the treatment group experienced diarrhea.28

Table 6.12.7: Cochrane Review of Diacerein Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Studies</th>
<th>Patients</th>
<th>WMD (0-100)</th>
<th>Lower CI</th>
<th>Higher CI</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>5</td>
<td>1228</td>
<td>-5.16</td>
<td>-9.75</td>
<td>-0.57</td>
<td>yes</td>
</tr>
</tbody>
</table>


Glucosamine

Glucosamine is an amino sugar found naturally in the body and comprises an important step in the synthesis of cartilage. There was hope that glucosamine might help to reverse the effects of OA, a task that have proved to be unsuccessful. A 2009 Cochrane Review found inconclusive results from glucosamine treatment. Some studies found that treatment improved both pain and function but others found no significant difference from the effects of placebo.29
Herbal therapies

Of all herbal therapies tested, avocado-soybean unsaponifiables have shown the most promising results in pain reduction (mean difference on a visual analog scale from 0-100, -8.06 [95% CI -11.53 to -4.60] (Table 6.12.8). The current recommendation is that patients be given avocado-soybean unsaponifiables for a trial period of several months to see if they will benefit from its effects. Individual differences seem to play a large role in the effectiveness of avocado-soybean unsaponifiables, with patients with OA of the knee benefitting more than patients with OA of the hip.

Table 6.12.8: Patient outcomes in Avocado/Soybean Unsaponifiables vs. placebo

<table>
<thead>
<tr>
<th></th>
<th>Studies</th>
<th>Patients</th>
<th>MD</th>
<th>Lower CI</th>
<th>Higher CI</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>2</td>
<td>325</td>
<td>-7.61</td>
<td>-11.79</td>
<td>-3.42</td>
<td>Yes</td>
</tr>
<tr>
<td>Function</td>
<td>1</td>
<td>162</td>
<td>-13.20</td>
<td>-20.00</td>
<td>-6.40</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Intra-articular corticosteroids

Treatment with corticosteroids injected directly into the joint (intraarticular) has been shown to be effective, especially in OA of the knee. A 2009 Cochrane Review found intra-articular corticosteroids to be more effective than an intrarticular placebo at reducing pain at one week post injection (weighted mean difference on a visual analog scale from 0-100, -21.91 [95% CI -29.93 to -13.89]) (Table 6.12.9). However, questions still remain about the long term efficacy of treatment and the patient subgroups which will benefit most.

Table 6.12.9: Patient pain outcomes in corticosteroids vs. placebo

<table>
<thead>
<tr>
<th></th>
<th>Studies</th>
<th>Patients</th>
<th>WMD</th>
<th>Lower CI</th>
<th>Higher CI</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>3</td>
<td>161</td>
<td>-21.91</td>
<td>-29.93</td>
<td>-13.89</td>
<td>Yes</td>
</tr>
<tr>
<td>6 weeks</td>
<td>1</td>
<td>84</td>
<td>7.10</td>
<td>18.39</td>
<td>4.19</td>
<td>No</td>
</tr>
</tbody>
</table>

Viscosupplementation

Hyaluronan is a polysaccharide that is found naturally throughout the body and is one of the main components of the extracellular matrix. Viscosupplementation involves a series of injections of either hyaluronan or hylan products. It is thought that viscosupplementation changes the fluid of the joint in a way that increases the joint’s function and reduces pain. A Cochrane Review indicated that the treatment was effective in reducing pain compared to a placebo at 5-13 weeks following treatment (weighted mean difference on a visual analog scale from 0-100, -9.04 [95% CI -14.10 to -3.98]) (Table 6.12.10). Treatment also appears to have a significantly positive effect on joint function and patient global assessment. However,
many of these studies had small sample sizes and thus more research is needed to definitively determine the efficacy of viscosupplementation.\textsuperscript{33} In 2011, Bannaru et al reported on a systematic review of 54 eligible trials involving 7545 patients. They reported that intraarticular injection of hyaluron was effective at four weeks, reached maximal effectiveness at eight weeks and still had detectable effect at six months after injection.\textsuperscript{34}

### Table 6.12.10: Pain improvement outcomes in patients treated with hyalgan versus placebo

<table>
<thead>
<tr>
<th>Studies</th>
<th>Patients</th>
<th>WMD</th>
<th>Lower CI</th>
<th>Higher CI</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain in walking after 5-13 weeks</td>
<td>14</td>
<td>1095</td>
<td>-9.04</td>
<td>-14.10</td>
<td>-3.98</td>
</tr>
<tr>
<td>Pain at rest after 5-13 weeks</td>
<td>5</td>
<td>155</td>
<td>-9.65</td>
<td>-14.18</td>
<td>-5.13</td>
</tr>
</tbody>
</table>


### S-Adenosylmethionine

S-Adenosylmethionine (SAMe) is a product that is often sold as a nutritional supplement in many parts of the world. A 2009 Cochrane Review of its effectiveness was inconclusive due to small sample sizes and poor quality data. A total of four studies with 542 patients failed to show any significant differences in outcomes measured by changes in pain intensity or function. Table 6.12.11 below summarizes these results. Adverse effects were not significantly different between intervention and control groups.

### Table 6.12.11: Cochrane Review of SAMe Outcomes

<table>
<thead>
<tr>
<th>Studies</th>
<th>Patients</th>
<th>WSMD</th>
<th>Lower CI</th>
<th>Higher CI</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>2</td>
<td>533</td>
<td>-0.17</td>
<td>-0.35</td>
<td>0.01</td>
</tr>
<tr>
<td>Function</td>
<td>3</td>
<td>542</td>
<td>0.02</td>
<td>-0.68</td>
<td>0.71</td>
</tr>
</tbody>
</table>


The authors’ conclusion was that SAMe should not be recommended until further trials of adequate sample size and methodology were undertaken.\textsuperscript{35}

### Autologous Chondrocyte therapy

Autologous chondrocyte implantation (ACI), involves the surgical implantation of healthy cartilage cells into the damaged areas. A 2010 Cochrane Review reported on six heterogeneous trials involving 442 participants. The authors conclusion was that there was insufficient evidence to draw conclusions on the use of ACI for treating full thickness articular cartilage defects in the knee. Further good quality randomised controlled trials with long-term functional outcomes are required.\textsuperscript{36}
3.3.3 Surgical Management

When non-pharmacological and pharmacological management strategies are not effective at controlling OA symptoms, surgical options should be considered.

Joint replacement

Joint replacement is a serious and permanent intervention for patients who have few other options. Patients who experience severe daily pain and show extensive narrowing of joint space are eligible for joint replacement surgery. While this is an expensive treatment option, cost effective analyses have indicated that the costs from long term medication use and lost productivity outweigh the price of surgery in patients with severe symptoms. A 2012 systematic review found that the estimated incremental cost-effectiveness ratio (ICER) for knee replacement in a United States Medicare-aged population varied from US$13 000 per QALY (quality-adjusted life year) over a five-year time horizon from the payer perspective to US$ 22 000 per QALY from the societal perspective and over the lifetime horizon. Table 6.12.12 summarizes the incremental cost-effectiveness ratio of total knee arthroplasty stratified by level of risk of perioperative complications. The 2012 study found the incremental cost-effectiveness ratio in a similar population of total hip arthroplasty patients to be similar.
Table 6.12.12: incremental cost-effectiveness ratios of total knee arthroplasty (TKA)

<table>
<thead>
<tr>
<th>TKA Status</th>
<th>Cost</th>
<th>QALYs. No.</th>
<th>ICER Compared With Next Least Expensive Strategy</th>
<th>ICER Compared With No TKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No TKA</td>
<td>37,100</td>
<td>0.822</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>TKA</td>
<td>37,900</td>
<td>7.357</td>
<td>18,800</td>
<td>NA</td>
</tr>
<tr>
<td>Low-risk population</td>
<td>26,800</td>
<td>8.715</td>
<td>NA</td>
<td>Dominate</td>
</tr>
<tr>
<td>TKA</td>
<td>44,000</td>
<td>10.589</td>
<td>9,700</td>
<td>Dominate</td>
</tr>
<tr>
<td>Medium-risk population</td>
<td>19,800</td>
<td>6.574</td>
<td>NA</td>
<td>Dominate</td>
</tr>
<tr>
<td>TKA</td>
<td>39,900</td>
<td>7.649</td>
<td>15,700</td>
<td>Dominate</td>
</tr>
<tr>
<td>High-risk population</td>
<td>86,800</td>
<td>5.713</td>
<td>NA</td>
<td>Dominate</td>
</tr>
<tr>
<td>TKA</td>
<td>111,500</td>
<td>6.594</td>
<td>28,100</td>
<td>Dominate</td>
</tr>
</tbody>
</table>


Osteotomy

Osteotomy is the cutting and reshaping of bones with the purpose of altering the area of the joint which bears weight. A Cochrane Review found that osteotomies reduced pain and improved function, though there is no evidence whether an osteotomy is more effective than conservative treatment.38 There is also evidence that osteotomies may eliminate or delay the need for joint replacement surgery.32

Arthroscopic debridement and lavage

Arthroscopic debridement and lavage are two processes that involve removing damaged cartilage, bone, and excess debris surrounding the joint. This is still a very controversial process and a Cochrane Review found that the treatment did not improve pain or function when compared to a sham surgery. However, for specific population of patients, the surgery may be beneficial and more research is needed to identify these subgroups.3
4. Major Problems and Challenges for Disease Control (Why Does the Disease Burden Persist?)

Because there is such a wide variety of risk factors (see Table 6.12.12) for this disease, it is unlikely that OA can be prevented entirely. Protective factors such as exercise, healthy diet, and occupational injuries can all be addressed, but many risk factors such as gender, age, and genetics are not modifiable. The physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity. Though there is a wide range of devices and palliative medicines available that relieve pain and improve quality of life for patients, there is no pharmaceutical product that halts or reverses the onset of osteoarthritis.

Thus, as the population ages, the disease burden of osteoarthritis will naturally increase accordingly unless (1) primary prevention efforts such as healthy diet and exercise are scaled up around the world (2) diagnostics and secondary prevention methods are developed that detect the onset of OA very early, perhaps through testing genetic or biochemical markers, and (3) therapies are developed that stop or even reverse the progression of OA when it is identified. Otherwise, people around the world will continue to develop the currently-incurable disease, osteoarthritis.

Table 6.12.13: Risk Factors for Incidence and Progression of Osteoarthritis

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Normal ageing processes cause increased OA progression</td>
</tr>
<tr>
<td></td>
<td>Incidence increases with age but levels off around age 80</td>
</tr>
<tr>
<td>Trauma</td>
<td>Collateral ligament, meniscal tears and joint fractures lead to increased risk for OA</td>
</tr>
<tr>
<td>Occupation</td>
<td>More common in those performing heavy physical work</td>
</tr>
<tr>
<td></td>
<td>Significant relationship between OA and occupational kneeling or repetitive use of joint during work</td>
</tr>
<tr>
<td></td>
<td>Certain occupations, such as farming, construction work, physical education teaching, are risk factors for the development of OA</td>
</tr>
<tr>
<td>Exercise</td>
<td>High-impact sports present an increase for knee OA</td>
</tr>
<tr>
<td>Gender and ethnicity</td>
<td>Men under the age of 50 have a higher prevalence and incidence</td>
</tr>
<tr>
<td></td>
<td>Women over 50 have a higher prevalence and incidence of OA than men of the same age</td>
</tr>
<tr>
<td></td>
<td>Generally more common in Europeans than in Asians</td>
</tr>
<tr>
<td>Genetics</td>
<td>There is genetic susceptibility to the disease</td>
</tr>
<tr>
<td></td>
<td>Children of parents with early onset OA are at a higher risk of developing OA themselves</td>
</tr>
<tr>
<td>Obesity</td>
<td>Strongest modifiable risk factor</td>
</tr>
<tr>
<td></td>
<td>Overweight or obese people have almost 3 times the risk of developing OA as people with a normal weight (OR 2.96 [95% CI 2.56 to 3.43])</td>
</tr>
<tr>
<td></td>
<td>Weight loss can substantially decrease the risk of developing OA</td>
</tr>
<tr>
<td>Bone density</td>
<td>Decreased bone mineral density is a risk factor for OA</td>
</tr>
</tbody>
</table>

5. Past and Current Research into Pharmaceutical Interventions for Osteoarthritis

Currently all the treatment advances in OA offer palliative care and help to reduce the symptoms of pain. Unfortunately, there have been no new drugs that can prevent, halt or reverse OA progression, although pharmaceutical companies are actively pursuing development of such therapies. The following information summarizes the highlights of osteoarthritis over the past decade:

A US-based public-private partnership between the National Institutes of Health (NIH) and private industry companies, called the Osteoarthritis Initiative (OAI), was started in the early 2000s with the intention to combine resources for the purpose of finding biological markers related to the progression of OA. Nearly 5,000 people who are either at risk of developing knee OA, in the early stage of the disease, or with more advanced OA are participating in the initiative at four centers around the United States. Participants provide biological specimens (blood, urine, DNA), images (X-rays and magnetic resonance scans), and clinical data such as dietary intake, medication use, pain, function, and other general health assessments. These patients are evaluated at 12-month intervals for five years; almost all of the patient records were complete as of December 2012. The preliminary data that has already been gathered from patients and is available online includes patient symptoms, measure of pain, nutrition, prescription medicines, and alternative therapies used by the participants. When fully complete, the OAI should provide an “unparalleled state-of-the-art database showing both the natural progression of the disease and information on imaging and biochemical biomarkers and outcome measures”.

Another research initiative under Europe’s FP7 is “Evaluation of Osteoarthritis Progression in a Patient-Specific Manner using Magnetic Resonance Imaging and Computational Modeling” (OAPROGRESS) was started in February 2012. Its objectives are to:

“(1) combine MRI with computational modeling for the estimation of stresses and possible failure points within human knee joints
(2) develop second generation adaptive models of articular cartilage for the prediction of altered tissue structure and composition during OA progression. For the model validation, cartilage structure, composition and biomechanical properties as well as cell responses in situ are characterized. At the end of the project these main aims will be merged
(3) estimate the effect of loading on cartilage degeneration during the progression of OA in a patient-specific manner.”

The results of this study, expected to be finished in 2017, will help in making decisions regarding clinical treatments and interventions for the prevention or further progression of osteoarthritis.
6. Opportunities for Future Research into New Pharmaceutical Interventions

There are currently no existing pharmaceutical therapies on the market that can prevent, reverse, or halt the progression of osteoarthritis. Without such medicines, the disease burden of osteoarthritis will naturally increase as the population continues to age. New analgesics therapies that are not disease modifying are in development and may offer an alternative approach to therapy. These products in development include NGF blockers such as tanezumab or fulranumab. Ion channel blockers most notably subtype selective sodium channel blockers (Nav1.7 and Nav1.8) and calcium channel blockers (N type and T type) are also in clinical development for pain indications including osteoarthritis. A 2012 Cochrane Review highlighted one therapy that has shown promising results: platelet-rich therapies (PRT) for long bone healing in adults. There have been encouraging results from a number of in-vitro animal studies, but clinical evidence is thus far unclear. In human patients with osteoarthritis of the knee, those who received platelet-rich therapy had a higher proportion of healed bones after one year, as measured by X-ray (RR 2.67, 95% CI: 1.03 - 6.91). However, the 21-person study found no difference in patient-reported functional outcomes after one year. Thus, “while a potential benefit of platelet-rich therapies to augment bone healing in adults cannot be ruled out, the currently available evidence from a single trial is insufficient to support the routine use of this intervention in clinical practice. Future trials should focus on reporting patient-reported functional outcomes from all trial participants for a minimum follow-up of one year.”

Another area of research that may be translatable to the healing of osteoarthritis is applications of free radicals and reactive oxygen species (ROS). Free radicals are molecules or molecular fragments with an unpaired electron. This charge imbalance then makes the molecule highly reactive with adjacent molecules such as DNA, protein, and lipids, and can cause alterations in their structure. Under normal circumstances, ROS are produced during aerobic cell metabolism, help facilitate intracellular signalling, and play a role in priming the immune system. However, a 2009 study demonstrates that abnormal amounts of ROS results in oxidative stress and contributes to cartilage degradation. These findings support the concept of antioxidant therapy to treat knee OA, though much research is needed in this area before it could be tested in the future.

A principal reason that drug developments to heal or stop OA have been lacking is that, in order to develop these therapies, issues regarding biomarkers, imaging techniques, and other diagnostic issues must first be addressed. The current evaluation methods (mainly X-rays, clinical diagnosis, and blood tests) are insufficient to precisely determine the progression and outcome of new treatments. Fifty per cent of patients in the general population with radiographic knee osteoarthritis do not report having pain. Furthermore, 50% of subjects who complain of knee pain, and who are at or above the age when osteoarthritis starts to become common (about 55 years), have no definite radiographic evidence of osteoarthritis. As cartilage is radiolucent and destruction of cartilage is not possible to visualize, changes in the X-ray appearances of joints appear relatively late in pathogenesis of the disease. Experts in the field have expressed that further research into new imaging technologies, diagnostics, and biomarkers will be especially useful for the management of osteoarthritis. These areas are important because they will bridge the gap between basic science and clinical trials, and allow health professionals to determine:
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- Who is likely to get osteoarthritis?
- How severe is the disease, and how quickly is it progressing?
- How is the patient responding to drugs, and which drugs are the most effective?

Additionally, there is a gap in the research surrounding the cost-effectiveness, safety, and efficacy of long-term OA management and the pharmaceutical therapies that are currently on the market. This information is important for patients, health professionals, policymakers, and other actors in the OA arena to know in order for them to make adequately informed decisions about care options for this disease.

The European League Against Rheumatism (EULAR) is an organization which represents the patient, health professional and scientific societies of rheumatology of all the European nations. They aim to promote the research, prevention, treatment, and rehabilitation of rheumatic diseases, which they define as including rheumatic diseases of the connective tissue, locomotor, and musculoskeletal systems. Their activities include an annual Congress, promoting education and translational research in the field of rheumatology, and partnering with European policymakers to develop policies and framework agendas, such as the Framework Programmes.

Framework Programme 7, the current phase of the EU-funded Framework Programmes for Research and Technological Development, has a budget of over €50 billion over seven years to encourage research in the European Research Area. Almost €12 million of this budget has been allocated to the research initiative “Translational Research in Europe Applied Technologies for Osteoarthritis (Treat-OA).” Treat-OA is a large-scale collaborative project to address the need for better treatment and diagnostics for OA. Their goal is to identify diagnostic and prognostic genetic markers for disease risk and progression and potential therapeutic targets (treatoa.eu) through the following key objectives:

1) “Identify genes and biochemical markers consistently associated with the risk and progression of OA
2) Define the roles of these genes to further our understanding of the molecular pathways involved in disease aetiology
3) Analyze the molecular pathways to identify targets for pharmacological intervention
4) Develop in vivo models by the use of transgenic animal laboratory OA model systems
5) Develop a panel of genetic and biochemical diagnostics for risk and progression of OA
6) Disseminate results to the scientific community and use results and technologies for training within the EU Treat-OA will health develop European clinical and scientific excellence in the diagnosis and treatment of OA”

The knowledge derived from this initiative will provide valuable insight into the future direction of OA pharmaceutical research, as it will reveal novel drug targets and protein therapeutics for OA. There have been 55 published articles from this study so far, including:

Update on 2004 Background Paper, BP 6.12 Osteoarthritis

- Valdes AM, McWilliams D, Arden NK, et al. “Different risk factors are involved in clinically severe large joint osteoarthritis according to the presence of hand interphalangeal nodes.” *Arthritis Rheum.* 2010 May 24

An additional area of therapy that is gaining popularity with consumer groups suffering from OA is complementary or alternative medicine. A Cochrane Review of herbal therapy for treating osteoarthritis concluded that “the evidence for avocado-soybean unsaponifiables in the treatment of osteoarthritis is convincing, but evidence for the other herbal interventions is insufficient to either recommend or discourage their use.”27 A Cochrane Review of acupuncture therapy for OA determined that there is a statistically significant benefit of such therapy, though it is quite small and may be partially due to placebo effects from incomplete blinding.49 Larger-scale research is needed to evaluate the efficacy and cost-effectiveness of these therapies in all types of patients.

7. Conclusion

Osteoarthritis is a chronic progressive disease that is one of the leading causes of disability among elderly populations throughout the world. It causes pain, disability and impaired movement, which places a large burden (both in terms of health and economics) on individuals, communities, and health systems. While there are several therapies available for symptomatic treatment that mitigate pain, there are no medicines that can reverse or halt the progression of the disease. This pharmaceutical gap must be addressed in order to reduce the burden of OA.

One major reason for this gap is because there is a lack of effective biomarkers and diagnostics for OA, which makes it difficult to diagnose, track progression of, and monitor improvements in the patient’s condition. These issues are especially important to address because OA is a condition that requires long-term careful management, so detailed information regarding the effectiveness of medicines is essential. Future research should be directed at addressing this gap in diagnostics and biomarkers which will improve disease monitoring and allow the development of medicines that can reverse the progression of this high-burden condition.
Update on 2004 Background Paper, BP 6.12 Osteoarthritis

References


7 European Musculoskeletal Conditions Surveillance and Information Network. “Musculoskeletal Health in Europe: Report v5.0” 2012


Annexes

Annex 6.12.1: Use of healthcare resources by patients with osteoarthritis

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Use of healthcare resources by patients with RA, OA, and hypertension in a 6 month period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RA (n = 253)</td>
</tr>
<tr>
<td></td>
<td>OA and HBP (n = 191)</td>
</tr>
<tr>
<td></td>
<td>OA (n = 140)</td>
</tr>
<tr>
<td></td>
<td>HBP (n = 142)</td>
</tr>
<tr>
<td>At least one visit to a health professional</td>
<td>253 (100)</td>
</tr>
<tr>
<td>Family physician visit</td>
<td>215</td>
</tr>
<tr>
<td>Non-surgical specialist visits</td>
<td>253</td>
</tr>
<tr>
<td>Surgical specialists</td>
<td>87</td>
</tr>
<tr>
<td>Allied health professionals</td>
<td>97</td>
</tr>
<tr>
<td>Dentists</td>
<td>115</td>
</tr>
<tr>
<td>At least one test or investigation</td>
<td>239</td>
</tr>
<tr>
<td>x Ray</td>
<td>117</td>
</tr>
<tr>
<td>CT or MRI</td>
<td>7</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>40</td>
</tr>
<tr>
<td>Electrodiagnostic tests (ECG, etc)</td>
<td>17</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>228</td>
</tr>
<tr>
<td>Bone density</td>
<td>223</td>
</tr>
<tr>
<td>Other tests or investigations</td>
<td>26</td>
</tr>
<tr>
<td>Patients hospitalised</td>
<td>9</td>
</tr>
<tr>
<td>Other drugs</td>
<td>198</td>
</tr>
<tr>
<td>Community services used</td>
<td>27</td>
</tr>
<tr>
<td>Adaptive aids or devices purchased</td>
<td>50</td>
</tr>
<tr>
<td>Unable to do chores (h)</td>
<td>135</td>
</tr>
<tr>
<td>Needed paid help</td>
<td>68</td>
</tr>
<tr>
<td>Needed unpaid help (h)</td>
<td>149</td>
</tr>
<tr>
<td>Patient time off work (h)</td>
<td>42</td>
</tr>
<tr>
<td>Caregiver time off work (h)</td>
<td>16</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Table 3</th>
<th>Cost of illness estimates for 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RA (n=253)</td>
</tr>
<tr>
<td></td>
<td>OA (n=191)</td>
</tr>
<tr>
<td></td>
<td>OA (n=140)</td>
</tr>
<tr>
<td></td>
<td>HBP (n=142)</td>
</tr>
<tr>
<td>Total costs</td>
<td>$ 4674</td>
</tr>
<tr>
<td>Direct costs: total</td>
<td>$ 2575</td>
</tr>
<tr>
<td>Drugs: total</td>
<td>$ 1237</td>
</tr>
<tr>
<td>Arthritis drugs</td>
<td>$ 769</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>$ 52</td>
</tr>
<tr>
<td>Gastroprotective drugs</td>
<td>$ 110</td>
</tr>
<tr>
<td>Complementary medicine products</td>
<td>$ 66</td>
</tr>
<tr>
<td>Other prescription drugs</td>
<td>$ 240</td>
</tr>
<tr>
<td>Health professionals: total</td>
<td>$ 554</td>
</tr>
<tr>
<td>Family doctors</td>
<td>$ 71</td>
</tr>
<tr>
<td>Non-surgeon specialists</td>
<td>$ 146</td>
</tr>
<tr>
<td>Surgeon specialists</td>
<td>$ 55</td>
</tr>
<tr>
<td>Dentists/dental surgeons</td>
<td>$ 227</td>
</tr>
<tr>
<td>Allied health professionals</td>
<td>$ 56</td>
</tr>
<tr>
<td>Separately ordered tests: total</td>
<td>$ 278</td>
</tr>
<tr>
<td>Hospitalisations: total</td>
<td>$ 264</td>
</tr>
<tr>
<td>Inpatient hospitalisation costs</td>
<td>$ 153</td>
</tr>
<tr>
<td>Outpatient visit costs</td>
<td>$ 86</td>
</tr>
<tr>
<td>Additional CHF billings</td>
<td>$ 25</td>
</tr>
<tr>
<td>Community services</td>
<td>$ 186</td>
</tr>
<tr>
<td>Aids and devices</td>
<td>$ 57</td>
</tr>
<tr>
<td>Indirect costs: total</td>
<td>$ 2098</td>
</tr>
<tr>
<td>Lost time doing chores incl. paid help</td>
<td>$ 1729</td>
</tr>
<tr>
<td>Time lost from work</td>
<td>$ 326</td>
</tr>
<tr>
<td>Support person time lost from work</td>
<td>$ 44</td>
</tr>
</tbody>
</table>