Priority Medicines for Europe and the World 2013 Update

Background Paper 6 - Priority diseases and reasons for inclusion

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Background Paper 6.13
Chronic Obstructive Pulmonary Disease (COPD)

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What’s new since 2004?

The fact that in 2013, available treatments for chronic obstructive pulmonary disease (COPD) are mainly palliative and there are no therapies available that halt the decline in lung function or the progressive destruction of the airways associated with the disease, suggests that not much has changed since the original Priority Medicines Report. While, our knowledge of COPD has grown over the past few years many questions still remain.1, 2

- One of the biggest advances in COPD is greater understanding of the disease burden in different countries and cultures. It is important to establish how important COPD is, particularly in view of the disease’s consistent under-diagnosis at sites where it has been investigated.

- There are striking differences between COPD prevalence in different countries even when using identical detection methods.

- We do not know if undiagnosed COPD is clinically important and a predictor of bad outcomes.

- We understand more about the systemic nature of COPD disease, as some of the most important effects arise in organs outside the respiratory system.

- COPD is a disease of ageing. Furthermore, if every smoker in the world were to stop smoking today, the rates of COPD would probably continue to increase for the next 20 years.

- Since 2004, large-scale, integrated research efforts, both national and international are contributing to knowledge about COPD risk factors and epidemiology (e.g. COPD Biomarkers Qualification Consortium (CBQC) (See Section 8.3.2), SPIROMICS (See Section 8.3.2), COPDGene (See Section 8.3.2), COPDMAP and IMI PROactive (See Section 8.3.1)).

- The heterogeneity of COPD and the lack of validated (or qualified) drug development tools still limits the ability to assess novel medicines that may impact disease progression or extra-pulmonary manifestations of COPD. This process requires large (over 10 000 patients and 3-4 years in duration), but if efforts of large-scale initiatives such as those listed above are successful, we may be able to conduct stratified medicine trials, selecting patients at risk for poor outcomes.

- Major pharmaceutical companies have been conservative with their business model and have invested in management of currently marketed medicines and developing next-generation versions of well-established classes. As a result of this bias towards low risk efforts in COPD, genuinely novel pipeline medicines for COPD are still relatively scarce among such companies, although the situation is improving.
Executive Summary

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. COPD is the fourth leading cause of death worldwide and it is largely preventable. The main cause in developed countries is exposure to tobacco smoke. Other preventable causes include exposure to indoor and outdoor air pollution, such as occupational exposure (firefighters, farm workers) and the burning of biomass fuel for cooking and heating which impacts many women in Africa, China, and India.

In 2010, COPD was estimated to account for 2.7% of the disease burden and 3.2% of deaths in Europe, and for 3.1% of the global disease burden and 5.5% of deaths worldwide. Worldwide prevalence of ‘moderate’ COPD estimated by the Global Initiative on Obstructive Lung Disease (GOLD) in adults aged 40 years and older is 9–10%. Stage III COPD (generally considered as “severe”) drives most of the costs of COPD. Its prevalence across 12 sites around the globe ranged from 0.8% (Hannover, Germany) to 6.7% (Cape Town, South Africa). The Burden of Obstructive Lung Disease initiative used standardized methods to investigate the prevalence of COPD around the world and showed important differences between countries. Prevalence ranged from 9% in Reykjavik, Iceland to 22% in Cape Town, South Africa, for men, and from 4% in Hannover, Germany to 17% in Cape Town for women.

Chronic obstructive pulmonary disease is associated with major morbidity and mortality such as cardiovascular disease, muscle wasting, type 2 diabetes, and asthma. Smoking cessation will probably have the most important effects on COPD as a public health problem in Europe and the world as it slows disease progression and lowers mortality.

None of the existing medications for COPD has been shown to modify the long-term disease progression such as decline in lung function in many patients or worsening of health status. Therefore, pharmacotherapy for COPD is used to alleviate symptoms and/or prevent complications. Inhaled bronchodilators are the mainstay treatment for COPD. Two large-scale, long-term, landmark studies have confirmed the efficacy of a fixed dose combination of a long-acting β2 agonist (salmeterol) and inhaled corticosteroid (fluticasone) and a long-acting anticholinergic agent (tiotropium).

Substantial unmet needs remain in COPD preventing the progression of COPD. Drug development for COPD is difficult owing to the chronic and slowly progressive nature of the disease. Not a single new therapy has come from information on pathogenic inflammatory processes. What is needed are surrogate markers of inflammation that may predict the clinical usefulness of new management and prevention strategies for COPD, new clinical end points to assess the impact of different COPD interventions and standardized methods for tracking trends in COPD prevalence, morbidity, and mortality over time.

New medicines for the treatment of COPD are greatly needed and there has been an enormous effort now invested by the pharmaceutical industry to find such treatments. While preventing and quitting smoking is the obvious preferred approach, this has proved to be very difficult. Not all COPD is due to cigarette smoking, especially in low- and middle-income countries (LMIC).
1. Introduction

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The pathology of COPD includes emphysema and chronic bronchitis, although only one of these may be present in some people with COPD. Emphysema is the abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls, and without obvious fibrosis. Chronic bronchitis is chronic cough or mucous production for at least three months in at least two successive years when other causes of chronic cough have been excluded.

Chronic obstructive pulmonary disease progresses over many decades and tends to present in advanced stages, thus most treated patients are middle aged or elderly. Chronic obstructive pulmonary disease is the fourth leading cause of death worldwide resulting in more than 2.7 million deaths in 2000. The United States National Heart, Lung, and Blood Institute has estimated that it has resulted in a US$ 32.1 billion loss to the USA economy in direct and indirect costs in 2003, with direct costs totaling US$ 18 billion. By 2020, COPD is expected to become the third most common cause of death.

Yet despite the high disease burden and financial costs incurred, efforts to address the problem of chronic respiratory diseases, and COPD in particular, have never received adequate funding in any country, whether for research, prevention, or clinical services.

Chronic obstructive pulmonary disease is largely preventable. The main cause in developed countries is exposure to tobacco smoke. In developed countries, 85% to 90% of people with COPD have smoked at some point. Other preventable causes include exposure to indoor and outdoor air pollution, such as occupational exposure (firefighters, farm workers) and the burning of biomass fuel for cooking and heating which impacts many women in Africa, China, and India.

The disease is, unfortunately, relatively common in lifelong non-smokers that have been exposed to these passive conditions. See Section 5. Other proposed causes include allergy, bronchial hyper-responsiveness, and genetic predisposition (the most well-characterized is hereditary A1AT deficiency). See Section 3.3.

Current therapies address the symptoms only and they range from bronchodilators, anti-inflammatory agents (e.g. corticosteroids, anti-inflammatories, and PDE4 inhibitors) to oxygen. There are no effective cures and there is no single diagnostic test for COPD. Making a diagnosis relies on clinical judgment based on a combination of history, physical examination, and confirmation of the presence of airflow obstruction using lung function testing (spirometry).

The public health situation with regard to COPD is, in broad outline, similar to other preventable chronic conditions such as alcoholic liver disease (See updated Chapter 6.14) where the relatively limited success of primary and secondary prevention of alcohol...
consumption is coupled with the notion that alcohol-induced liver disease is largely a self-inflicted disease.

Smoking cessation will probably have the most important effects on COPD as a public health problem in Europe and the world. Indeed, patients who stop smoking experience less decline in lung function over time. Nonetheless, this document is a summary of pharmacological interventions and gaps to treat existing COPD from that viewpoint.

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

Chronic obstructive pulmonary disease is associated with major morbidity and mortality. A number of co-morbid conditions not directly related to COPD are included in this such as cardiovascular disease, muscle wasting, type 2 diabetes, and asthma. Although the association between COPD and its systemic comorbidities is not fully understood, it may involve the persistent, low-grade pulmonary, and systemic inflammation seen in COPD. This systemic inflammation is independent of cigarette smoking status and persists after smoking cessation.

One of the most frequently reported co-morbidities of COPD is asthma. Both COPD and asthma are major chronic obstructive airway diseases that involve underlying airway inflammation, but the type of inflammatory process differs; the airway inflammation in asthma is typically reversible and is mediated by white blood cells called eosinophils, whereas COPD is characterized by inflammation mediation by white blood cells called neutrophils that does not respond well to standard asthma therapies.

By 2012, COPD drug costs are expected to reach almost 6 billion dollars per year in the USA, Japan, and part of Western Europe alone. This estimate excludes many large and populous areas, such as India and China, where COPD is becoming an increasingly recognized and prevalent condition, both due to smoking and other sources of air pollution.

It is likely that the impact of COPD has been under-estimated due to a lack of accurate epidemiologic data from some countries, misdiagnosis, and inconsistent use of the International Classification of Diseases (ICD) codes when reporting causes of death in patients with COPD. Particularly worrying is the marked increase in deaths (in most, but not all countries) due to COPD over the past couple of decades, a trend that is predicted to continue. Another cause for concern is the dramatic rise in COPD mortality seen in women in many countries. In addition to the considerable mortality and morbidity burden of COPD, this condition also incurs significant financial costs associated with the care of patients and lost productivity of patients and caretakers.

- Improved treatment of COPD, and the ability of a therapeutic intervention to improve survival, therefore represents an important goal.

Currently, smoking cessation is the single most effective intervention to improve outcomes in patients with COPD; however, even in the best programs less than one-third of patients sustain abstinence, and even nonsmokers will usually continue to experience dyspnea and
other symptoms as airflow limitation persists. A recent structured and comprehensive literature review identified published data on the prevalence, incidence, and mortality in COPD, and/or trends in those data.\textsuperscript{12}

2.1 Prevalence

There is a wealth of data on the prevalence of COPD in eleven countries (Australia, Canada, France, Germany, Italy, Japan, the Netherlands, Spain, Sweden, the UK, and the USA).\textsuperscript{12} When all studies were taken into account, prevalence estimates were remarkably wide, ranging from 0.2\%–37\%, which was in line with earlier reviews (2.1\%–26.1\%).\textsuperscript{12}

Worldwide prevalence of ‘moderate’ COPD estimated by the Global Initiative on Obstructive Lung Disease (GOLD) in adults aged 40 years and older is 9–10\%.\textsuperscript{12} Stage III COPD (generally considered as “severe”) drives most of the costs of COPD. Its prevalence across 12 sites around the globe ranged from 0.8\% (Hannover, Germany) to 6.7\% (Cape Town, South Africa).\textsuperscript{13}

The Burden of Obstructive Lung Disease initiative used standardized methods to investigate the prevalence of COPD around the world and showed important differences between countries.\textsuperscript{13} Prevalence ranged from 9\% in Reykjavik, Iceland to 22\% in Cape Town, South Africa, for men, and from 4\% in Hannover, Germany to 17\% in Cape Town for women.

COPD clearly increases with age in both genders, with few exceptions, as patients with earlier disease often go undiagnosed.

Younger ages see great variation in reported prevalence as well as gender differences in which men usually show higher prevalence than women. Prevalence increases dramatically with age and the gender differences tend to remain, except in China, South Africa, Iceland.
Figure 6.13.1 and Figure 6.13.2. Estimated population prevalence of GOLD stage II or higher COPD, separated by age.
Update on 2004 Background Paper, BP 6.13 COPD

Source: Data in Annex 6.13.1, adapted from reference\textsuperscript{13}
2.2  Mortality

There is no doubt variability in this metric due, in part, owing to the variation in the numbers of countries analyzed. For instance, mortality within the overall population (range: 3–111 per 100 000) should be compared with a European-based study (7.2–36.1 per 100 000). The latter found a greater mortality rate in European men compared with European women. The Rycroft review also reported that, although COPD mortality rates have increased over time (starting from the 1970s), rates have declined within the last decades, which suggests improvements in COPD management.

The lowest and highest mortality estimates were from Japan and the USA, respectively, which were not captured in the European-focused literature review noted above. With regard to the USA, age-adjusted mortality for COPD in the USA doubled from 1970 to 2002, although in other developed countries there are suggestions of a decline in the incidence and prevalence. These declines are related to decreases in the prevalence of smoking and reductions in air pollutants. In developing countries prevalence has risen strikingly, owing to increased smoking rates and reductions in other causes of death, particularly from severe infections.

The difference in these trends may be explained by trends in smoking prevalence in the countries of interest. Several countries had a clear difference in COPD mortality trends that was observed between men and women (i.e. Australia, France, and the USA). These countries all showed an overall decline in smoking rates with the greatest prevalence change in men.

2.3  Under-diagnosis and under-treatment of COPD

Another important feature in the epidemiology of COPD is the high risk of underdiagnoses. Sixty to 85% of patients, mainly with mild to moderate disease, are thought to remain undiagnosed. In a survey in Spain, 10% of adults aged 40–80 years had COPD, but only 27% of them had been previously diagnosed.

A recent study in the USA demonstrated a major impact of COPD on the population of USA war veterans (Veterans Administration (VA)). Almost 10% of patients in the south-eastern United States seen in the VA health care system had COPD. This prevalence is generally comparable to estimates from the National Heart Lung and Blood Institute (NHLBI). Perhaps the most striking finding was the apparent under-treatment of the COPD population in the VA system. Approximately 40% of these VA patients were not receiving any of the medications recommended in global treatment guidelines at baseline.

The most common respiratory medication class prescribed for VA patients with COPD was short-acting beta-2 agonists, which according to treatment guidelines are to be used as rescue medications and not as maintenance treatment. Maintenance treatment with guidelines-recommended long-acting bronchodilators was prescribed in the minority of VA patients. These findings are consistent with results of studies from Canada, Japan, and Europe, using non-veteran patients.

Clearly, there are difficulties with burden of diseases measures of COPD. For example, the estimated COPD death rate in Japan of 4.4/100 000 is nearly 30 times lower than that in China.
Findings of an epidemiological study of COPD in Japan, however, showed that 16.4% of men and 5.0% of women aged 40 years and older had disease of GOLD stage I or higher, which is similar to the 15.3% of men and 7.6% of women with a similar COPD stage in a Chinese BOLD study. The difference between Japan and China in COPD mortality rates versus the similarity in prevalence suggests that other factors (e.g. stigma of a diagnosis of COPD) might affect how disease is diagnosed and cause of death is attributed between countries.

2.4 Co-morbidities

Patients with COPD typically have comorbid conditions, such as lung cancer, cardiovascular disease (e.g. ischemic heart disease, depression, muscle wasting, reduced fat-free mass, osteopenia, and chronic infections). One explanation for this is that tobacco use drives disease in multiple organs. These disorders contribute to a high disease burden and early mortality in patients with COPD. Deaths in individuals with COPD are frequently attributed to a cause other than COPD. For example, in a large prospective cohort from the USA of deaths in people with advanced COPD, 31.5% were recorded as a respiratory cause, 23.9% were due to lung cancer, 13.0% were due to cardiovascular disease, and 31.5% were from other causes.

Several studies suggest that cardiovascular diseases are more frequent in COPD patients than in the general population and may represent a burden greater than that of lung disease itself. In addition, among COPD comorbidities, depression deserves particular attention. Chronic obstructive pulmonary disease (especially at severe levels) leads to impairments in activities of daily living, social, and psychological functioning and recreational activities. Depression has been found to occur in 7%–42% of COPD patients which is up to four times more frequent than in subjects without COPD.

Skeletal muscle dysfunction is a frequent and clinically relevant systemic manifestation of COPD that has been associated with morbidity and mortality independently from the severity of lung function impairment in COPD. In spite of the unequivocal benefit of exercise training in the context of pulmonary rehabilitation at reducing disability and healthcare utilization and improving survival, there remains an unmet need for therapy.

- These observations highlight the fragmentary nature of available information, and at the same time the importance of studying COPD comprehensively, considering often-associated concomitant conditions and quantifying the burden of illness that these conditions cause in this population
3. What is the Control Strategy? Is There an Effective Package of Control Methods Assembled into a “Control Strategy” for Most Epidemiological Settings?

The overall approach to managing stable COPD is characterized by a stepwise increase in treatment, depending on the severity of the disease. These treatments fall into three broad areas: prevention of disease progression, management of stable disease, and management of exacerbations.

- Given that there is no cure for the underlying inflammation of COPD, we can say that there is a pharmaceutical “gap”.
- Formerly, the pharmaceutical industry relied on variations of existing palliatives, but there is now a major effort generally by the industry to change the way novel medicines are studied and approved. Still, third party payers are focused on COPD as a whole and less on subsets of patients based on unmet need.

3.1 Stable COPD

The most recent guideline (December 2011) for treatment is the GOLD strategy\(^2^0\). This replaces a previous guideline\(^2^1\) as it considered a more personalized approach including history of exacerbations and comorbidities.

For all patients, smoking cessation, reduction in exposure to environmental and occupational risk factors, and yearly influenza vaccinations are recommended. The first step is usually smoking cessation. **This intervention slows disease progression and lowers mortality.**

Inhaled bronchodilators are the mainstay treatment for COPD (Appendix 6.13.1). For very severe disease (GOLD stage 4) surgical options include lung transplantation and lung-volume reduction is an option if quality of life is unacceptably low. Respiratory rehabilitation is usually considered at all stages in patients with muscle weakness, deconditioning, and poor quality of life. This treatment is aimed at improving quality of life and exercise capacity. Oxygen supplementation for those with chronic hypoxemia is very important and may reduce mortality. Treatment for associated comorbidities is also vital.

Two large-scale, long-term, landmark studies have confirmed the efficacy of a fixed dose combination of a long-acting β2 agonist (salmeterol) and inhaled corticosteroid (fluticasone) and a long-acting anticholinergic agent (tiotropium).\(^2^2\)

None of the existing medications for COPD has been shown to modify the long-term disease progression such as decline in lung function in many patients or worsening of health status. Therefore, pharmacotherapy for COPD is used to alleviate symptoms and/or prevent complications. While disease prevention is the ultimate goal, once COPD has been diagnosed, effective management should be aimed at the following goals:

- Prevent disease progression: airflow obstruction, emphysema, extrapulmonary disease
- Relieve symptoms of dyspnea, cough and sputum
- Improve the ability to perform activities of daily living (exercise tolerance)
Update on 2004 Background Paper, BP 6.13 COPD

- Improve health status
- Prevent and treat exacerbations
- Reduce mortality

Only two interventions have been shown to increase survival of smokers who develop chronic obstructive pulmonary disease. The first is stopping smoking, which is beneficial at all stages of the disease. The second is long term oxygen therapy, which increases the life expectancy of patients with chronic respiratory failure. In the TORCH study, the reduction in mortality showed a trend in favor of the salmeterol/fluticasone combination.

3.2 Exacerbations of Symptoms in COPD

Acute exacerbations of respiratory symptoms requiring medical intervention are important clinical events in COPD. Common causes of an exacerbation are viral upper respiratory infections, and lower respiratory infections (acute bronchitis, pneumonia).

Inhaled steroids (ICS)/long-acting bronchodilator combinations and the long-acting antimuscarinic tiotropium all improve health status and exacerbation rates and may have an effect on mortality but perhaps only with prolonged use. Chronic antibiotic use (e.g. erythromycin) has been shown to decrease the rate of COPD exacerbations. Indacaterol is an ultra-long-acting beta-adrenoceptor agonist and was approved by the European Medicines Agency (EMA) under the trade name Onbrez® on November 30, 2009 and by the Food and Drug Administration (FDA) under the trade name Arcapta Neohaler® on July 1, 2011.

3.3 Genotypic risk factors:

Severe α1 antitrypsin (α1AT) deficiency is a proven genetic risk factor for COPD yet increasing evidence suggests that other genetic determinants also exist. The presence of genetic determinants of lung function that do not depend on prior smoking exposure has been suggested by previous studies of heritability and has been clearly proven in 2010 using a genetic study of 2.5 million sites across the human genome involving samples from 20,000 people across the world.

Smoking is the major risk factor for both COPD and lung cancer. Because both COPD and lung cancer are inheritable, the genetic characteristics conferring this dual susceptibility might overlap. Recently, eleven genome-wide association studies (GWAS) have reported several susceptibility loci for COPD and lung cancer. All these studies have revealed that the single nucleotide polymorphisms (SNPs) located in nicotinic acetylcholine receptor genes (CHRNA3, CHRNA4, CHRNA5) mapped to chromosome 15q25 are shared by the two diseases. To be fair, this particular shared genetic etiology may simply be due to nicotine-dependence, because these SNPs are also associated with smoking behavior.

- In the past it has been difficult to develop new treatments because the molecular pathways that affect the health of the lung are not completely understood. It is hoped genetic studies will lead to new pathways that could in the future be targeted.
4. What is Known of the Affordability, Feasibility, and Sustainability of the Control Strategy?

Chronic obstructive pulmonary disease treatment, particularly in the elderly, has been expensive because of the high rate and length of hospital admissions in these patients.\textsuperscript{27, 28} It must also be noted that current therapies, however, are limited in important ways.

The bronchodilators that were developed originally for the treatment of asthma, exploit the small degrees of smooth muscle tone that are present in COPD patients. By inducing smooth muscle relaxation, airflow can be improved, but only very modestly. These small gains, perhaps unsurprisingly, can be exceedingly meaningful for some COPD patients.

Unlike asthma, however, COPD patients are often given anticholinergic bronchodilators in addition to beta-2 agonists with benefit. Combinations of long-acting beta-2 agonist and anticholinergic bronchodilators provide greater bronchodilation than either agent alone. Fixed combination products containing a long acting beta-2 agonist (LABA) and an ICS are superior to either component alone for lung function. The most benefit for lung function is obtained when patients take triple therapy (e.g. a LAMA, LABA, and ICS), a strategy often used in the most severe patients.

While current therapies can clearly be beneficial in treating the symptoms and exacerbations of COPD, new treatments are needed. In particular, the development of novel medicines that ameliorate the inflammatory and abnormal airway secretory responses initiated in response to chronic irritation from inhaled smoke - processes which are often resistant to inhaled steroids - may provide useful steps toward reduction of the ongoing destruction of the lung tissue and the progressive, relentless deterioration in pulmonary function that culminates in respiratory failure and death. This is the “holy grail” of therapy in patients with COPD.

4.1 Economic Burden

Chronic obstructive pulmonary disease is a progressive and debilitating disease, in its severe form, is not very responsive to therapy and its symptoms limit exercise tolerance and impair patients’ ability to work.\textsuperscript{29}

The European Lung White Book (2003) estimated that the total annual cost of COPD in Europe was €38.7 billion (including €4.7 billion for ambulatory care, €2.7 billion for medicines, and €2.9 billion for in-patient care). As these data exclude mortality costs, the actual cost incurred by COPD may be much higher.\textsuperscript{6}

4.1.1 Global estimates of costs

Globally, costs vary between countries that have reported them, although more severe disease consistently incurs more costs than less severe disease. One means of measuring costs is to ascertain how expensive a specific intervention would be per quality-adjusted life year of improvement. Using this approach, WHO estimated in 2001 that costs per quality-adjusted life year (QALY) for COPD range from US$ 6 700–8 900 for inhaled ipratropium to US$ 13 400 for inhaled corticosteroids to US$ 238 200 for lung transplantation. \textsuperscript{30} These estimates need updating.
More recent estimates put, for instance, the cost per QALY for lung transplantation to be closer to US$ 80 000 \(^{31}\) and the cost/QALY for inhaled corticosteroids to be between US$ 5 000-10 000. \(^{32}\) Although one would expect smoking cessation to also be very cost effective, this invention has not been assessed with respect to quality-adjusted life years for COPD.\(^{1,7}\)

4.1.2 United Kingdom

In the UK, early estimates of the total costs to the National Health Service (NHS) for COPD are somewhere between £486 million (€719 million) \(^{33}\) and £848 million (€1 255 million)\(^{33}\) per year. Additionally, societal costs, most notably productivity costs (costs arising from loss of income through inability or absence from work), pushes total costs for COPD up to £982 million (€1 453 million) per year.\(^{33}\) This translates to a per patient cost of between £781(€1 156) and £1 154 (€1 708) per year (€1 639 (€2 425) when including societal costs.

All these estimates are over 10 years old. A recent 2010 modeling study (Appendix 6.13.2) estimates that, in the UK alone, the economic burden is £1.2 billion per annum. This includes not only direct healthcare costs, but factors such as lost income tax, payment of state benefits and productivity loss due to COPD. These calculations are based on the current age of retirement — if this is increased then the economic impact will also rise. More specifically, the annual healthcare costs due to COPD in patients aged 45–64 years are £277.7 million (or €315.7 million / $440.1 based on 2009 values) The annual costs of lost productivity due to early retirement among people with COPD aged 45–64 years amounted to £522.9 million (or €592.6 million / $828.5 million), representing 21% of the productivity that would have been generated by these people if they had not retired early.

The major drivers of this burden are disease severity and exacerbations. These are discussed below in Section 4.1.4.

4.1.3 United States

Studies evaluating COPD costs have generated widely variable estimates. A review in 2006 summarized and critically compared recent estimates of the annual national and per-patient costs of COPD in the USA\(^{34}\) Few papers reported indirect costs of COPD (lost work and productivity). The National Heart, Lung, and Blood Institute (NHLBI) provided the single current estimate of the total (direct plus indirect) annual cost of COPD to the USA, $38.8 billion in 2005 dollars. More than half of this cost ($21.8 billion) was direct. For per-patient direct costs (in US$ 2005), studies using recent data yield attributable cost estimates (costs deemed to be related to COPD) in the range of $2 700-$5 900 annually, and excess cost estimates (total costs incurred by COPD patients minus total costs incurred by non-COPD patients) in the range of $6 100-$6 600 annually. Hospitalization is a major cost driver in COPD management in various health care systems with hospital care projected to account for 45% of direct COPD costs in the USA in 2010.\(^{34}\)

However, published data appear to be lacking regarding costs for USA commercially insured patients and USA costs according to COPD severity. One study of managed care patients in the USA found mean annual COPD-related health care costs (in US$ 2008) ranging from $2 003 ($3 238) to $43 461 ($76 159) per patient.\(^{35}\) Medical costs comprised 96% of health care costs for an intensive care unit (ICU) cohort. Adjusted mean episode-level costs were $305 ($310) for an outpatient visit, $274 ($336) for an urgent outpatient visit, $327 ($65) for an
emergency department visit, $9,745 ($2,968) for a standard admission, and $33,440 for an ICU stay.

In 2010, COPD accounted for $49.9 billion in health care expenditures in the United States alone ($29.5 billion in direct health care expenditures, $8.0 billion in indirect morbidity costs, and $12.4 billion in indirect mortality costs.

4.1.4 Drivers of cost: Severity and Exacerbations

Costs increase substantially as disease severity moves from moderate to severe. As lung function (e.g., FEV1) declines, a general shift from outpatient care to hospitalization, an increase in the use of oxygen therapy, and a subsequent increase in total costs, especially in the most advanced stages of the disease, has been shown to occur.

Exacerbations are the leading driver of cost in COPD. A serious exacerbation will lead to hospitalization; indeed, an exacerbation is the main reason why a COPD patient would attend hospital. The cost of exacerbations has been found to increase in line with the severity of exacerbations; a Swedish study reports: €13 for a mild, €38 for mild/moderate, €225 moderate, and €2,326 for a severe exacerbation. Exacerbations account for between 35–40% of total health care costs for COPD patients. Treatment which acts to reduce or prevent disease progression and or an exacerbation (particularly severe exacerbations) will have a direct effect on the total cost for COPD.

4.1.5 Productivity costs

Productivity costs are generally regarded as the cost of time off work due to illness. Productivity costs for COPD represent a substantial burden on society as COPD is a major cause of absenteeism from work. Within the 15 original EU member states, COPD is estimated to annually account for 41,300 lost work days per 100,000 people and productivity losses of around 28.5 billion per year.

5. Why Does the Disease Burden Persist?

- There is presently no cure for COPD. The condition is not currently well controlled by available medicines, which are unable to fully resolve inflammation and to prevent lung tissue destruction, as well as the associated progressive decline in pulmonary function. Novel and more effective therapies are urgently needed.

Most significantly, its etiology is confounded with the culture of tobacco, smoking, and poverty. The prevalence of chronic obstructive pulmonary disease, indeed for many chronic diseases, is greatest in socio-economically deprived people. The reasons for its persistence may be more related to health policy/health system dysfunctions than a lack of treatment options.

- Chronic respiratory diseases and COPD in particular have never, in any area of the world, been accorded a priority relative to their extent and impact. No political jurisdiction (rich or poor) proportionally commits resources to chronic respiratory
diseases equivalent to the burden they represent in the community, whether for research, prevention, or clinical services.

It was only in 2005, that the World Health Organization (WHO) released a report highlighting the high burden of chronic diseases particularly in developing countries and the need for urgent action in the prevention and control of chronic diseases including chronic respiratory diseases (See Appendix 6.13.3). The reasons for this neglect are unclear. Several possible explanations can be offered.

These diseases have traditionally been stigmatized. It has been virtually impossible to mobilize either patients or society to address them as has been done for HIV/AIDS. With conditions related to tobacco smoke exposure (lung cancer and chronic obstructive pulmonary disease) there has been a ‘blame the victim’ approach which promotes stigmatization.

Some guidelines have been published for the management of COPD in developing countries. A standard case management approach for COPD for Asia and Africa has been proposed. Notwithstanding, such guidelines are usually developed by professional societies and/or specialists and rarely involve service providers at the primary care level. Additional bottlenecks in developing countries are: the low priority accorded to chronic diseases as compared with infectious diseases; lack of organization of follow-up; cultural barriers; poor education of health workers; lack of spirometry in low-income countries; and lack of access to, and the high cost of necessary medicines.

5.1 COPD and the “never smoker”

Lambrecht et al. analyzed data from 14 countries that participated in the international, population-based Burden of Obstructive Lung Disease (BOLD) study. Participants were aged ≥ 40 years. Among 4,291 never smokers, 6.6% met criteria for mild (GOLD stage I) COPD and 5.6% (n=240) met criteria for moderate to very severe (GOLD stage II+) COPD.

Although never smokers were less likely to have COPD and had less severe COPD than ever smokers, never smokers nonetheless comprised 23.3% (240/1,031) of those classified with GOLD stage II+ COPD. This multicenter international study confirmed previous evidence that never smokers comprise a substantial proportion of individuals with COPD.

Among younger ages, the study showed that exposure to indoor air pollution was the most important cause for COPD because of exposure to biomass fuel since childhood. Compared to 1.1 billion smokers more than three billion people (50% of the global population) use biomass fuels (wood, crop residue, and cow dung cakes) for cooking and heating. In India alone, 75% of the homes use biomass fuel, exposing over 700 million people to high levels of indoor air pollution. Women and young children are the most vulnerable group that are affected due to this exposure.
6. What Can Be Learned from Past/Current Research into Pharmaceutical Interventions for this Condition?

The key points below were extracted from the summary provided by BMJ Clinical Evidence:²

- The main risk factor for the development and deterioration of chronic obstructive pulmonary disease (COPD) is still smoking.

Inhaled anticholinergics and beta-2 agonists improve lung function and symptoms and reduce exacerbations in stable COPD compared with placebo.

- It is unclear whether inhaled anticholinergics or inhaled beta-2 agonists are the more consistently effective drug class in the treatment of COPD.
- Short-acting anticholinergics seem to be associated with a smaller improvement in quality of life compared with beta-2 agonists.
- Long-acting inhaled anticholinergics may improve lung function more when compared with long-acting beta-2beta-2 agonists.
- Combined treatment with inhaled anticholinergics plus beta-2 agonists may improve symptoms and lung function and reduce exacerbations compared with either treatment alone, although long-term effects are unknown.

Inhaled corticosteroids reduce exacerbations in COPD and reduce decline in lung function, but the beneficial effects are small.

- Oral corticosteroids may improve short-term lung function, but have serious adverse effects.
- Combined inhaled corticosteroids plus long-acting beta-2 agonists improve lung function, symptoms, and health-related quality of life, and reduce exacerbations compared with placebo, and may be more effective than either treatment alone.

Long-term domiciliary oxygen treatment may improve survival in people with severe daytime hypoxaemia.

Theophylline may improve lung function compared with placebo, but adverse effects limit its usefulness in stable COPD.

We do not know whether mucolytic medicines, prophylactic antibiotics, or alpha₁ antitrypsin improve outcomes in people with COPD compared with placebo.²

Although not within the ambit of this Background document, inasmuch as it is a non-pharmacologic treatment, we briefly note that pulmonary rehabilitation using physical activity has been shown to be beneficial.

One of the main challenges in developing new therapeutic agents for the treatment or prevention of acute exacerbations of COPD is that their potential success cannot be entirely known until the investigational therapies enter relatively large Phase II studies, assessing clinical outcome over a three to six month period or longer.²
6.1 Overview of the existing Medications

Pharmacologic therapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. None of the existing medications for COPD has been shown to conclusively modify the long-term decline in lung function that is the hallmark of this disease. The medications are presented in the order in which they would normally be introduced in patient care, based on the level of disease severity.

6.1.1 Bronchodilators

Medications that increase lung function by altering airway smooth muscle tone, are termed bronchodilators, since the improvements in expiratory flow reflect widening of the airways rather than changes in lung elasticity. Regular bronchodilation with medicines that act primarily on airway smooth muscle does not modify the decline of function in mild COPD and, by inference, the prognosis of the disease. Bronchodilator medications are central to the symptomatic management of COPD. The side effects of bronchodilator therapy are pharmacologically predictable. However, COPD patients tend to be older than asthma patients and more likely to have comorbidities, so their risk of developing side effects is greater.

ß2-agonists

Long-acting ß2-agonists improve lung function, improve health status, and reduce exacerbations. Oral therapy is slower in onset and has more side effects than inhaled treatment.

Anticholinergics

Anticholinergic medications are a class of drugs that have long been used to improve symptomatology of patients with COPD. An inhaled anticholinergic medication, tiotropium bromide (Boehringer Ingelheim, Ingelheim, Germany), is now being used in this patient population. This medication appears to be more effective in treating patients with COPD compared with older anticholinergics.

Methylxanthines

Controversy remains about the exact effects of xanthine derivatives. Data on duration of action for conventional or even slow-release xanthine preparations are limited in COPD. Theophylline is effective in COPD but toxicity is dose related. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose.

6.1.2 Glucocorticosteroids (GCs)

Glucocorticosteroids are not effective at controlling the chronic inflammatory response in COPD. To date, there are no effective treatments to control this persistent inflammatory response and the associated decline of lung function of COPD. This is largely due to a lack of understanding of the nature of the inflammatory response in COPD and the impact of key underlying factors such as oxidative stress on this inflammatory response.
Update on 2004 Background Paper, BP 6.13 COPD

Oral glucocorticosteroids.

Many existing COPD guidelines recommend the use of a short course (two weeks) of oral glucocorticosteroids to identify COPD patients who might benefit from long-term treatment with oral or inhaled glucocorticosteroids. A short course of oral glucocorticosteroids is a poor predictor of the long-term response to inhaled glucocorticosteroids in COPD.

Oral glucocorticosteroids - long-term.

Based on the lack of evidence of benefit, and the large body of evidence on side effects, long-term treatment with oral glucocorticosteroids is not recommended.²

Inhaled glucocorticosteroids.

Although both inhaled and oral GCs are effective at controlling inflammatory lung diseases such as asthma, their effectiveness is substantially less in COPD; therefore, their contribution to the management of stable COPD is limited.⁵³

Although results published from the Towards a Revolution in COPD Health (TORCH) study of patients with COPD indicated that regular use of inhaled GCs may decrease the rate of decline of lung function, the majority of studies have concluded that the use of regular inhaled GCs has no impact on the long-term progressive decline in lung function.²

Combination therapy (inhaled corticosteroids + long acting beta agonists).

In clinical trials with COPD, combined budesonide–formoterol administered via a dry powder inhaler has proven more effective in improving lung function and reducing exacerbations when compared with the same dose of budesonide or formoterol given alone. Budesonide–formoterol combination therapy is also safer and tolerated better than the same dose of budesonide or formoterol given alone.⁵⁴

6.1.3 Phosphodiesterase-4 inhibitors

Phosphodiesterases (PDEs) are important modulators of inflammation and wound healing. In this capacity, specific targeting of PDEs for the treatment of many diseases, including COPD, has been investigated. PDE4 modulates the inflammatory response of the lung, and inhibition of PDE4 may be a novel, COPD-specific approach toward more effective treatment strategies.⁵⁹

Roflumilast, the first new class of treatment for COPD in more than a decade, is a selective long-acting phosphodiesterase 4 (PDE4) enzyme inhibitor recently approved for treatment of patients with severe COPD (Daxas® was approved in the in June 2010 for severe associated with history of exacerbations and chronic bronchitis).⁵⁶ In March 2011, Daliresp® gained FDA approval for reducing COPD exacerbations.⁵⁷

Roflumilast, an oral specific phosphodiesterase 4 inhibitor was associated with a 17% reduction in the frequency of exacerbations in patients with GOLD stage 3–4 COPD and history of exacerbations, cough, and sputum changes.⁵⁵ In June 2010, roflumilast (Daxas®, Daliresp®) was approved in the EU for severe COPD associated with chronic bronchitis. In March 2011, Daliresp® gained FDA approval in the USA, but had no effect on health-related
quality of life or systemic for reducing COPD exacerbations. Similar effects were seen in patients who received roflumilast in addition to salmeterol or tiotropium. Although effective in clinical trials, roflumilast produced several dose-limiting side effects and development is continuing in an attempt to minimize the incidence of side effects while retaining clinical efficacy.\(^57\)

### 6.1.4 Chronic use of macrolide antibiotics

Acute COPD exacerbations are also treated with antibiotics. Among these medicines, macrolide antibacterials exert anti-inflammatory or immunomodulatory effects. Clinical effects have also been observed in COPD patients.

### 6.1.5 Other Pharmacologic Treatments

**Vaccines**

Vaccinations against influenza and pneumococcus are recommended in NICE guidelines for COPD.\(^58\) Despite a level A recommendation by the Centers for Disease Control and Prevention, the use of pneumococcal polysaccharide vaccination in patients with COPD is supported by limited data.

To date no randomized-controlled trial of pneumococcal vaccination for COPD patients has demonstrated any beneficial effect. The implementation of a pneumococcal vaccine trial in the COPD population is problematic because of the large sample size required for studies examining clinical outcomes and the fact that no adequate in vitro assays have been available to serve as surrogate measures of vaccine protection.

However, new laboratory methods have been developed and more accurate determination of the immunogenicity of pneumococcal vaccines is now possible. There is considerable interest in the development of an improved pneumococcal vaccine for patients with COPD, and advances in vaccine design hold considerable promise for improved prevention against pneumonia and acute exacerbations caused by *Streptococcus pneumoniae*.

A recent study analysis of the Health Improvement Network (THIN) database was used to test if influenza and/or pneumococcal vaccination was associated with a reduced risk of all-cause mortality in COPD. The former, but not the latter was associated with reduced risk.\(^59\)

For all-cause mortality the adjusted relative risks associated with influenza vaccination were 0.59 (95% CI 0.57 to 0.61) during the influenza season and 0.97 (95% CI 0.94 to 1.00) outside the season in patients not vaccinated against pneumonia, and 0.30 (95% CI 0.28 to 0.32) and 0.98 (95% CI 0.96 to 1.11), respectively, in patients vaccinated against pneumonia. The relative risk associated with pneumococcal vaccination was greater than one at all times of the year.

These results are unlike a recent Cochrane review \(^60\) which showed no effect of influenza vaccination on mortality. NICE guidelines advise vaccination of patients with chronic obstructive pulmonary disease against influenza and *Pneumococcus*.  

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6.13-22
Mucolytic (mucokinetic, mucoregulator) agents (ambroxol, erdosteine, carbocysteine, iodinated glycerol).

Most studies showed no effect of mucolytics on lung function or symptoms, although some old studies have reported a reduction in the frequency of acute exacerbations.\textsuperscript{61, 62, 63}

Mucolytics do not have any significant adverse effects. The evidence suggests that if patients take these medicines regularly through the winter months this could result in a 21% reduction in the number of exacerbations, especially in people not already taking inhaled corticosteroids. These medicines do not alter the loss of lung function in COPD, but they are very safe and well tolerated.\textsuperscript{64}

### 6.1.6 Summary of Cochrane Reviews

Various Cochrane Reviews on the subject of COPD are summarized in Annex 6.13.2. Annex 6.13.2 lists presents the risk ratios (relative risk and odds ratios) and their respective 95% confidence intervals for 11 Cochrane Reviews, consisting of 30 different summaries of placebo-controlled clinical trials testing various treatments. The data in Annex 6.13.2 are visualized as Figure 6.13.3, below in which the risk ratios are Relative risks (trials #1-13) and Odds ratio for trials #14-30 (trial #1 on the left side of the X axis):

Beta-2-agonists for acute bronchitis (#1-3), tetracyclines as prophylactic therapy (#4), any antibiotic as prophylactic therapy (#5) any antibiotic for acute bronchitis (#6-10), fluticasone/salmeterol for COPD (#11-12), budesonide/formoterol for COPD (#13-14), mucolytics for COPD (#15-16), systemic corticosteroids for COPD (#17-18), tiotropium for chronic COPD (#19-21), inhaled corticosteroids for COPD (#22), tiotropium for stable COPD (#23-25), oral corticosteroids (#26-27), salmeterol for COPD (#28-29), phosphodiesterase 4 inhibitors-roflumilast or cilomilast for COPD (#30). Ratios greater than one are beneficial events (See Background Chapter 4).
To date, only two interventions—smoking cessation and long term treatment with oxygen (in people with hypoxaemia)—have been found to alter the long term course of chronic obstructive pulmonary disease and neither of these are considered. We do not consider pulmonary rehabilitation in this review, which is a standard-of-care in COPD patients and involves components such as patient assessment, exercise training, education, nutritional intervention, and psychosocial support.

RCTs found short term benefits (as opposed to long term effects on progression) from: anticholinergic drugs, beta-2 agonists, inhaled corticosteroids (alone and in combinations with LABAs); oral steroids and an oral PDE4 inhibitor. The effects of anticholinergic drugs and beta-2 agonists are not seen in all people with chronic obstructive pulmonary disease, and the two agents combined are slightly more effective than either alone.

Adverse effects and the need for frequent monitoring of blood concentrations limit the usefulness of theophyllines. There are similar adverse events challenges for the recently launched oral PDE4.

It is not clear that anticholinergic agents affect decline in lung function; mucolytics have been shown to reduce the frequency of exacerbations, but with a possible deleterious effect on lung function; beta-2 agonists, oral corticosteroids, and antibiotics have not yet been evaluated for their long term effects.
7. What is the Current “Pipeline” of Products that Are to Be Used for this Particular Condition?

7.1 Pre-clinical and Clinical Development of novel targets

Substantial unmet needs remain in COPD. Although new products might confer significant advantages over the currently available treatments, there is still a huge unmet need for medicines that prevent the progression of COPD. Drug development for COPD is difficult owing to the chronic and slowly progressive nature of the disease; therefore, large studies carried out over long periods are needed to obtain the necessary statistical power to identify improvements.

- However, the targets listed below all suffer from the lack of drug development tools to identify patients likely to benefit from therapy as well as to predict long term efficacy.

Recent advances in understanding the pathogenetic mechanisms that underlie COPD have led to the identification of many novel therapeutic targets and exploration of alternative treatment pathways in recent clinical trials world-wide and have several novel classes of medicines for COPD in development including inhibitors of oxidative stress, leukotriene B4 receptors, and chemokine receptors, which are involved in the migration of inflammatory neutrophils in COPD, and inhibitors of phosphodiesterase 4 (PDE4), and p38 MAP Kinase, a significant anti-inflammatory target.66

Enhanced disease modification is expected from other inflammatory blockers that includes agents targeting CD8+ T cells, and inhibitors of NF-κB, chemokine-receptors, and T-helper-17 cells. Peroxisome proliferator-activated receptors PPARs are a family of ligand-activated nuclear hormone receptors (i.e. PPARγ, PPARα, and PPARδ) belonging to the nuclear receptor superfamily, and there is now sufficient evidence that the activation of these receptors induces anti-inflammatory and immunomodulatory effects in the lung as well as in other tissues.67

Indeed, classes of drugs that are used for cardiovascular disease may be useful in COPD. Observational studies suggest that COPD patients treated with statins, angiotensin-converting enzyme inhibitors, and angiotensin II type 1 receptor blockers, and β-adrenoceptor blockers may have improved survival and reduced hospitalization from exacerbations. 68

- From a diagnostic point of view, specific disease biomarkers, improved methods for early detection and diagnosis of exacerbations, and enhanced understanding of the relations between COPD and comorbidities are considered by academics, regulators, and industry experts as critical. 69

- Additionally, an important question that so far remains unanswered is whether different phenotypes of the disease exist and, if so, whether they respond differently to treatment. There is clear evidence supporting the heterogeneity of the disease (e.g. frequent/infrequent exacerbates, persistent systemic inflammation, 70 and the requirement for a more personalized medicine approach.71
Table 6.13.1: Drugs in Development for COPD in 2010

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Clinical development</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTB4 antagonists</td>
<td>development stopped</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>development stopped</td>
</tr>
<tr>
<td>CXCR2 antagonists</td>
<td>in early clinical development</td>
</tr>
<tr>
<td>MMP-9 inhibitors</td>
<td>in early clinical development</td>
</tr>
<tr>
<td>Neutrophil elastase inhibitor</td>
<td>in early clinical development</td>
</tr>
<tr>
<td>PDE4 inhibitors</td>
<td>phase III trials but side effects a major limitation</td>
</tr>
<tr>
<td>p38 MAPK inhibitors</td>
<td>phase I studies but problems with side effects and toxicity</td>
</tr>
<tr>
<td>NF-κB (IKK2) inhibitors</td>
<td>pre-clinical but concerns about side effects</td>
</tr>
<tr>
<td>PI3K-γδ inhibitors</td>
<td>early clinical development</td>
</tr>
<tr>
<td>PPAR-γ agonists</td>
<td>already developed for diabetes, clinical studies in progress</td>
</tr>
</tbody>
</table>


A list of medicines for COPD was located in the United States clinical trials database\(^{72}\) December 2102: open enrollment trials with patients still being recruited, all phases, interventional drug trials only: See Annex 6.13.3, also in Table 6.13.2. Table 6.13.2 is different than Table 6.13.1, most likely because the former relates to trials that have already provided results and the latter relates to trials that are still in the process of enrollment.

* “Phase 4” trials are post approval studies.

Table 6.13.2: List of medicines in United States clinical trials still open for enrollment.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Medicine</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>simvastatin (HMG-CoA reductase inhibitor-lowers cholesterol)</td>
<td>VA Loma Linda Health Care System</td>
</tr>
<tr>
<td>Phase 1</td>
<td>RV568 (Inhaled, narrow-spectrum kinase inhibitor)</td>
<td>Respivert Ltd</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Tiotropium (high dose) + Olodaterol</td>
<td>Boehringer Ingelheim Pharmaceuticals</td>
</tr>
<tr>
<td>Phase 1/Phase 2</td>
<td>Cyclosporine (reversible inhibitor of interleukin-2 synthesis)</td>
<td>University of Pittsburgh</td>
</tr>
<tr>
<td>Phase 1/Phase 2</td>
<td>V0162 (anticholinergic compound)</td>
<td>Pierre Fabre Medicament</td>
</tr>
<tr>
<td>Phase 1/Phase 2</td>
<td>Quercetin (flavonoid antioxidant)</td>
<td>University of Michigan</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Drug Name</td>
<td>Developer</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>PEP03 (5-lipoxygenase inhibitor)</td>
<td>PharmaEngine</td>
<td></td>
</tr>
<tr>
<td>GW685698 Fluticasone Furoate /GW642444 Vilanterol</td>
<td>GlaxoSmithKline/GlaxoSmithKline</td>
<td></td>
</tr>
<tr>
<td>tetomilast (phosphodiesterase-4 inhibitor)</td>
<td>Otsuka Pharmaceutical Development &amp; Commercialization, Inc.</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin (HMG-CoA reductase inhibitor-lowers cholesterol)</td>
<td>University Hospital, Akershus/AstraZeneca/Haukeland University Hospital, Bergen</td>
<td></td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>Medical University of Vienna</td>
<td></td>
</tr>
<tr>
<td>BCT197</td>
<td>Novartis Pharmaceuticals</td>
<td></td>
</tr>
<tr>
<td>Iodinated Active Charcoal (IodoCarb)</td>
<td>PharmaLundensis AB</td>
<td></td>
</tr>
<tr>
<td>Roflumilast (phosphodiesterase-4 inhibitor)</td>
<td>Nycomed (Takeda)</td>
<td></td>
</tr>
<tr>
<td>Losmapimod (oral p38 MAP kinase inhibitor)</td>
<td>Cambridge University Hospitals NHS Foundation Trust/Technology Strategy Board/GlaxoSmithKline/Royal Brompton &amp; Harefield NHS Foundation Trust</td>
<td></td>
</tr>
<tr>
<td>PH-797804 (p38 MAP kinase inhibitor)</td>
<td>Pfizer</td>
<td></td>
</tr>
<tr>
<td>AZD5423 (inhaled selective glucocorticoid receptor agonist)</td>
<td>AstraZeneca</td>
<td></td>
</tr>
<tr>
<td>QMF149 (indacaterol maleate/mometasone furoate)</td>
<td>Novartis Pharmaceuticals</td>
<td></td>
</tr>
<tr>
<td>glycopyrronium bromide (anticholinergic)</td>
<td>Prosonix Limited</td>
<td></td>
</tr>
<tr>
<td>TD-4208 (inhaled, long-acting muscarinic antagonist)</td>
<td>Theravance</td>
<td></td>
</tr>
<tr>
<td>CHF6001 (phosphodiesterase 4-inhibitor)</td>
<td>Chiesi Farmaceutici S.p.A.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 3</th>
<th>Drug Name</th>
<th>Developer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erdosteine (mucolytic)</td>
<td>Edmond Pharma</td>
<td></td>
</tr>
<tr>
<td>simvastatin (HMG-CoA reductase inhibitor-lowers cholesterol)</td>
<td>National Heart, Lung, and Blood Institute (NHLBI)</td>
<td></td>
</tr>
<tr>
<td>fluticasone furoate/vilanterol (inhaled corticosteroid/long-acting β2 agonist)</td>
<td>GlaxoSmithKline</td>
<td></td>
</tr>
<tr>
<td>Prednisolone (precursor to corticosteroid)</td>
<td>Hopital Universitaire Fattouma Bourguiba</td>
<td></td>
</tr>
<tr>
<td>Fluticasone/Formoterol (corticosteroid/long acting β2-agonist)</td>
<td>Ache Laboratorios Farmaceuticos S.A.</td>
<td></td>
</tr>
</tbody>
</table>
### Phase 3

<table>
<thead>
<tr>
<th>Medication</th>
<th>Sponsor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin (synthetic fluoroquinolone antibacterial)</td>
<td>University College, London</td>
</tr>
<tr>
<td>Roflumilast (phosphodiesterase-4 inhibitor)</td>
<td>Nycomed: A Takeda Company</td>
</tr>
<tr>
<td>glycopyrronium bromide (anticholinergic)</td>
<td>Novartis Pharmaceuticals</td>
</tr>
<tr>
<td>Tiotropium/olodaterol (long-acting anticholinergic/long acting β2 agonist)</td>
<td>Boehringer Ingelheim Pharmaceuticals</td>
</tr>
<tr>
<td>Tiotropium (long-acting anticholinergic)</td>
<td>Boehringer Ingelheim Pharmaceuticals</td>
</tr>
<tr>
<td>theophylline (phosphodiesterase inhibitor)</td>
<td>Hospital Son Espases</td>
</tr>
<tr>
<td>aclidinium bromide (muscarinic antagonist)</td>
<td>Daewoong Pharmaceutical Co. LTD.</td>
</tr>
<tr>
<td>GSK573719 (umeclidinium: long-acting muscarinic antagonist)</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Zabofloxacin (fluoroquinolone antibiotic)</td>
<td>Dong Wha Pharmaceutical Co. Ltd.</td>
</tr>
<tr>
<td>Fluticasone Furoate (inhaled corticosteroid)</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Indacaterol Maleate/Glycopyrronium Bromide (long acting β2 agonist/anticholinergic)</td>
<td>Novartis Pharmaceuticals</td>
</tr>
<tr>
<td>GSK573719 (umeclidinium + vilanterol ) (long-acting muscarinic antagonist/long-acting beta-2 agonist)</td>
<td>GlaxoSmithKline</td>
</tr>
</tbody>
</table>

Source: United States clinical trials database

### 7.2 Current and future market analysis

Inhaled corticosteroid/long-acting 2-agonist (ICS/LABA) combinations constitute the leading class in terms of sales, and are set to remain the dominant class until at least 2016, generating approximately one-third of total market sales over this period. The leading ICS/LABA combination product is GlaxoSmithKline’s Advair/Seretide® (fluticasone/salmeterol) with US$ 6.3 billion sales in 2006, making it the top-selling respiratory drug that year and the
third best-selling drug globally. In 2011, combined sales of these therapies constituted nearly two-thirds of the global COPD market.

The market for COPD will increase from nearly US$ 9 billion in 2011 to US$ 13.3 billion in 2021 in the United States, France, Germany, Italy, Spain, the United Kingdom, and Japan. Growth in the market will be in part driven by uptake of a new drug class—fixed-dose combination inhalers containing a long-acting beta-2 agonist (LABA) and a long-acting muscarinic antagonist (LAMA)—that will launch in 2014 and offer more potent bronchodilation than currently available treatments. In 2019, LABA/LAMA combinations are expected to become the sales-leading drug class in COPD.

Several new long-acting beta-2 agonist (LABA)/inhaled corticosteroid (ICS) combinations will probably be launched in the major markets, including such as GlaxoSmithKline/Theravance’s vilanterol/fluticasone furoate and Novartis’s indacaterol/mometasone. Several new monotherapies from existing classes will reach the COPD market also, such as long-acting muscarinic antagonists (LAMAs) including once-daily Novartis/Eisai’s glycopyrronium (Seebri®: See Table 6.13.2) and GlaxoSmithKline’s umaclidinium.

Governments and private insurance payers are increasingly reluctant to pay for higher-priced therapies without strong evidence that the drug is more efficacious or safer than competitors. This is easier to demonstrate for specific subpopulations, which in turn drives increased market segmentation, dividing it into a number of niches with high unmet needs. In turn, drug developers targeting current unmet needs must focus on developing targeted therapies to treat subpopulations. Key examples of unmet needs include:

- Efficacious anti-inflammatories for COPD (given that current therapies neither arrest nor reverse inflammation and the resulting decline in lung function or health status)
- Finding better ways to prevent and control COPD exacerbations
- Developing therapies for the 10% of patients with refractory asthma whose symptoms cannot be controlled with currently available medicines

Although higher-priced niche therapies will power future market growth, in-house R&D productivity and innovation capture remain key issues for big pharmaceutical companies developing respiratory medicines.

- Part of this problem has been the lack of novel validated targets and drug development tools after significant delays and failures in developing classes such as phosphodiesterase 4 (PDE4) inhibitors.
- Big pharmaceuticals has, therefore, chosen to be more conservative approach and invest in management of currently marketed medicines, and developing next-generation versions of well-established classes such as ICS/LABAs (for example, GlaxoSmithKline’s ‘Beyond Advair’ fluticasone furoate/vilanterol programme).
- As a result of big pharmaceutical’s bias towards low risk efforts in COPD, genuinely novel pipeline medicines for COPD are scarce among such companies. It could be argued that, instead, future innovation is likely to be primarily captured by smaller companies.
- However, the problem remains that smaller biotechnology and ‘small molecule’ companies simply cannot afford large scale studies. There is a risk that in the absence of new approaches, nobody would develop medicines for COPD
8. What is the Current Status of Institutions and Human Resources Available to Address the Disease?

8.1 Institutions

8.1.1 Global Initiative on Obstructive Lung Disease (GOLD)\textsuperscript{75}

GOLD, a collaboration between the National Heart, Lung and Blood Institute, National Institutes of Health, USA, and the World Health Organization, has a mission to create a set of evidence-based guidelines. The GOLD committee is composed of leading experts from many nations around the world. The GOLD Guidelines recommend effective COPD management and prevention strategies. It strives to increase awareness of the medical community, public health officials, and the general public that COPD is a public health problem. The objective is to reduce morbidity and mortality from COPD through implementation and evaluation of effective programs for diagnosis and management. GOLD has recently released a new strategy for the management of COPD which reflects improved disease understanding and a more holistic approach relative to 2006 guidelines.\textsuperscript{75}

8.1.2 Canadian Thoracic Society COPD Guidelines\textsuperscript{76}

The Canadian Guidelines were designed to meet the specific need of Canadians in the context of their available resources. While recognizing GOLD as exemplary, their panel felt the need to improve upon specific aspects of the GOLD document. They specifically sought to develop a new chronic care model to replace the existing reactive acute care models.

8.1.3 American Thoracic Society - European Respiratory Society: Standards for Diagnosis and Management of Patients with COPD\textsuperscript{77}

See also Appendix 6.13.4.

This is a combined effort of both societies to create a web-based, live modular document that emphasizes some of the issues important to USA and European audiences. This guideline is sponsored by the American Thoracic Society and European Respiratory Society and was approved by the boards of both societies. It had input from clinicians, researchers, nurses and respiratory therapists. Some of these individuals also served on GOLD.

8.1.4 National Institute for Clinical Excellence (NICE), United Kingdom: Management of COPD in Adults in Primary and Secondary Care\textsuperscript{78}

National Institute for Health and Clinical Excellence (NICE) creates guidelines available as PDF files that are downloadable from their website.

8.2 Private Sector

Some of the largest pharmaceutical companies in the world (Pfizer, Novartis, AstraZeneca, Takeda, Boehringer Ingelheim, GlaxoSmithKline, Schering Plough) are involved on R&D directed to respiratory conditions, including COPD. They understand that, because of its chronic and progressive nature, COPD represents a massive and growing burden, both in direct and indirect costs. In developing countries where smoking continues to be extremely
prevalent, COPD is on the increase. It is difficult to ascertain exactly how much private sector R&D is relegated to COPD, as the available information (usually in the form of annual reports or SEC filings) usually do not separate out R&D expenses into specific disease conditions.

Several companies are investing financially and collaborating in pre-competitive efforts to improve disease understanding and develop drug development tools through international consortia including the COPD Foundation Biomarker Consortium, NHLBI’s SPIROMICS and COPDGene, CanCOLD, ECLIPSE, and IMI’s PROActive. In short, there is evidence of investment by GSK, as well as Pfizer, BI, Novartis, and Astra Zeneca in disease understanding studies. This investment of funding and human resources are well beyond most public funding.

8.3 Public Funding

8.3.1 Funding Sources: Europe

Framework Programmes:

Health research is financed (See also Chapter 2) by the current Seventh Framework Programme (FP 7) for Research and Technological Development 2007-2013 at about 50 billion euros. The future Horizon 2020, the Framework Programme for Research and Innovation (2014-2020) is set at about 80 billion euros.

Within the FP7 Health programme, two projects, EVA "Markers for emphysema versus airway disease in COPD" and COPACETIC "COPD Pathology: Addressing Critical gaps, Early Treatment and Innovative Concepts" have received cumulative funding of 12 million euros. At the same time, the FP7 Information and Communications Technology (ICT) programme funded a large-scale project AirPROM "Airway Disease Predicting Outcomes through Patient Specific Computational Modelling", in which 34 partners from the already existing consortia of the FP7 project EVA, IMI project U-BIOPRED, and the British Thoracic Society project Severe Asthma joined forces to build a model of airway disease for better diagnostics based on the genomics data and ex vivo models at the genome cell-tissue scale by applying tomographic (CT) and functional magnetic resonance imaging (MRI) coupled to detailed physiology at the tissue-organ scale utilizing Europe’s largest airway disease cohort. The project was awarded an 11.7 million euro grant.

Thus, total FP7 contribution to the study of COPD (2007-2012) was almost 59 million euros, of which the majority was provided to the collaborative projects (52.3 million), and 2.8 million was attributed to the frontier research grants by the European Research Council, while 3.8 million Euros has been distributed within the Marie Curie programme to support mobility, training, and knowledge transfer activities.

However, the actual extent of public funding for COPD-related R&D in Europe is difficult to estimate, although we have some limited information. In general, the amounts are far less than public funding in the United States. The second programme of ‘Community action in the field of health (2008-13)’ covering the period from 1 January 2008 to 31 December 2013 was established in October 2007. See Appendix 6.13.5.
Innovative Medicines Initiative

The PROactive project is a European project funded by the Innovative Medicines Initiative (IMI: See Chapter 2). Under this initiative, the PROactive consortium that includes academic government and industry members aims to improve care for COPD patients. PROactive will be developed with input from the regulatory authorities such as the European Medicines Agency (EMA). Once appropriately validated, PROactive will be used to evaluate the benefit of new treatments such as new medicinal products for COPD patients.83

The British Lung Foundation is the only charity in the UK that funds research into COPD-related topics.1 In 2011, out of total spending of about €8.5 million, scientific and medical research was funded with €2.2 million.

The UK Medical Research Council84

The MRC receives annual ‘grant-in-aid’ funding from the UK Parliament. Although government-funded, the MRC is independent in its choice of which research to support. In 2011/2012, the MRC spent about €941 million on research. We summarize several MRC initiatives related to COPD:

1. The current inability to target therapy for COPD exacerbations means that some patients with COPD are inappropriately treated and this places a vulnerable population at risk. This is a one year study to assess mediators that can be measured in sputum and blood that are already known to closely relate to infections and inflammation (€728 289).

2. While corticosteroids are highly effective in suppressing airway inflammation in asthmatic patients, they are essentially ineffective in COPD. These studies should shed light on the molecular mechanisms of corticosteroid resistance in COPD, but may also be relevant to other chronic inflammatory diseases. They may also lead to new therapeutic approaches aimed at reversing this resistance mechanism (€350 035).

3. The London COPD Exacerbation Cohort (EXCEL Cohort) is a small established cohort of COPD patients recruited and specifically trained and monitored to report their attacks (exacerbations) to the research team to enable the exacerbation to be studied (and also the patient to receive treatment as quickly as possible) (€653 477).

The MRC is interested to promote focused priority setting in inflammatory disease research between academic researchers and the pharmaceutical industry. The workshops brought together a range of experts with an interest in COPD in order to identify challenges, barriers, and opportunities for collaboration. This resulted in the development of research consortiums involving both academia and industry. The MRC has now invested €7.2 million in the COPD consortia over a four-year period.

1 Throughout Europe there are many organizations directed to providing educational and training materials related to COPD and therapeutic guidelines. Such organizations include the Alpha-1 Association (http://alpha1.org); Alpha-1 Foundation (more than $15million has been funded in Alpha-1 research http://www.alphaone.org); British Lung Foundation (http://www.lunguk.org); Global Initiative for Chronic Obstructive Lung Disease (GOLD) (define treatments; increase awareness and prevention of COPD worldwide http://www.goldcopd.com); EFA is the European Federation of Allergy and Airways Diseases Patients’ Associations, an alliance of 41 organizations in 23 different countries across Europe http://www.efanet.org).
The COPD-MAP project was formed in 2011 as part of the UK Medical Research Council (MRC)/Association of the British Pharmaceutical Industry (ABPI) Inflammation and Immunology Initiative. Its purpose is to bring together academics and industry at the early R&D stages to develop a stratified approach to disease (targeting the right treatments to the right people), enabling effective clinical trials as well as identifying novel biomarkers, mechanisms and targets. ABPI Consortium members include Astra Zeneca, Pfizer, GlaxoSmithKline, Novartis, and Merck. Several areas of relevant research include: mechanisms, impact and therapeutic targeting of microbial and viral colonisation in COPD, and elucidation of the mechanisms of defective innate immune responses and identification of novel therapeutic targets for COPD.

8.3.2: Funding Sources: United States

Research on COPD is funded through a number of federal programs, including the National Institutes of Health and its institutes such as primarily the National Heart Lung and Blood Institute (NHLBI).

The NHLBI Lung Diseases program supports research on the causes, diagnosis, treatment, and prevention of lung diseases and sleep disorders. Research areas include asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, critical care and acute lung injury, developmental biology and pediatric pulmonary diseases, immunology and fibrosis, lung cell and vascular biology, and pulmonary complications of AIDS and tuberculosis. In fiscal year (FY) 2011, the NHLBI funded research to explore common pathogenetic mechanisms of lung cancer and COPD.

The FY 2013 President’s Budget request for the NHLBI Lung Diseases program is $637.09 million, an increase of just $0.048 million or barely 0.01 per cent from the FY 2012 enacted level. See Appendix 6.13.6. To put this into context, the total NIH funding (all institutes including NHLBI) for COPD specifically is about $108 million for FY 2012 so this is about 16% of the “Lung Disease” program. In contrast, NIH funding (all institutes) for diabetes is about $1 billion for FY 2012.

Other sources of funding including industry support, private donors and organizations such as the COPD Foundation, Alpha-1 Foundation, Foundation of the American Thoracic Society, and the Chest Foundation.

COPD Biomarkers Quantification Consortium

The COPD Foundation embarked on the creation of a COPD Biomarkers Qualification Consortium (CBQC) in 2010. The CBQC is supported by member pharmaceutical companies (currently Astra Zeneca, Boehringer Ingleheim, GlaxoSmithKline, Novartis and Pfizer), each of which contribute financial support, unpublished clinical trial data and expertise. The consortium also includes experts from academia with the FDA, EMA, and NHLBI acting in an advisory role. The CBQC efforts were focused initially on three biomarker efforts: plasma fibrinogen for stratification of subjects at risk for hospitalization and mortality, six minute walk distance for stratification of subjects at risk for mortality, and St. George’s Respiratory Questionnaire (SGRQ) for subject stratification and as an outcome measure. The goal is to assemble data under the auspices of the Consortium that will permit official recognition of biomarkers that can improve disease monitoring and expedite new COPD.
The SPIROMICS Study\textsuperscript{87} SPIROMICS, which stands for Subpopulation and Intermediate Outcome Measures in COPD Study, was initiated by the National Heart, Lung and Blood Institute (NHLBI) along with several universities contracted as study sites. Among those participating in SPIROMICS are Columbia University, Johns Hopkins University, University of California Los Angeles, University of California San Francisco, University of Utah, Wake-Forest University, and University of Michigan. In addition, through a partnership established by the Foundation for the National Institutes of Health, several representatives of the pharmaceutical and biotherapeutic industry are participating as members of an external scientific board.

This study will recruit approximately 3,000 individuals of different backgrounds (men and women of different age groups and ethnicities) to assess their lung function, conduct CT scans and bronchoscopy, and take biochemical measurements from their blood, urine and sputum.

The COPDGene Study\textsuperscript{88}
COPDGene is a 21 site observational study designed to identify genetic factors associated with COPD. It will also characterize chest CT phenotypes in COPD subjects including assessment of emphysema, gas trapping, and airway wall thickening. Finally, subtypes of COPD based on these phenotypes will be used in a comprehensive genome-wide study to identify COPD susceptibility genes. COPDGene is intended to provide new information about genetic factors in COPD and will characterize the disease process using high resolution CT scans. Understanding genetic factors and CT phenotypes that define COPD will potentially permit earlier diagnosis of this disease and may lead to the development of treatments to modify progression.

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 if eliminated.

- While new treatment initiatives have come from information on the physiology of COPD, \textit{not a single new therapy has come from information on pathogenic inflammatory processes.}

- Surrogate markers of inflammation, possibly derived from the analysis of sputum (cells, mediators, enzymes) or exhaled condensates (lipid mediators, reactive oxygen species, cytokines), that may predict the clinical usefulness of new management and prevention strategies for COPD need to be developed and qualification as tools in drug development will require a major investment in order to generate data in large cohorts and apply systems medicine to improve the application of emerging data.\textsuperscript{89}
Update on 2004 Background Paper, BP 6.13 COPD

- New clinical end points are needed to assess the impact of different COPD interventions. The cornerstone of clinical assessment has been a reduction in the decline of the forced expiration volume (FEV1) of the lung for inhaled corticosteroids and an improvement of FEV1 with bronchodilators. Both measures fail to take into account the multi-component nature of COPD. Rehabilitation therapy would have failed these tests despite its clear beneficial impact.

- Standardized methods for tracking trends in COPD prevalence, morbidity, and mortality over time need to be developed so that countries can plan for future increases in the need for health care services in view of predicted increases in COPD. This need is especially urgent in developing countries with limited health care resources.

- Since COPD is not fully reversible (with current therapies) and slowly progressive, it will become ever more important to identify early cases as more effective therapies emerge. Consensus on standard methods for detection and definition of early disease need to be developed.

- New medicines for the treatment of COPD are greatly needed and there has been an enormous effort now invested by the pharmaceutical industry to find such treatments. While preventing and quitting smoking is the obvious preferred approach, this has proved to be very difficult. Not all COPD is due to cigarette smoking, especially in low- and middle-income countries (LMIC).

- It is important to identify the genetic factors that determine why only a minority of heavy smokers develop COPD, and identification of genes that predispose to the development of COPD may provide novel therapeutic targets in the future.

- However, it will be difficult to demonstrate the efficacy of novel treatments on the rate of decline in lung function, since this requires large studies over many years. Hence, there is a need to develop novel outcome measures and surrogate biomarkers, such as analysis of sputum parameters (cells, mediators, enzymes) or exhaled condensates (lipid mediators, reactive oxygen species).

- Public health advocacy/research/evidence based on biomass/indoor air pollution is required as is this the major risk factor for COPD in women and younger persons.

9.2 What is the comparative advantage of the EU with regard to public funding of pharmaceutical R&D for COPD?

Given the scale of their human and economic costs, managing lung diseases should become a high priority for all European countries. The pharmaceutical industry is beginning to recognize this and it is probable that new and more effective therapies will become available, although not in the short term.

As the outlook is poor in the short and medium term for development of emerging therapies to treat or reverse COPD, the overriding imperative in low- and middle-income countries and in the expanded EU is to reduce the prevalence and incidence of smoking.
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11 Mannino DM, VA Kiri Changing the burden of COPD mortality International Journal of COPD 2006;1(3) 219-233


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AirPROM (Airway Disease Predicting Outcomes through Patient Specific Computational Modelling) [website] [accessed 25 April 2013] Available at: http://www.airprom.european-lung-foundation.org/


The-PROActive-Project - PROactive COPD at http://www.proactivecopd.com/about/the-proactive-project/

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SPIROMICS - Subpopulations and intermediate outcome measures in COPD study [website] [accessed 25 April 2013] Available at: http://www.sccc.unc.edu/spir/about.php

COPDGene® – Genetic COPD epidemiology [website] [accessed 25 April 2013] Available at: http://www.copdgene.org/study-design
Annexes

Annex 6.13.1: Estimated population prevalence of GOLD stage II or higher COPD, separated by age

Men

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## Update on 2004 Background Paper, BP 6.13 COPD

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### Annex6.13.2: Cochrane Reviews on the subject of COPD

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<td>Becker LA, Hom J, Villasis-Keever M, van der Wouden JC. Beta-2-agonists for acute bronchitis. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD001726. DOI: 10.1002/14651858.CD001726.pub4</td>
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<td>There is no evidence to support the use of beta-2-agonists in children with acute cough who do not have evidence of airflow obstruction. There is also little evidence that the routine use of beta-2-agonists is helpful for adults with acute cough. These agents may reduce symptoms, including cough, in people with evidence of airflow obstruction. However, this potential benefit is not well-supported by the available data and must be weighed against the adverse effects associated with their use.</td>
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<tr>
<td>Beta-2-agonists for acute bronchitis.</td>
<td>Becker LA, Hom J, Villasis-Keever M, van der Wouden JC. Beta-2-agonists for acute bronchitis. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD001726. DOI: 10.1002/14651858.CD001726.pub6</td>
<td>Beta-2-agonists for acute bronchitis/placebo</td>
<td>night cough after 7 days</td>
<td>RR</td>
<td>There is no evidence to support the use of beta-2-agonists in children with acute cough who do not have evidence of airflow obstruction. There is also little evidence that the routine use of beta-2-agonists is helpful for adults with acute cough. These agents may reduce symptoms, including cough, in people with evidence of airflow obstruction. However, this potential benefit is not well-supported by the available data and must be weighed against the adverse effects associated with their use.</td>
<td>1.16 (0.67 - 1.46)</td>
<td></td>
</tr>
</tbody>
</table>
Prophylactic antibiotics in chronic bronchitis/COPD have a small but statistically significant effect in reducing the days of illness due to exacerbations of chronic bronchitis. They do not have a place in routine treatment because of concerns about the development of antibiotic resistance and the possibility of adverse effects. The available data are over 30 years old, so the pattern of antibiotic sensitivity may have changed and there is a wider range of antibiotics in use.

### Chronic bronchitis


<table>
<thead>
<tr>
<th>Study Details</th>
<th>Comparator</th>
<th>Effect Measure</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staykova T, Black PN, Chacko EE, Poole P.</td>
<td>Placebo</td>
<td>Proportion of patients with exacerbations</td>
<td>RR 1.11 (1.03 - 1.18)</td>
</tr>
<tr>
<td>Nine trials involving 1055 subjects</td>
<td>Tetracyclines</td>
<td>Proportion of patients with exacerbations</td>
<td>RR 1.09 (1.01 - 1.16)</td>
</tr>
</tbody>
</table>

There was limited evidence to support the use of antibiotics in acute bronchitis.

At follow-up, patients receiving antibiotics were marginally more likely to be clinically improved than those receiving placebo treatment.

### Antibiotics for acute bronchitis


<table>
<thead>
<tr>
<th>Study Details</th>
<th>Comparator</th>
<th>Effect Measure</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith SM, Fahey T, Smucny J, Becker LA.</td>
<td>Placebo</td>
<td>Number of patients in total</td>
<td>RR 1.33 (1.17 - 1.46)</td>
</tr>
<tr>
<td>Fifteen trials with 2618 patients IN TOTAL</td>
<td>ANY antibiotic prophylaxis</td>
<td>Number of patients with night cough</td>
<td>RR 1.36 (1.15 - 1.51)</td>
</tr>
<tr>
<td>Smith SM, Fahey T, Smucny J, Becker LA.</td>
<td>Placebo</td>
<td>Number of patients with cough</td>
<td>RR 1.06 (1.02 - 1.1)</td>
</tr>
<tr>
<td>Antibiotics for acute bronchitis. Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD000245. DOI: 10.1002/14651858.CD000245.pub2.</td>
<td>ANY antibiotic</td>
<td>Number of patients with cough</td>
<td></td>
</tr>
<tr>
<td>Nine studies</td>
<td>ANY antibiotic</td>
<td>Number of patients clinically improved</td>
<td></td>
</tr>
</tbody>
</table>

There was limited evidence to support the use of antibiotics in acute bronchitis.

At follow-up, patients receiving antibiotics were marginally more likely to be clinically improved than those receiving placebo treatment.
### Antibiotics for acute bronchitis


<table>
<thead>
<tr>
<th>ANY antibiotic</th>
<th>placebo</th>
<th>number of patients with abnormal lung exams</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.46 (1.3 - 1.59)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Antibiotics for acute bronchitis


<table>
<thead>
<tr>
<th>ANY antibiotic</th>
<th>placebo</th>
<th>Number of patients with limitations</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25 (0.78 - 1.54)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Combined corticosteroid and long-acting beta-agonist


- **Rate of exacerbations**: 6427 participants randomised, fluticasone propionate/salmeterol vs. placebo, *RR 0.74 (0.69 - 0.8)*

- **Mortality**: 6427 participants randomised, fluticasone propionate/salmeterol vs. placebo, *OR 1.21 (1.02 - 1.35)*

Compared with placebo, combination therapy led to a significant reduction of a quarter in exacerbation rates. There was a significant reduction in all-cause mortality with the addition of data from the TORCH trial.
## Update on 2004 Background Paper, BP 6.13 COPD

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study Details</th>
<th>Key Findings</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined corticosteroid and long-acting beta-agonist</strong></td>
<td>Nannini LJ, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003794. DOI: 10.1002/14651858.CD003794.pub3.</td>
<td>6427 participants randomised</td>
<td>Budesonide/formoterol placebo Mortality OR 1.22 (0.27 - 1.65)</td>
</tr>
<tr>
<td><strong>Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease</strong></td>
<td>Poole P, Black PN, Cates CJ. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD001287. DOI: 10.1002/14651858.CD001287.pub4.</td>
<td>30 trials recruiting a total of 7436</td>
<td>Mucolytic placebo no exacerbation in study period (2-36 months) ALL STUDIES OR 1.88 (1.68 - 2.11)</td>
</tr>
<tr>
<td><strong>Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease</strong></td>
<td>Poole P, Black PN, Cates CJ. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD001287. DOI: 10.1002/14651858.CD001287.pub4.</td>
<td>30 trials recruiting a total of 7436</td>
<td>Mucolytic placebo no exacerbation in study period (2-36 months) STUDIES POST 2000 OR 1.24 (1.01 - 1.54)</td>
</tr>
<tr>
<td><strong>Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease</strong></td>
<td>Walters JAE, Gibson PG, Wood-Baker R, Hannay M, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD001288. DOI: 10.1002/14651858.CD001288.pub3.</td>
<td>10 studies contributed data for analyses (n=1051) in TOTAL</td>
<td>Systemic corticosteroids placebo relapse within thirty days of original admission for COPD outpatients OR 1.22 (0.69 - 1.54)</td>
</tr>
<tr>
<td><strong>Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease</strong></td>
<td>Walters JAE, Gibson PG, Wood-Baker R, Hannay M, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews</td>
<td>Systemic corticosteroids placebo relapse of exacerbation within 30 days rate of relapse of exacerbation within 30 days OR 1.22 (1.03 - 1.37)</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with a clinically significant improvement (4 units) in quality of life (SGRQ)</td>
<td>Tiotropium placebo OR 1.54 (1.4 - 1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with one or more exacerbations Follow-up: 3 to 48 months</td>
<td>Tiotropium placebo OR 1.22 (1.13 - 1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with one or more exacerbations requiring hospitalisation Follow-up: 3 to 48 months</td>
<td>Tiotropium placebo OR 1.15 (1 - 1.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fifty-five primary studies with 16,154 participants</td>
<td>Inhaled corticosteroids placebo mortality OR no consistent long-term benefit in the rate of decline in breathing capacity. Death rates were unchanged. Inhaled steroids were beneficial in slowing down the rate of decline in quality of life and reducing the frequency of exacerbations. Inhaled steroids increased the risk of side effects including thrush (candida) infection in the mouth and 1.02 (0.84 - 1.17)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Tiotropium for stable chronic obstructive pulmonary disease


<table>
<thead>
<tr>
<th>Comparison</th>
<th>Study</th>
<th>RCTs</th>
<th>Patients</th>
<th>Mean Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium vs placebo</td>
<td>nine RCTs (6,584 patients)</td>
<td>Tiotropium</td>
<td>placebo</td>
<td>hospitalizations</td>
<td>OR 0.65 (0.5 - 0.85)</td>
</tr>
<tr>
<td>Tiotropium vs placebo</td>
<td>Tiotropium vs placebo</td>
<td>COPD exacerbation</td>
<td>OR 1.26 (1.17 - 1.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiotropium vs placebo</td>
<td>Tiotropium vs placebo</td>
<td>all cause mortality</td>
<td>OR 1.27 (0.61 - 1.65)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tiotropium does reduce exacerbations and related hospitalisations and improves quality of life and symptoms in people with moderately severe COPD.

### Oral corticosteroids for stable chronic obstructive pulmonary disease


<table>
<thead>
<tr>
<th>Comparison</th>
<th>Study</th>
<th>RCTs</th>
<th>Patients</th>
<th>Mean Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral corticosteroids vs placebo</td>
<td>Withdrawal due to exacerbations COPD</td>
<td>Oral corticosteroids</td>
<td>placebo</td>
<td>OR 0.44 (0.17 - 1.18)</td>
<td></td>
</tr>
<tr>
<td>Oral corticosteroids vs placebo</td>
<td>Oral corticosteroids vs placebo</td>
<td>patient FEV1 response greater than 20% from baseline with high dose</td>
<td>OR 2.74 (1.64 - 4.01)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There is no evidence to support the long-term use of oral steroids at doses less than 10-15 mg prednisolone though some evidence that higher doses ( 30 mg prednisolone) improve lung function over a short period. Potentially harmful adverse effects e.g., diabetes, hypertension, osteoporosis would prevent recommending long-term use at these high doses in most patients.
### Update on 2004 Background Paper, BP 6.13 COPD

<table>
<thead>
<tr>
<th>Disease</th>
<th>Oral Steroid Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-acting beta-2-agonists</strong></td>
<td></td>
</tr>
<tr>
<td>Phosphodiesterase 4 inhibitors</td>
<td></td>
</tr>
<tr>
<td>Chong J, Poole P, Leung B, Black PN. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD002309. DOI: 10.1002/14651858.CD002309.pub3</td>
<td>Roflumilast (nine trials, 9211 patients) Roflumilast or cilomilast (fourteen trials, 6457 patients) Cilomilast placebo likelihood of COPD exacerbation OR 1.22 (1.15 - 1.28)</td>
</tr>
</tbody>
</table>

These medicines improve lung function and reduce the likelihood of a flare-up of COPD, however they have little effect on symptoms or quality of life over and above existing treatments. This may be due to side effects, although these are not serious.
Annex 6.13.3: List of medicines in United States clinical trials

<table>
<thead>
<tr>
<th>Compound</th>
<th>Funder</th>
<th>Clinical Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aclidinium bromide</td>
<td>Schering-Plough, Novartis, Astra Zeneca, Mayo Clinic, Boehringer Ingelheim Novartis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Arformoterol, tiotropium</td>
<td>Takeda, U. Florida Novartis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>AZD1236</td>
<td>Dep’t Veterans Affairs (USA)</td>
<td>Phase 2</td>
</tr>
<tr>
<td>AZD4818</td>
<td>Takeda, U. Florida</td>
<td>?</td>
</tr>
<tr>
<td>AZD9164</td>
<td>Boehringer Ingelheim</td>
<td>?</td>
</tr>
<tr>
<td>AZD9668</td>
<td>GlaxoSmithKline, Novartis, Takeda Novartis</td>
<td>Phase 3, 4*</td>
</tr>
<tr>
<td>Budesonide/formoterol</td>
<td>Astellas Pharma Inc</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Boehringer Ingelheim</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Fluticasone propionate/salmeter</td>
<td>Takeda, U. Florida</td>
<td>?</td>
</tr>
<tr>
<td>Glycopyrronium bromide</td>
<td>GlaxoSmithKline, Novartis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Glycopyrronium bromide</td>
<td>Dep’t Veterans Affairs (USA)</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Indacaterol</td>
<td>Novartis, Astra Zeneca, Pfizer, NHLBI, Takeda, Scheering-Plough, Fondiazone Salvatore Maugeri, Forest Laboratories, Weill Medical College, Sunovion</td>
<td>Phase 2,3,4</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Merck</td>
<td>Phase 2</td>
</tr>
<tr>
<td>MP-376</td>
<td>Novartis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>NVA237</td>
<td>Novartis, Sunovion, Astra Zeneca</td>
<td>Phase 2, 4</td>
</tr>
<tr>
<td>Roflumilast</td>
<td>Takeda, Astra Zeneca, Novartis</td>
<td>Phase 2, 3, 4</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>Astra Zeneca, GlaxoSmithKline, Forest Laboratories, U. Sao Paolo, Boehringer Ingelheim, Novartis</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Zileuton</td>
<td>Novartis</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>
Appendices


Appendix 6.13.2  COPD: The New Workplace Epidemic - Education For Health (COPD Uncovered: Updated September 2011.)


Appendix 6.13.6  FY 2013 Budget, DEPARTMENT OF HEALTH AND HUMAN SERVICES NATIONAL INSTITUTES OF HEALTH National Heart, Lung, and Blood Institute (NHLBI)
Background Paper 6.14
Harmful use of Alcohol
Alcohol Use Disorders and Alcoholic Liver Diseases

By Rene Soria Saucedo (MD, MPH, PhDc)

January 2013
Update on 2004 Background Paper, BP 6.14 Alcohol Use Disorders

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10.8 Combination of pharmaceutical options

11. For which of these gaps are there opportunities for pharmaceutical research (possible ways to go forward with regards to public funding?)

11.1 Alcohol pathogenesis
11.2 Public and private funding needs to be increased

12. Conclusion

References

APPENDIX
## Abbreviations:

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<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAS</td>
<td>Anabolic-androgenic steroids</td>
</tr>
<tr>
<td>AC</td>
<td>Alcohol Cirrhosis</td>
</tr>
<tr>
<td>ACo</td>
<td>Alcohol Consumption</td>
</tr>
<tr>
<td>AD</td>
<td>Alcohol dependence</td>
</tr>
<tr>
<td>AH</td>
<td>Alcohol Hepatitis</td>
</tr>
<tr>
<td>ALD</td>
<td>Alcohol Liver Diseases</td>
</tr>
<tr>
<td>AUD</td>
<td>Alcohol Use Disorders</td>
</tr>
<tr>
<td>BAC</td>
<td>Blood Alcohol Concentration</td>
</tr>
<tr>
<td>DALYs</td>
<td>Disability Adjusted Life Years</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>MHD</td>
<td>Mental Health Disorders</td>
</tr>
<tr>
<td>NIAAA</td>
<td>National Institute on Alcohol Abuse and Alcoholism</td>
</tr>
<tr>
<td>PTU</td>
<td>Propylthiouracil</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive Oxygen Species</td>
</tr>
<tr>
<td>SAMe</td>
<td>S-adenosyl-L-methionine</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
</tr>
<tr>
<td>TB</td>
<td>Pulmonary Tuberculosis</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Update on 2004 Background Paper, BP 6.14 Alcohol Use Disorders

Executive Summary

Burden of Disease

- According to the World Health Organization (WHO), alcohol emerges as the third largest risk factor for premature mortality, disability and loss of health. Alcohol caused about 3.8 per cent of all deaths (2.5 million) and about 4.5 per cent of ‘disability adjusted life years’ lost (DALYS) (69.4 million).
- Worldwide, alcohol is the third leading cause of ill health, behind low birth weight and unsafe sex. Europe is the largest consumer of alcohol in the world and alcohol consumption appears as the third leading risk factor for disease and mortality.
- Even though alcohol is a causal factor in 60 types of diseases and injuries and a component cause in 200 others, and accounts for 20% to 50% of cirrhosis of the liver prevalence, it remains a low priority for public and health policy interventions.
- Alcohol Consumption (ACo) is responsible for increasing the risk of liver cirrhosis, certain cancers, raised blood pressure, stroke and congenital malformations. Furthermore, ACo increases the risk of many family, work and social problems.
- Excessive ACo (more than 14 standard drinks per week for men and seven standard drinks per week for women) is significantly associated with the burden of disease of infectious conditions, cancer, cardiovascular disease, and liver cirrhosis. Interestingly however, mild and moderate patterns of alcohol consumption also has beneficial effects on the burden of disease, mainly on diabetes and the ischemic disease subcategory of cardiovascular diseases. Yet the latter effects are by far outweighed by the detrimental consequences of excessive ACo.
- European countries estimates report that one in seven male deaths and one in 13 female deaths in the 15-64 age categories were caused by alcohol. That ratio translates into 95 000 men and over 25 000 women dying from alcohol-attributable causes in one year.
- Alcohol Use Disorders (AUD) constitutes a major part of neuropsychiatric disorders and markedly contributes to the global burden of disease. However, they only account for less than one-third of the overall impact of ACo. Alcohol dependence accounts for 71% of all alcohol-related deaths and for about 60% of social costs attributable to alcohol. Acute effects of ACo on the risk of both unintentional and intentional injury also account for a sizable effect on the global impact of burden of disease.
- Alcoholic liver disease (ALD) is the commonest cause of cirrhosis in the western world, and ALD is currently one of the ten most common causes of death. Liver fibrosis caused by alcohol abuse and its end stage, cirrhosis, presents enormous worldwide healthcare problems. Over 60% of patients with cirrhosis of the liver and superimposed alcoholic hepatitis have a life expectancy of only four years. Overall, stopping drinking has been shown to improve the survival of patients with all stages of ALD.

ALD comprises a spectrum of disease, including alcoholic fatty liver, AH, alcoholic fibrosis, cirrhosis, and hepatocellular cancer. Worldwide, the common causes of liver fibrosis and cirrhosis include alcohol, hepatitis B and hepatitis C.
Treatment Options

- Only 14.6 per cent of those with a lifetime history of alcohol abuse or dependence have received treatment. In Europe, only an estimated 8% of people with alcohol dependence receive treatment. Efforts to identify and properly care this population are warranted.
- Several policy options have been tested to decrease ACo. For example, drinking and driving reduction; education, communication, training and public awareness; alcohol market regulation; reduction of harm in drinking and surrounding environments; and interventions for individuals. The evidence is still weak to identify the true effectiveness of such interventions.
- Currently approved for treating AUD are disulfiram, naltrexone, and acamprosate. Other drugs are being investigated, used off-label (topiramate and ondansetron) or recently approved in Europe (nalmefene) for use in patients with alcohol dependence who want to reduce their alcohol consumption, either as a treatment goal or as a step towards abstinence. While some of them have shown promise in terms of efficacy (nalmefene, topirimate, and ondansetron), none has been found effective when used as a single treatment method without some sort of concurrent behavioral therapy.
- Coexisting diseases (especially mental disorders, but also noncommunicable diseases such as cardiovascular disease, cancer, diabetes or liver disorders) are highly prevalent among those subjects suffering from AUD. Latest evidence supports changing the current practice of treating both diseases (mental disorders and alcohol dependence) separately; to a new approach of incentivizing better coordination between clinics and centers to treat addictions.
- Overall, stopping drinking has been shown to improve the survival of patients with all stages of ALD. Thus, this condition can be prevented. However, progress in developing specific treatments for acute AH has been hampered by a poor understanding of disease pathogenesis. There are no FDA approved therapies for ALD.
- Many treatment modalities have been tried in patients with AH, however, few have been consistently shown to have a beneficial effect and, accordingly, none have achieved consensus status among practicing hepatologists. Thus, current therapy still focuses predominantly on supportive care.
- Current treatments for alcoholic cirrhosis are severely limited. One can attempt to have patients abstain from alcohol (where possible); eradicate existing viruses using interferon, ribavirin, and lamivudine (in cases involving viral hepatitis); and liver transplantation. The vast majority of patients with ALD in clinical practice have advanced fibrosis or cirrhosis. No adjunctive pharmacotherapies have been consistently shown to improve survival in more than one randomized controlled trial, although some have shown promise.
- There is little private-sector funding directed to AUD and ALD. Public sector funding may be insufficient as well, particularly when compared to the enormous economic and social burdens placed on the healthcare system by ALD.
1. Introduction

Around two billion people worldwide consume alcoholic beverages regularly and over 76 million people suffer from AUD. Many interacting issues are at work when dealing with alcohol abuse: the medical sequelae, alcohol intoxication, alcohol tolerance, alcohol dependence, and alcohol withdrawal. From a public health viewpoint, the diseases associated with alcohol abuse are preventable with abstention and such behavioral modifications should be considered as the primary intervention. The present review will offer an overview of the strategies to prevent Alcohol Consumption (ACo), pharmacological interventions for alcohol abuse and dependence (collectively termed AUD) and alcohol’s hepatotoxic effects that result in ALD. This background paper update reviewed the latest evidence from 2002 through 2012, on the basis of an analysis of published systematic reviews and meta-analyses, which were identified through searches of The Cochrane Library, Medline, Web of Science, Google Scholar and National Institute on Alcohol Abuse and Alcoholism (NIAAA), with specific search terms for alcohol use disorders, alcoholic liver diseases and alcohol consumption. If relevant references within the timeframe described above were not found, older ones were considered. Reference sections of identified papers were cross-checked to identify other relevant studies contributing to this review.

1.1 Alcohol Consumption (ACo) and its relationship with Alcohol Use Disorders (AUD)

Evidence is overwhelming about the link between excessive use of alcohol and a wide range of harmful outcomes, including AUD; mortality and morbidity from chronic medical conditions, such as ALD and acute causes, such as vehicular accidents, intentional and unintentional injury; and a host of social and legal problems. WHO risk assessment framework illustrates the multidimensional association between ACo and health and social problems (Figure 6.14.1).

The conditions that lead to excessive ACo in some individuals and not in others are very complex. Alcoholism is a multigenic disorder involving interactions between genetic, psychosocial, environmental, and neurobiological factors. The pharmacological effects of ethanol that support alcohol reward and alcohol seeking behavior involve actions at multiple receptors and neurochemical systems occurring throughout the body. Neuropharmacologic studies in animals have provided evidence for specific neurochemical mechanisms in the brain that are involved in AD. There are many neurotransmitter systems that become deregulated during the development of alcohol dependence, including gamma (γ)-aminobutyric acid (GABA), opioid peptides, glutamate, serotonin and dopamine systems.
Figure 6.14.1. The relationship between alcohol consumption, intermediate variables and alcohol related outcomes.


1.2 Alcohol Use Disorders (AUD)

Prolonged excessive ACo promotes neuroadaptive changes in the brain’s reward and stress systems. It is theorized that AUD development is linked with the presence of a constant alcohol challenge to regulatory systems that attempt (but ultimately fail) to defend the normal equilibrium of various homeostatic set points. This mechanism is postulated to contribute to the transition from controlled alcohol use to uncontrollable drinking (Figure 6.14.2 offers a contextual framework to elucidate the vicious circle between dependence and relapse).

Briefly, alcohol has two major actions on the brain: increasing neuronal inhibition mediated through the inhibitory GABA and other receptors. Prolonged alcohol use down-regulates these receptors and decreases inhibitory neurotransmission. Prolonged alcohol use inhibits excitatory neurotransmission by inhibiting both N-methyl-d-aspartate (NMDA) and non-NMDA (e.g., α-amino-3-hydroxy-5-methisoxizole-4-propionic acid [AMPA]) receptors. Cessation or reduction of alcohol use initiates an imbalance between the decreased neuroinhibition and increased neuroexcitation. This causes the clinical manifestations of alcohol withdrawal: e.g., tremors, hallucinations, insomnia, anxiety or agitation, and possibly seizures. Alcohol also affects numerous other neurotransmitters (for additional details, go to Appendix 6.14.3 and 6.14.4). Although about 30% of all alcohol-dependent patients are admitted to general hospitals, usually to treat the alcohol-related physical diseases emphasized in this document, AUD themselves are often ignored or not diagnosed.
1.3 Alcoholic Liver Diseases (ALD)

The pathogenesis of ALD is multifactorial. Hepatocytes and parenchymal cells are the main targets of alcohol and its toxic metabolites, producing an excessive generation of molecules called free radicals, known as reactive oxygen species (ROS). ROS modify the signaling pathways regulating lipid or glucose metabolism, and can directly modulate proteins and DNA. Alcohol can also induce the permissiveness of the intestine cell wall, allowing larger amounts of endotoxins to pass into the blood. The body coordinated immune response by activation of immune cells residing in the liver (Kupffer cells), which affect the liver tissue by two mechanisms: a) become inflammatory cytokines, and their excessive amount have dire consequences, pushing the immune system response into overdrive, promoting the progression of liver disease b) Kupffer cells are the major source of ROS in the liver, leading to oxidative stress. The spectrum of ALD ranges from fatty liver (steatosis), present in most, if not all heavy drinkers, through steatohepatitis, fibrosis and ultimately cirrhosis. (Appendix 6.14.1 illustrates the systemic mechanism of alcohol-induced liver damage).

1.3.1 Alcoholic Fatty Liver

Alcoholic fatty liver is predominantly an asymptomatic condition that develops in response to a short duration (a few days) of alcohol abuse. Patients with fatty liver are asymptomatic so that they rarely present with liver related problems. Fatty liver is reversible with abstinence but it is a risk factor for progression to fibrosis and cirrhosis in those patients who continue drinking.
1.3.2 Alcohol Hepatitis (AH)

Between 20-40% of persistent heavy drinkers will develop more serious liver disease. In some of these patients, they will get AH, while others will present with complications of portal hypertension, and other conditions. People with ALD can also be asymptomatic and may even have normal liver blood tests. The level of alcohol consumption necessary for the development of these advanced forms of ALD is probably 80 g of alcohol per day, the equivalent to six to eight drinks daily for several years.

1.3.3 Alcoholic Cirrhosis (AC)

Alcoholic cirrhosis may occur at any time before, during, after, or independent of a bout of AH. Liver fibrosis and cirrhosis (clinically distinct conditions but, unless specifically mentioned, they are used interchangeably in this report) represent a continuous disease spectrum characterized by an increase in total liver collagen and other matrix proteins which disrupt the architecture of the liver and impair liver function. Fibrosis results from sustained wound healing in the liver in response to chronic or iterative injury. The wound healing response is an integral part of the overall process of inflammation and repair: it is dynamic and has the potential to resolve without scarring, however, hepatic fibrosis is a healing process gone awry in response to ongoing liver injury in ALD. As the liver becomes increasingly fibrotic, the number of functional hepatocytes decreases and the liver loses its capacity to remove toxic substances from the blood. At present, there are few interventions available to alter the underlying fibrotic process in many patients with liver disease, although data from clinical and laboratory based research show that cirrhosis may be reversible.

1.4 Definition of AUD: Search for a consensus

Consensus around diagnostic criteria for AUD becomes critical to signal which patterns of behaviour or physiological characteristics constitute symptoms to properly recognize the disorders. Diagnostic criteria allow clinicians to plan treatment and monitor treatment progress; make communication possible between clinicians and researchers; enable public health planners to ensure the availability of treatment facilities; help health care insurers to decide whether treatment will be reimbursed; and allow patients access to medical insurance coverage.

1.4.1 ICD Criteria

The World Health Organization (WHO) develops diagnostic criteria for the purpose of compiling worldwide statistics on all causes of death and illness, including those related to AUD. The International Classification of Diseases (ICD-10 codes) defines AUD in a way that is similar to the Diagnostic and Statistical Manual of Mental Disorders (DSM). The diagnosis focuses on an interrelated cluster of psychological symptoms, such as craving, physiological signs (such as tolerance and withdrawal) and behavioural indicators such as the use of alcohol to relieve withdrawal discomfort. However, in a departure from the DSM, rather than include the category "alcohol abuse," ICD-10 includes the concept of "harmful use." This category was created so that health problems related to alcohol and other drug use would not be underreported. Harmful use implies alcohol use that causes either physical or mental damage in the absence of dependence. Some differences between the two major diagnostic
criteria still exist, but they have been revised by consensus as to how AUDs are best characterized for clinical purposes.

### 1.4.2 The DSM Criteria

Researchers and clinicians in the United States (US) usually rely on the DSM diagnostic criteria, found in the DSM, currently in its Fourth Edition (DSM-IV). DSM-IV, like its predecessors, includes non-overlapping criteria for AUDs. However, in a departure from earlier editions, DSM-IV provides for the subtyping of dependence based on the presence or absence of tolerance and withdrawal. The criteria for abuse in DSM-IV were expanded to include drinking despite recurrent social, interpersonal, and legal problems as a result of alcohol use. In addition, DSM-IV highlights the fact that symptoms of certain disorders, such as anxiety or depression, may be related to an individual’s use of alcohol or other drugs. The 2013 update (published draft guidelines) no longer separate the categories of abuse and dependence. Therefore, both disorders are defined as single AUD. Research found that a single dimensional construct offered a simpler solution that better fit the research results.9

### 2. What is the size and nature of the disease burden that is caused by ACo, AUD, and ALD?

#### 2.1 General Epidemiological trends for Europe and the World

Alcohol Consumption (ACo) has accompanied humans since the beginning of recorded history. The harmful use of alcohol significantly associates with more than 60 types of diseases and injuries, resulting in approximately 2.25 million deaths each year, after controlling for the beneficial impact of low risk alcohol use on morbidity and mortality in some diseases (e.g. diabetes, cardiovascular disease). Thus, approximately 4% of all deaths worldwide are attributable to alcohol.16 NIAAA estimated in 2007 that more than 17 million people in the United States have an AUD, with a cost to society of over US$ 180 billion annually.17

Even though accurate estimates for the incidence and prevalence of ALD are difficult to obtain, it is estimated that 20% to 50% of cirrhosis of the liver is attributable to ACo. The ICD-10 codes include more than 30 items with alcohol as part of the name or definition (necessary cause). Moreover, it has been identified as a component cause for over 200 ICD-10 disease codes.18

The impact of ACo is associated with two consumption domains: (a) the volume of alcohol consumed and (b) the pattern of drinking (Figure 1). In terms of volume, it is clear that most of the burden associated with alcohol is positively associated with regular heavier drinking patterns (commonly defined as drinking more than 40 grams of pure alcohol per day for men and 20 grams of pure alcohol per day for women).19 In addition, irregular patterns of drinking are strongly related with the burden of disease and injury (e.g. binge drinking, defined as drinking at least 60 grams of pure alcohol or five standard drinks in one sitting).20 In European settings, heavy episodic drinking patterns are more prevalent in poorer than in richer settings, and explain 25% of the differences in life expectancy between eastern and
western Europe. Rising levels of consumption are most pronounced in women and young people, with the latter more prone to heavy binge drinking.

### 2.1.1 Unintentional injuries

The relationship between alcohol and unintentional injuries has been established in published literature. It depends on the blood alcohol concentration (BAC) and shows an exponential dose-response relationship. Alcohol affects psychomotor abilities, with a threshold dose for negative effects generally found at BACs of approximately 0.04 to 0.05 per cent (about two to three drinks in an hour); accordingly, people with BACs at this level are more likely to injure themselves or others. Literature has also linked alcohol’s acute effects with the consumption pattern. People who drink less frequently are more likely to be injured or to injure others at a given BAC compared with regular drinkers, presumably because of less tolerance.

### 2.1.2 Intentional injuries

Alcohol consumption is linked to patterns of self-harm and aggression. For example, Borges and colleagues found a positive association between volume of ACo and suicide risk. There also is a clear link between ACo and aggression, including, but not limited to, homicides. Cultural factors may also have an effect to both differences in drinking patterns and aggression.

### 2.2 Prevalence of Alcohol Use Disorders (AUD)

With the exception of Islamic regions, alcohol is ubiquitous in the modern world. It seems possible that the role of alcohol as a major factor in the burden of disease will increase in the future. Even though a five year change in alcohol use (2001-2005) showed a relatively stable global ACo in most developed regions, developing regions such as Africa and South East Asia have reported consumption increase. Alcohol is linked to conditions also predicted to increase (e.g. accidents and injuries, cardiovascular disease). In terms of younger populations, there are some indications that relatively healthful patterns of drinking are deteriorating in young people, particularly in Europe. Globalization seems to lead to converging patterns of drinking around the world, and not necessarily to convergence to the most favorable patterns (i.e. regular light to moderate drinking with meals). It is arguable that the deterioration of the favorable pattern in young people in Europe has been linked to aggressive marketing focused to this age group. Drinking is being promoted as a lifestyle in association with recreation.

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a large general-population survey conducted in 2001–2002, estimated the prevalence of alcohol abuse and dependence at 4.65 per cent and 3.81 per cent, respectively. Cohen and colleagues reported from the same survey that only 14.6 per cent of those with a lifetime history of alcohol abuse or dependence have received treatment. The results from this survey suggested a wide range of recovery from AD in the general population, from partial remission to full abstinence. Indeed, most prevalence studies have been carried out in North America, so that the results may not be generalizable to other cultures. Rates of AUD also vary depending on the diagnostic criteria used. Community-based studies have estimated the prevalence of alcohol misuse or dependence as 2-4%, with much higher rates...
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of 17% (men) and 7% (women) when looser criteria such as excessive ACo are used. For hospital based studies, the same difficulties exist as the definitions for AUD are not clearly specified in many studies.

Notwithstanding the above, what is known is that the average volume of ACo and patterns of drinking are not related to each other. There is a marked variation between geographic regions (based on WHO sub-regions) on both dimensions. The average volume of drinking is highest in established market economies in Western Europe and the former Socialist economies in the Eastern part of Europe and in North America, and lowest in the Eastern Mediterranean region and parts of South-East Asia including India. Patterns are most detrimental to health in the former Socialist economies in the Eastern part of Europe, in Central and South America and parts of Africa (Figure 6.14.3). Overall, exposure to alcohol around the world varies considerably between regions, the overall exposure by volume is quite high and patterns are relatively detrimental.

Global patterns of consumption are changing (Figure 6.14.3). Overall, developed countries have higher amounts of consumption compared to other countries and regions. However, low-income and middle-income countries (especially in South-East Asia and the western Pacific regions) have markedly increased their ACo over time, partially attributable to supply growth. In addition, the alcohol industry is particularly interested to increase their operations in the emerging economy countries (Brazil, India, China, and Russia). Low consumption is consistently reported in the regions of the world with large populations of Islamic faith, which have very high rates of abstention.

ACo has been recognized as the main risk factor for alcohol abuse. Ecologically, there is a very close association between a country’s total alcohol per head consumption and its prevalence of alcohol-related harm and AUD (21). A large portion of this consumption – 28.6% or 1.76 litres per person – was homemade and illegally produced alcohol or, in other words, unrecorded alcohol. The latter forms of alcohol production may be associated with an increased risk of harm because quality and safety standards for alcohol production are often lacking (30). In the EU, Just under half of this alcohol is consumed in the form of beer (44%), with the rest divided between wine (34%) and spirits (23%).

Excessive ACo can lead to AUD, which affects 12.5 per cent of people in the United States across their lifetime. Nearly 80 000 people die annually from the short- and long-term consequences of alcohol use in the United States.

In terms of alcohol-related mortality, almost one third of the alcohol-attributable deaths (29.6%) is related to unintentional injuries, with 21.6 per cent due to cancer and about 17 per cent due to liver cirrhosis. Cardiovascular diseases and intentional injuries are the next most important categories, accounting for 14 per cent and 12 per cent respectively (Figure 6.14.4). Worldwide, alcohol caused about 4 per cent of all deaths (2.5 million).

In terms of alcohol-related morbidity, about 4.5 per cent (men: 7.6 per cent; women:1.4 per cent) of ‘disability adjusted life years’ lost (DALYS) (69.4 million) is related to alcohol-attributable burden of disease. However, Present estimates of health effects probably underestimate the harm caused by alcohol, because the full range of social costs have not been properly quantified by research yet.
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Figure 6.14.3: Total Adult (15+) per capita consumption, in liters of pure alcohol, 2005 a.

![Figure 6.14.3: Total Adult (15+) per capita consumption, in liters of pure alcohol, 2005 a.](image)


Figure 6.14.4: Global distribution of all alcohol-attributable deaths by disease or injury, 2004

![Figure 6.14.4: Global distribution of all alcohol-attributable deaths by disease or injury, 2004](image)

2.3 Prevalence of Alcohol Liver Disease (ALD)

ALD is the commonest cause of cirrhosis in the western world, and ALD is currently one of the ten most common causes of death. In addition, it remains the most common endpoint associated with ACo and accelerates the progression of other liver diseases such as hepatitis C virus (HCV), hepatocellular carcinoma, and hemochromatosis. ALD comprises a spectrum of disease, including alcoholic fatty liver, AH, AC, and hepatocellular cancer. In 2008, 0.95% of all deaths registered in people aged ≥ 20 years in England and Wales were attributed to ALD. Patients with cirrhosis and superimposed AH have a four-year mortality of more than 60%.

Worldwide, the common causes of liver fibrosis and cirrhosis include hepatitis B and hepatitis C and alcohol. Other causes include immune mediated damage, genetic abnormalities, and non-alcoholic hepatitis, which is associated with obesity and diabetes type 2. Changing patterns of ACo in the west and the increasing rates of obesity and diabetes mean that advances in preventing and treating viral liver infections may be offset by an increasing burden of fibrosis and cirrhosis related to alcohol and non-alcoholic abuse.

2.4 The European Burden of ACo, AD and ALD

The European Union is the heaviest drinking region in the world, as Figure 6.14.5 illustrates. Specifically, ACo is responsible for increasing the risk of liver cirrhosis, certain cancers, raised blood pressure, stroke and congenital malformations. Furthermore, ACo increases the risk of many family, work and social problems. For instance, in the European Region of the WHO, between 40 and 60 per cent of all deaths from intentional and unintentional injuries are estimated to be attributable to ACo. Moreover, in parts of Central and Eastern Europe alcohol abuse has been significantly associated with decreasing rates of male life expectancy.

Data from European countries from 2004 estimated that one in seven male deaths and one in 13 female deaths in the 15-64 age categories were caused by alcohol. That ratio translates into 95 000 men and over 25 000 women dying from alcohol-attributable causes. Middle-aged adults (mostly men) die from alcohol more frequently than any other age group. In terms of life-course, the longer the onset of consumption is delayed, the less likely AUD will emerge.

Rehm and colleagues clustered the European countries in four regions:

- EU10 (joined EU after 2004): Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia;
- EU 15 (old EU): Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden and the United Kingdom
- Baltic countries
- Russian federation
The alcohol-attributable mortality rate in EU10 was more than twofold increased, compared to EU15 for men, and 40 per cent increased for women. Baltic countries alcohol-attributable mortality was fourfold higher for men and three fold higher in women, compared to EU15 countries. The Russian federation showed an almost sevenfold increased mortality for men and fourfold for women, compared to EU15 countries.19

In addition, socially disadvantaged people are more likely to experience more harm per gram of alcohol compared to more privileged sectors. The WHO’s 2004 Global Burden of Disease Study found that alcohol was the third most important risk factor, after smoking and raised blood pressure, for European ill-health and premature death.40 Partial estimates indicate that in 2004, over four million disability-adjusted life-years (DALYs) – years of life lost due to either premature mortality or to disability – were caused by ACo in the EU, corresponding to 15 per cent of all DALYs in men and 4 per cent of all DALYs in women (30). This level of alcohol-related death is highest in Europe and the Americas, where it ranges from 8 per cent to 18 per cent for males and 2 per cent to 4 per cent for females.40 In 2004, a total of 4 043 000 DALYS were estimated to be lost due to alcohol-attributable causes in the group aged 15-64 years in the EU (3 359 000 in men and 684 000 in women).40

Figure 6.14.6 shows the burden of AUD among men and women within European regions. Men seem to be more consistently susceptible in all regions, compared to women. The burden for European women in this age group is much less but is generally in the range of the global values. Overall for both sexes, Central Eastern and Eastern Europe have the higher rates of lost DALYs due to alcohol-attributable causes.
Figure 6.14.6: Regional variation of standardized DALY rates per 100,000 by gender in the group aged 15–64 years, for Alcohol Use Disorders, year 2004.

In terms of cirrhosis (the most lethal consequence of AUD), its prevalence was estimated at 0.15 per cent or 400,000 both in Europe and the United States. However, the high rates of undiagnosed cirrhosis should caution about the accuracy of these estimates. Figure 6.14.7 shows the burden of liver cirrhosis as a per cent of the total DALY burden across various age group and regions. This burden peaks between the ages 45-59 at about 4-5% of all DALYs for men in Europe. The burden for European women in this age group is much less but is generally in the range of the global values. Over all age groups and both sexes, the EU10 countries have higher liver cirrhosis disease burdens than the EU15 countries, a situation reversed from that of alcohol abuse disorders.

The peak in distribution of disease burden for liver cirrhosis follows that for AUD by about 20 years. Although liver cirrhosis can be caused by infective agents (e.g. viral hepatitis), the time lag is not unreasonable under the hypothesis that the liver cirrhosis is in large part the result of the earlier alcohol abuse. Figures 6.14.7 reports frequency plots of the fraction of total DALYs attributed to each age group for the particular geographic area. European regions systematically report the highest burden of disease (with exception of EU 15 women), compared to world estimates. In addition, the timeframe between 15-29 and 45-59 years of age account for the largest amount of DALYs lost for all regions.

Table 6.14.1 summarizes alcohol-attributable burden of disease in Europe. It is worth noting the differences between alcohol-attributable mortality and alcohol-attributable burden of disease (morbidity). Mental disorders represent the largest amount of variability for morbidity (measured in DALYs), and the proportion is almost the same for men and women (46% and 44% respectively). AUD are less fatal compared to diseases such as cancer or
cardiovascular diseases, however, it contributes more to alcohol attributable burden of disease.\textsuperscript{30}

**Figure 6.14.7: Burden of Liver Cirrhosis as a per cent of the total DALY burden, 2002**

![Liver Cirrhosis (Percent of All DALYs by age group)](image)

Source: Casswell S, Thamarangsi T. Alcohol and Global Health 3 Reducing harm from alcohol: call to action. development. 2009;9:10.\textsuperscript{32}

**Table 6.14.1. Alcohol Attributable burden of disease in DALYs in Europe by broad diseases categories in the group aged 15-64 years, 2004.**

<table>
<thead>
<tr>
<th>Effects</th>
<th>Men</th>
<th>Woman</th>
<th>Men (%)</th>
<th>Woman (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Detrimental effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>251 691</td>
<td>151 671</td>
<td>6.9</td>
<td>17.5</td>
</tr>
<tr>
<td>Cardiovascular diseases other than</td>
<td>128 338</td>
<td>25 969</td>
<td>3.5</td>
<td>3.0</td>
</tr>
<tr>
<td>ischemic heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental and neurological disorders</td>
<td>1 891 310</td>
<td>382 584</td>
<td>48.3</td>
<td>44.2</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>512 660</td>
<td>212 676</td>
<td>14.0</td>
<td>24.6</td>
</tr>
<tr>
<td>Unintentional injury</td>
<td>834 659</td>
<td>50 938</td>
<td>17.4</td>
<td>5.9</td>
</tr>
<tr>
<td>Intentional injury</td>
<td>347 225</td>
<td>24 147</td>
<td>9.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Other detrimental</td>
<td>83 640</td>
<td>18 149</td>
<td>2.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Total detrimental</td>
<td>3 849 821</td>
<td>866 131</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Beneficial effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>275 588</td>
<td>87 687</td>
<td>94.8</td>
<td>48.3</td>
</tr>
<tr>
<td>Other beneficial</td>
<td>15 049</td>
<td>94 054</td>
<td>5.2</td>
<td>51.7</td>
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<tr>
<td>Total beneficial</td>
<td>290 637</td>
<td>181 941</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

2.5 Several Specific Epidemiologic Issues related to AUD and ALD.

2.5.1 Data collection challenges

Disease frequency may be measured either by the pool of existing cases (prevalence) or by the occurrence of new cases (incidence). As the onset of many types of liver disease is insidious, there is often a long time interval (latent period) between disease occurrence and detection. Further, many patients with liver disease remain asymptomatic until their livers fail. Thus, it is very difficult, if not impossible, to accurately ascertain incidence rates of liver disease. While estimating prevalence may in general be more feasible than incidence rates, many epidemiologic investigations are conducted based on referral patients, which may not represent the true disease prevalence in entire populations. Population-based studies of liver disease are necessary for accurate information on the burden of disease and the contribution of specific etiologies of liver disease to this burden.

2.5.2 Alcohol and co-occurring chronic diseases

Table 6.14.2 summarizes chronic consequences of alcohol use and highlights the relationship between higher consumption and increased risk for both males and females, and protective effects for diseases such as diabetes mellitus and some CVDs (coronary heart disease, cerebrovascular disease, ischemic stroke, and haemorrhagic stroke) among those individuals with mild and moderate consumption patterns. With respect to treatment, persons exhibiting comorbid alcohol-related and medical or psychiatric disorders often fall through the cracks of the health care system because of administrative distinctions among addiction, medical, and mental health-related services.

Patients are often forced to choose between clinical settings, often resulting in neglect of one condition.

Alcoholism and other disorders might be related in a number of ways, including the following:
(a) Alcoholism and a second disorder can co-occur, either sequentially or simultaneously, by coincidence. For example, Jane-Llopis and colleagues found that 41 per cent of the individuals suffering from AUD who sought treatment had at least one current independent mood disorder, while more than 33% had at least one current independent anxiety disorder; (b) A strong direct association has also been found between the magnitude of comorbidity and an increased severity of AUD; (c) Comorbid disorders might cause alcoholism; (d) Both alcoholism and the comorbid disorder may be caused, separately, by some third condition; (e) Alcohol use or alcohol withdrawal can produce symptoms that mimic those of an independent psychiatric disorder.

Alcohol abuse has been associated with increased odds of substance abuse and mental disorders. For example, Pickens and colleagues found that alcoholics were 7.1 times more likely to have a drug disorder and 2.3 times more likely to have a mental disorder than individuals in the general population. Another study found that a past history of AD was associated with a more than fourfold increased risk for a current or recent major depressive disorder.
Table 6.14.2. Relative Risk for Major Chronic Disease Categories, by gender and Average Drinking Category

<table>
<thead>
<tr>
<th>Disease</th>
<th>ICD-9 code</th>
<th>ICD-10 code</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>140-208</td>
<td>C00-C07</td>
<td>1.45</td>
<td>1.85</td>
</tr>
<tr>
<td>Mouth and oropharynx cancers</td>
<td>140-149</td>
<td>C00-C14</td>
<td>1.80</td>
<td>2.38</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>155</td>
<td>C22</td>
<td>1.45</td>
<td>3.03</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>174</td>
<td>C50</td>
<td>1.14</td>
<td>1.41</td>
</tr>
<tr>
<td>Under 45 years of age</td>
<td></td>
<td></td>
<td>1.14</td>
<td>1.38</td>
</tr>
<tr>
<td>Other neoplasms</td>
<td>210-230</td>
<td>D00-D48</td>
<td>1.10</td>
<td>1.30</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>250</td>
<td>E10-E14</td>
<td>0.92</td>
<td>0.87</td>
</tr>
<tr>
<td>Neuropsychiatric conditions</td>
<td>290-319</td>
<td>F01-F99, G00-G06, G08</td>
<td>3.00</td>
<td>2.00</td>
</tr>
<tr>
<td>Unipolar major depression</td>
<td>300.4</td>
<td>F32-F33</td>
<td>1.34</td>
<td>2.22</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>345</td>
<td>G40-G41</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Alcohol use disorders</td>
<td>291, 303, 306.0</td>
<td>F10</td>
<td>AF**</td>
<td>100%†</td>
</tr>
<tr>
<td>Cardiovascular diseases (CVD)</td>
<td>390-459</td>
<td>I00-I99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive disease</td>
<td>401-405</td>
<td>I10-I13</td>
<td>1.40</td>
<td>2.00</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>410-414</td>
<td>I20-I25</td>
<td>0.82</td>
<td>0.83</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>430-438</td>
<td>I60-I69</td>
<td>0.52</td>
<td>0.64</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>434-435</td>
<td>I62-I64</td>
<td>0.59</td>
<td>0.65</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>415-417, 423-424, 426-429, 440-441, 450-459</td>
<td>I00, I26-I28, I34-I37, I44-I51, I70-I79</td>
<td>1.50</td>
<td>2.20</td>
</tr>
<tr>
<td>Other CVD causes</td>
<td>416-417, 423-424, 426-429, 440-441, 450-459</td>
<td>I00, I26-I28, I34-I37, I44-I51, I70-I79</td>
<td>1.50</td>
<td>2.20</td>
</tr>
<tr>
<td>Digestive diseases</td>
<td>530-579</td>
<td>K20-K92</td>
<td>1.26</td>
<td>9.54†</td>
</tr>
<tr>
<td>Cirrhosis of the liver</td>
<td>571</td>
<td>K70, K74</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Relative risk estimates are shown to quantify the effect size of the risk relationships. For example, females in drinking category I are at a relative risk of 1.14, compared to females in drinking category III. The relative risk is 1.59, or 59% for diseases such as breast cancer. The same relationship can also be expressed as a risk increase of 59 percent.

Varying numbers of studies were used to report on the different diseases. Measurement problems for outcomes affected the reliability of the data for some endpoints, especially the different subsets of endpoints and the unspecialized categories such as “other cardiovascular disease” or “other neoplasms.” The results for these categories should be regarded with caution.

*Definition of drinking categories:
- Category I: for females, 0-19.99 g pure alcohol daily; for males, 0-39.99 g pure alcohol daily.
- Category II: for females, 20-49.99 g pure alcohol daily; for males, 40-59.99 g pure alcohol daily.
- Category III: for females, 40 g or more pure alcohol; for males, 50 g or more pure alcohol.

**AF** = attributable fraction—that is, the proportion of disease under consideration that is attributable to alcohol.

† For four diseases, a combined estimate was derived for drinking categories II and III.


By far, mood and anxiety disorders are the most common mental conditions associated with alcohol. Table 6.14.3 shows the high odds of co-occurrence of anxiety disorders (two to three times more likely) and mood disorders (almost two times more likely) than non-alcoholics to suffer from a comorbid disorder.

**Table 6.14.3. Prevalence of Comorbid Mood and Anxiety disorders in individuals with alcohol abuse and alcohol dependence. Focus on Major Depressive Disorder (MDD) and Posttraumatic Stress Disorder (PTSD).**

<table>
<thead>
<tr>
<th>Comorbid Disorder</th>
<th>Alcohol Abuse</th>
<th>Alcohol Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-year rate (%)</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Any Mood Disorder</td>
<td>12.3</td>
<td>1.1</td>
</tr>
<tr>
<td>MDD</td>
<td>11.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Any Anxiety Disorder</td>
<td>29.1</td>
<td>1.7</td>
</tr>
<tr>
<td>PTSD</td>
<td>5.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Any Mood Disorder</td>
<td>8.2</td>
<td>1.2</td>
</tr>
<tr>
<td>MDD</td>
<td>8.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Any Anxiety Disorder</td>
<td>11.8</td>
<td>1.1</td>
</tr>
</tbody>
</table>

[^1]: Adopted from Kessler et al. 1997
[^3]: Odds ratio was significantly different from 1 at 0.05 level. The odds ratio relates the probability of comorbid disorder compared with people without AUD.


Even though a large amount of individuals with AUD also suffer from co-occurring Mental Health Disorders (MHD), usually both disorders are commonly treated separately. Historically, health services frequently treated co-occurring disorders as individual entities; however, such treatment is not well suited to the special needs of this group. Differences between both services in terms of clinician beliefs, training, behaviour, and ideology pose significant barriers to effectively treat co-occurring disorders. Regarding pharmacological options, AUD programs do not commonly rely on evidence-based recommended medication, slowing the adoption of pharmaocotherapeutic interventions, whereas medication are commonplace in mental health programs. In addition, neither field seems to have the proper training to tackle both diseases (AUD providers often ignore or delay MHD treatment and clinicians may not feel equipped to treat with complex co-occurring disorders, preferring to refer them out to another agency for treatment). As a result, patients with co-occurring disorders receive suboptimal treatment.[^4]

Traditional 12-step programs have shown benefit for those patients with MHD, and tailored interventions for co-occurring disorders have been growing in number, delivering positive direct and indirect effects for patients with co-occurring disorders.[^6] Even though an...
integrated care system (care for both/all disorders is provided by the same cross-trained clinicians, resulting in clinical integration of services) has delivered better outcomes to other chronic conditions, evidence is still weak for co-occurring AUD and MHD. Published literature found integrated care as predictor for improved post-treatment outcomes, higher rates of abstinent individuals at six months, compared to those receiving usual independent medical care, favourable outcomes compared with other type of services, and enhanced training to clinicians about co-occurring patients was correlated with better mental health outcomes at 18 months, compared to those who received usual mental health services. Whatever the causes, patients with co-occurring AUD and MHD have not been served well by the traditional health services configuration. More research is needed comparing different interventions and combinations of interventions. Providers and decision makers are starting to realize the high prevalence of co-occurring disorders, in fact, the majority of patients with AUD most likely have a MHD. The United States Institute of Medicine has developed recommendations for implementing quality integrated care for individuals with co-occurring disorders (See Appendix 6.14.5).

The incidence of alcohol-related brain damage is approximately 10 per cent of adult dementias in the United States, whereas milder attention and memory deficits may improve gradually with abstinence. Alcoholics are far more likely to also have a diagnosis of antisocial personality disorder, drug abuse, mania, and schizophrenia as compared with non-alcoholics. Eating disorders are also associated with alcoholism. Between 33 and 83 per cent of bulimics may have a first-degree relative suffering from alcohol abuse or alcoholism. Studies indicate that approximately 10 to 30 per cent of alcoholics have panic disorder, and about 20 per cent of persons with anxiety disorders abuse alcohol. Among alcoholics entering treatment, about two-thirds have symptoms that resemble anxiety disorders. Alcoholics are 35 times more likely than non-alcoholics to also use cocaine. Similar odds ratios for other types of drugs are: sedatives, 17.0 times; opioids, 13.0 times; hallucinogens, 12.0; stimulants, 11.0; and marijuana and related drugs, 6.0. Surveys of both clinical and nonclinical populations indicate that at least 90 per cent of alcoholics are nicotine dependent. The progression of liver fibrosis and cirrhosis in patients with alcohol problems is enhanced by the presence of hepatitis B and hepatitis C virus markers.

2.5.3 Immunomodulatory effects of alcohol

There is an increased susceptibility to infections in alcohol related diseases. As a result, infection is one of the most common causes of death in patients with ALD, especially those with AH. Malnutrition, underlying liver cirrhosis and aggressive in-hospital medical procedures all contribute to the risk of infection. ALD and liver failure may even have a component of autoimmunity, in which the immune system turns on the body’s own tissues. A number of reviews provide an overview of current knowledge concerning alcohol’s effects on the human immune system. Several important infectious diseases that are highlighted in other sections of this report are also implicated in alcohol-related immunocompromised individuals. The incidence and severity of pulmonary tuberculosis (TB) is greater in alcoholics than in non-alcoholics. For example, data from United States in 2011 showed a 12.4 per cent of TB patients as alcohol abusers; the per centage ranges up to more than 66 per cent in some regions of the country. Significantly, long-term studies of drug and alcohol abusers who were followed for many years showed that these individuals had TB incidence rates from 15 to 200 times the rates for reference populations. In recent years, the incidence
of TB has been increased by the presence of human immunodeficiency virus (HIV) in drug and alcohol abusers.\textsuperscript{57} Alcohol abusers are more susceptible than non-abusers to septicemia, urinary tract infections, bacterial peritonitis lung abscess, empyema (an accumulation of pus in the chest), spontaneous bacterial peritonitis, diphtheria, cellulitis, and meningitis\textsuperscript{58,59,60}. It is clear that the increased incidence of infectious diseases in alcohol abusers represents a significant toll of individual suffering and of medical expense to society. The risk of untreatable infections in alcohol abusers will also increase as antimicrobial resistance increases. Most importantly however, is the association of ALD with hepatitis C. About 25\% of all patients with ALD have also markers of HCV infection, even in the absence of risk factors such as intravenous drug abuse\textsuperscript{35,61}. Alcohol may favour the acquisition, replication, or persistence of the virus so ACo is clearly a risk factor for the progression of liver disease caused by HCV.\textsuperscript{62} Total lifetime ACo is a risk factor for the progression of liver disease caused by HCV.\textsuperscript{63}

2.5.4 Alcohol and its carcinogen effect

Research from the International Agency for Research on Cancer (IARC) found causal links between alcohol and cancer of the oral cavity, pharynx, larynx, esophagus, liver, colon, rectum and female breast.\textsuperscript{30} Rehm and colleagues\textsuperscript{64} found an association between greater volumes of drinking and cancer risk increase.

2.5.5 Alcohol and the elderly

AUD in elderly people are common and associated with considerable morbidity. The ageing of populations’ worldwide means that the absolute number of older people with AUD is on the increase even though the prevalence of AUD in elderly people is generally lower than in younger people.\textsuperscript{65} Rates, however, may be underestimated because of under-detection and misdiagnosis. Age related changes in body composition means that equivalent amounts of alcohol produce higher blood alcohol concentrations in older people.\textsuperscript{66} Even so, elderly people have been shown to be at least as likely to benefit from treatment as younger people.\textsuperscript{67} AUD in elderly people may prove to be a silent epidemic, as media attention and public health initiatives related to AUD tend to focus almost exclusively on younger populations.\textsuperscript{68,69}

2.5.6 Alcohol and women

There is marked regional variability in the extent of gender differences with regard to alcohol-related morbidity and mortality. Female alcohol-attributable mortality ranges from a negative value (more deaths prevented than caused) in established market economies of Western Europe, North America and the Western Pacific regions to more than 5\% of all female deaths being attributable to alcohol in the former socialist countries of Eastern Europe around Russia.\textsuperscript{70} The differences among regions reflect the differences in the overall relationship between average volume of ACo and mortality generally. For DALY burdens, males have a far greater alcohol related DALY burden than females (Figure 6.14.6).

Meta-analysis of case control studies have found that women who drank three or more alcoholic beverages per day (or 40 grams of alcohol, with about 13 grams in a standard drink) had a 69 per cent higher risk of getting breast cancer compared with nondrinkers.\textsuperscript{71} In terms of consumption-risk, each additional 10 g of pure alcohol per day was associated with
an increase of 7% relative risk of breast cancer, whereas regular consumption of approximately 50 g of pure alcohol increases the relative risk of colorectal cancer by 10–20%, indicating that the association is stronger for female breast cancer. In addition, a range of one to six drinks per day results in a linear relationship between alcohol and breast cancer.

Controversy remains over the interpretation of these studies as the effect is modest in magnitude and is not restricted to one type of alcoholic beverage. The risk is most pronounced at high intakes of alcohol. Increased exposure to estrogens and androgens with ACo is one plausible—but unconfirmed—biological mechanism to explain alcohol’s effect on breast cancer risk.\textsuperscript{71,72}

For any given level of alcohol intake, women have an increased susceptibility to ALD\textsuperscript{71,73} (Table 6.14.4). However, the threshold of alcohol necessary for the development of advanced ALD varies substantially among individuals, and factors other than absolute ACo clearly have an important role in determining who will develop ALD and who will not. These observations highlight the role of genetic factors that may predispose specific persons to greater propensity toward alcohol-induced liver toxicity.

**Table 6.14.4. Relative Risk of Alcoholic Liver Disease at Different Levels of Alcohol Intake**

<table>
<thead>
<tr>
<th>Weekly units* of alcohol intake</th>
<th>Alcoholic cirrhosis</th>
<th>Alcohol liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>&lt;1</td>
<td>3.7</td>
<td>1.09</td>
</tr>
<tr>
<td>1–6</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>7–13</td>
<td>0.9</td>
<td>4.1↑</td>
</tr>
<tr>
<td>14–27</td>
<td>1.6</td>
<td>3.1↑</td>
</tr>
<tr>
<td>28–41</td>
<td>7.0↑</td>
<td>16.8↑</td>
</tr>
<tr>
<td>42–69</td>
<td>13.0↑</td>
<td>NR</td>
</tr>
<tr>
<td>≥70</td>
<td>18.1↑</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Unit represents 10 to 12 g of alcohol (12 oz of beer, 4 oz of wine, 1 oz of spirits).
†Represents a statistically significant increased relative risk of having alcoholic liver disease. NR = not reported.
Reprinted with permission from McCullough.\textsuperscript{8}


The mechanisms for the differential impact of alcohol on heart disease and mortality and on neurological function in women and men are also still unclear. There remain possibilities at every level of alcohol processing: its metabolism by enzymes (lower concentrations of alcohol-metabolizing enzymes in women’s gastrointestinal tracts), lower content in body water compared with men of similar body weight, leading to higher blood alcohol concentrations\textsuperscript{74}, its absorption into the bloodstream, and its actions on the physiology of end
organs—that might explain mechanisms that could contribute to gender related differences in the health consequences of drinking.\textsuperscript{75} Adverse effects have been observed at levels of consumption that many would regard as low—between seven to 13 drinks per week.\textsuperscript{76} Even though definitive evidence about the pathophysiology of gender differences over ACo is still lacking, it’s important to recognize the higher health risk through ACo among women, compared to men (73).\textsuperscript{74}

2.5.7 Alcohol and genetics

Published evidence has identified genetic factors associated with AUD risk, and researchers have sought to identify the genes involved since the relationship was displayed. However, AUD complexity has slowed progress in identifying these genes. Thus, existing data suggest that each individual genetic element has only a small influence and that it will be necessary to identify the relevant gene networks to gain a greater understanding of the contribution of genetics to AUD.\textsuperscript{31}

The overall genetic contribution to AUD has been historically tested by comparing the concordance among identical (i.e. monozygotic) and fraternal (i.e. dizygotic) twins. As expected, studies have shown higher concordance rates among monozygotic twins, confirming the presence of a genetic component in the risk for AUD. Another approach involved within-family studies to estimate the overall similarity among family members sharing differing proportions of their genome (e.g., comparing sons with fathers or grandfathers). For example, Tsuang and colleagues found that sons of alcohol-dependent fathers tend to be more tolerant to alcohol and to have fewer hangovers, a fact which renders alcohol more pleasurable to them.\textsuperscript{77} Both approaches provided convergent evidence that genetic factors account for 50 to 60 per cent of the total variance in the risk for AUD.\textsuperscript{31}

Latest developments of techniques to study the human genome have resulted in widespread use of genome-wide association research for AUD. Genome-wide association studies now offer a host of emerging opportunities, as well as challenges, for discovering the genetic aetiology of AUD and for unveiling new treatment strategies. The key findings of these earlier studies show that variations (i.e. polymorphisms) in the DNA sequences of the genes encoding alcohol dehydrogenase 1B, aldehyde dehydrogenase 2, and other alcohol-metabolizing enzymes mediate the risk for alcoholism; furthermore, these polymorphisms also have an impact on the risk of alcohol-related cancers, such as oesophageal cancer. In addition, a gene encoding one of the receptors for GABA known as GABRA2 seems to have a role in the development of AUD.\textsuperscript{31} In summary, genetic variations in many of the genes encoding alcohol-metabolizing enzymes contribute to differences in alcohol intake and, thus, the risk for development of AUD. The frequency of these genetic variants differs dramatically across human populations of Asian, African, and European ancestry.

2.5.8 AUD diagnosis and biochemical markers

The major clinical assessment necessary for diagnosing ALD is determining whether the patient is abusing alcohol, but this is not always easy. Unfortunately, there is still no satisfactory laboratory marker with higher diagnostic sensitivity compared to the clinical history.\textsuperscript{78} Alcoholic patients and even their family members often minimize or conceal alcohol use. Because of the inherent difficulties in obtaining a reliable history of alcohol use, various biochemical markers have been evaluated for their ability to detect surreptitious
alcohol abuse. A comprehensive marker for AUD has not been identified although a series of successful markers exist for determining drinking status. Several biochemical and hematological tests, such as γ-glutamyltransferase (GGT) activity, aspartate aminotransferase (AST) activity, high-density lipoprotein cholesterol (HDL-C) content of serum, and erythrocyte mean corpuscular volume (MCV) are established markers of alcohol intake. Many conventional tests have only limited sensitivity when used singly.

Although hepatitis C virus (HCV) is a leading risk factor for liver fibrosis, there is no standard laboratory serum analyses, imaging tests or virologic assays that currently can distinguish those with hepatitis C, or any other condition, who are at risk for progressive fibrosis. Thus, increasing numbers of patients will require assessment of fibrosis, exposing them to the potential risks, inconvenience and cost of liver biopsy and its interpretation. If a non-invasive assay were developed that reliably excludes the possibility of significant fibrosis, then such patients may not require treatment with antiviral therapies, and, moreover, could be followed regularly to confirm lack of fibrosis progression. Increasing evidence that advanced fibrosis may be reversible, such that more frequent and refined analysis may render even severe disease amenable to therapy. The expectation that as antifibrotic therapies are developed, there will be a need for early and regular monitoring of response in order to establish effectiveness and optimize dosing.

3. What is the Control Strategy?

3.1 Alcohol policy

Five main policies has been generally described in the literature to tackle alcohol harm and abuse: (a) drinking and driving reduction; (b) education, communication, training and public awareness; (c) alcohol market regulation; (d) reduction of harm in drinking and surrounding environments; (e) interventions for individuals. Limited evidence describes the effectiveness among these approaches though. For example, drinking driving policies have proven to be highly effective (however, limited evidence did not find an impact from parallel interventions such as designated driver and safe drive programs), while education and public awareness have shown non-significant effects to effectively decrease ACo.

The regulation of the alcohol market has been identified as a highly effective policy to reduce alcohol abuse. Published literature by economists and others support that increases in monetary prices (e.g. raising taxes) could have long-term effectiveness for reducing alcohol abuse and its social, health, and economic consequences. Several reviews published between 2002 and 2010 confirm an inverse relationship between alcohol prices and the demand for ACo. Moreover, WHO models showed dramatic effects over country income and decreased mortality (2003 estimates reported that a 10 per cent tax raise in EU15 countries would prevent 9 000 deaths during the following year and approximately 13 billion additional euros excise duty would be gained). Such effective intervention however, has not received enough attention in some countries. For example, the United States have increased federal taxes rates on wine and beer only once since 1951, and twice on distilled spirits. Consequently, the real tax rates (inflation-adjusted values) have systematically declined over the years, as Figure 6.14.8 illustrates. In terms of the EU, taxation has been identified as a
constant feature of European countries; however, the variability of enforcement and the lack of standardized excise duties have proven to be two of the main challenges to tackle. In terms of strictness, if different policy areas are combined into a single scale, 2003 data showed variation from 5.5 (Greece) to 17.7 (Norway) out of a possible maximum of 20, with an average of 10.8.7

Figure 6.14.8. Average real United States Federal excise taxes (in dollars per barrel) on alcoholic beverages (1951-2009)

In terms of large differences in tax rates between nearby countries, low-tax countries receive additional income as they become more attractive for shopping demands, resulting in lost revenue for high-tax governments. Moreover, some alcoholic drinks (e.g., wine) received 1.5 billion euros in subsidies through the common agricultural policy. In consequence, the public health perspective is still not a priority, compared to commercial and economic interests.7

Advertisement monitoring (restricting volume and content) may be an effective tool to decrease alcohol harm. WHO models measuring the impact on advertisement ban found an estimated 202 000 years of disability and premature death avoided in the EU if such regulatory scheme would be enforced.7

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If a comprehensive EU wide package of preventive measures would be enforced (including effective policies such as random breath testing, taxation, restricted access, advertising ban and brief physician advice). Published literature in 2004 estimated that it would avoid 1.4 million years of disability and premature death a year.7

Increased prices of alcoholic beverages have positive effects preventing a number of adverse consequences resulting from alcohol abuse. For example, Cook and colleagues found that increases in beer taxes and price significantly reduced fatal motor-vehicle crash rates.81 In addition, Sloan and colleagues reported that increases in alcohol prices were associated with a decline of homicide deaths. On the contrary, declining alcohol prices in England and Wales correlated with substantial increases in violence/related injury and trauma services.84 Other studies found a link between sexually transmitted diseases and alcohol price. For example, Canada’s higher taxes on beer and spirits significantly reduced the prevalence of gonorrhea and syphilis between 1981 and 2001 in Canada.81

3.2 Remediation of Alcohol Use Disorders (AUD)

Remediation of AUD has been the primary control strategy but it remains a great challenge for many reasons. Currently, the following strategies are used to control the disease progression:

Behavioral treatment and pharmacological options are commonly used to deal with AUD. Psychotherapies (cognitive behavioral treatment, motivational enhancement therapy, community reinforcement, and 12-step facilitation) are by far the most common approaches to deal with AUD. However, their true effectiveness remains controversial. For example, Dawson and colleagues found three-quarters of people with AUD reduce or stop drinking without any kind of professional treatment or even interaction with a community support group9, and project MATCH showed that psychotherapies offer very similar endpoints, even though their conceptual frameworks were quite different.9

In terms of pharmaceutical options, the United States FDA and the European Medicines Agency (EMA) have approved four medications for AUD: Disulfiram (Antabuse®), oral naltrexone, extended release naltrexone (Vivitrol®), and acamprosate (Campral®). Off-label utilization of medicines originally approved to treat other maladies different than AUD are being studied, For example, Topiramate (a medication used to treat epilepsy and migraine), has demonstrated efficacy in two clinical trials of AD.85 Calcium channel blockers86, dopaminergic agents86, serotonin antagonists87, serotonin uptake inhibitors87, and GABA-altering drugs88 have also been used. The current medication options block the cascade of AUD in different stages of the disease, as Figure 6.14.9 illustrates.
3.2.1 Disulfiram (Antabuse):

An inhibitor of acetaldehyde dehydrogenase has been used for many years in the management of alcohol-dependent patients. It induces an adverse reaction to alcohol intake characterized by nausea. Supervised administration of the medicine by a significant other or health care provider is key to guarantee treatment effectiveness. So far, controlled clinical trials have yielded inconsistent results about its therapeutic benefit. However, the main reason of ambiguous results may relate to the fact that the psychological deterrent effect of the medication rather than its biological effect is useful, hence, it’s difficult to demonstrate that effect in a classical double blind, placebo-controlled trial. Although disulfiram is potentially useful in the early stages of AD, it’s not useful as a long-term therapy.

3.2.2 Oral naltrexone:

It has been approved by the FDA as an adjunct to psychosocial treatment for alcoholism. Naltrexone is an opiate antagonist that primarily blocks u-receptors at the standard dose of 50 mg daily by reducing the positive-reinforcing pleasurable effects of alcohol and to reduce craving. Efficacy studies shown a reduction of number of drinks consumed and heavy drinking days. A meta-analysis found evidence of modest efficacy over three months on preventing relapse to heavy drinking, medication discontinuation, and return to any drinking. First results seem to suggest that only high-compliant subjects will have beneficial effects, and hepatic toxicity may be a concern. Table 6.14.5 summarizes most of the clinical
placebo-controlled trials, including the ones that were the basis for the approval of the drug in the United States.

Several studies from Table 6.14.5 also measured relapse into heavy drinking in terms of patients percentage. Figure 6.14.10 illustrates those results.

**Figure 6.14.10. Relapse into heavy drinking placebo versus naltrexone (percentage of patients)**

![Figure showing relapse rates](http://adisonline.com/cnsdrugs/Fulltext/2004/18080/Pharmacotherapy_of_Alcohol_Dependence___A_Rview_of_2.aspx)

Table 6.14.5. Published placebo-controlled clinical trials of naltrexone 50 mg/day in alcohol dependence

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>No. patients</th>
<th>Duration (months)</th>
<th>Outcome Measure</th>
<th>Result(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal et al.(^a)</td>
<td>2001</td>
<td>US</td>
<td>627</td>
<td>3 or 12</td>
<td>TFR</td>
<td>No effect</td>
</tr>
<tr>
<td>Gastpar et al.(^a)</td>
<td>2002</td>
<td>Germany</td>
<td>342</td>
<td>3</td>
<td>TFR</td>
<td>No effect</td>
</tr>
<tr>
<td>Guardia et al.(^a)</td>
<td>2002</td>
<td>Spain</td>
<td>202</td>
<td>3</td>
<td>TFR</td>
<td>Increased</td>
</tr>
<tr>
<td>Kranzler et al.(^a)</td>
<td>2000</td>
<td>US</td>
<td>183</td>
<td>3</td>
<td>TFR, TFD</td>
<td>No effect</td>
</tr>
<tr>
<td>Chick et al.(^a)</td>
<td>2000</td>
<td>UK</td>
<td>169</td>
<td>3</td>
<td>TFR</td>
<td>No effect</td>
</tr>
<tr>
<td>Anton et al.(^a)</td>
<td>1999</td>
<td>US</td>
<td>131</td>
<td>3</td>
<td>TFR, %DA, DDD</td>
<td>Increased Decreased</td>
</tr>
<tr>
<td>Heinala et al.(^a)</td>
<td>2001</td>
<td>Finland</td>
<td>121</td>
<td>3</td>
<td>%RHD</td>
<td>Reduced (CS group) No effect (ST group)</td>
</tr>
<tr>
<td>Baldin et al.(^a)</td>
<td>2003</td>
<td>Sweden</td>
<td>118</td>
<td>6</td>
<td>%HDD</td>
<td>Reduced (CS group)</td>
</tr>
<tr>
<td>Monti et al.(^a)</td>
<td>1999</td>
<td>US</td>
<td>116</td>
<td>3</td>
<td>HDD, DDD</td>
<td>(Decreased)(^c) (Decreased)(^c) No effect (ST group)</td>
</tr>
<tr>
<td>Morris et al.(^a)</td>
<td>2001</td>
<td>Australia</td>
<td>111</td>
<td>3</td>
<td>TFD, TFR</td>
<td>No effect Increased</td>
</tr>
<tr>
<td>Latt et al.(^a)</td>
<td>2002</td>
<td>Australia</td>
<td>107</td>
<td>3</td>
<td>%RHD, TFR</td>
<td>Decrease Increased</td>
</tr>
<tr>
<td>O'Malley et al.(^a)</td>
<td>1992</td>
<td>US</td>
<td>97</td>
<td>3</td>
<td>TFR</td>
<td>Increased (CS group) Increased (ST group)</td>
</tr>
<tr>
<td>Volpicelli et al.(^a)</td>
<td>1997</td>
<td>US</td>
<td>97</td>
<td>3</td>
<td>TFR</td>
<td>Increased in compliant patients</td>
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<tr>
<td>Volpicelli et al.(^a)</td>
<td>1992</td>
<td>US</td>
<td>70</td>
<td>3</td>
<td>TFR</td>
<td>Increased</td>
</tr>
<tr>
<td>Hersh et al.(^a)</td>
<td>1998(^d)</td>
<td>US</td>
<td>64</td>
<td>2</td>
<td>TFD</td>
<td>No effect</td>
</tr>
<tr>
<td>Oslin et al.(^a)</td>
<td>1997</td>
<td>US</td>
<td>44</td>
<td>3</td>
<td>%RHD</td>
<td>No change</td>
</tr>
<tr>
<td>Kranzler et al.(^a)</td>
<td>1998(^e)</td>
<td>US</td>
<td>20</td>
<td>2</td>
<td>%HDD</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

a Studies are ranked by size.
b The results of the studies are only identified as ‘increased’ or ‘decreased’ when the inter-group difference was statistically significant at the level of 0.05.
c Positive results were only obtained in this study once the 40 noncompliant patients were excluded from the analysis.
d This study was performed in patients with concomitant alcohol and substance abuse.
e This study used an injectable sustained-release preparation of naltrexone.
CS = coping skills training; DDD = drinks per drinking day; HDD = heavy drinking days; ST = supportive therapy; TFD = time to first drink; TFR = time to first relapse; %DA = % days abstinent; %HDD = % heavy drinking days; %RHD = % patients relapsing to heavy drinking.

3.2.3 Extended-release naltrexone (monthly injection):
This therapy may decrease non-adherence compared to the oral version. Naltrexone was significantly more effective in reducing heavy drinking rate, compared to placebo (84). Naltrexone’s main side effects include nausea, headache and dizziness.

3.2.4 Acamprosate:
Acamprosate was approved in the United States in 2004, following extensive use in many European countries. The medicine has been used in Europe for almost 20 years and has consistently been found to be significantly better than placebo in reducing both drinking frequency and cumulative drinking days. Kranzler and Gage found that acamprosate improved rates of continuous abstinence, per cent days abstinence, and time to first drink. A meta-analysis identified acamprosate as an effective and safe treatment strategy for supporting continuous abstinence after detoxification in alcohol dependent individuals. Acamprosate appears to normalize the balance between excitatory and inhibitory pathways altered by chronic alcohol consumption (Figure 6.14.1). However, the actual mechanism is still uncertain. However, published literature suggests that acamprosate depresses the elevated glutamatergic transmission and NMDA receptor activation that occur in AD and withdrawal. Side effects from the medication are most common on the gastrointestinal level. Table 6 summarizes high quality RCTs done in the last 20 years. The majority of these studies produced consistent results showing acamprosate treatment to be superior to placebo in maintaining abstinence.

Figure 6.14.11 illustrates results from comparing the effect of acamprosate versus placebo in terms of continuous abstinence. Most of the studies reported a significant effect of acamprosate over placebo; however, 31% of the studies did not find differences between groups in terms of the outcome of interest. In light of the extensive research into the neurochemical basis for alcohol addiction, it is curious that more approved interventions are not available. Perhaps this is because alcohol-seeking behaviour is complex and involves several neurotransmitter systems, which supports the switch to a range of medications instead of current monotherapies. However, research is still in early stages to empirically prove the adequacy of polytherapy protocols.
### 3.3 Alcoholic Liver Disease (ALD)

By the time of the study update, there are no FDA approved therapies for ALD, however, lifestyle changes, nutritional support, and off label therapies (such as pentoxifylline) may improve outcomes. In terms of policy options, increased prices of alcoholic beverages have been associated with lower rates of liver cirrhosis mortality.

Published evidence found that a 10 per cent increase in prices would lead to 8.3 to 12.8 per cent reductions in the cirrhosis mortality rate.\(^{120}\) Progress has been made to better understand the pathogenesis of the disease (described above), and the findings also provide possible mechanisms for developing therapeutics for ALD.\(^{10}\)

However, highly effective ALD treatment options remains to be developed. Historically, clinical trials have targeted different components of the pathogenesis of ALD (inflammation, increased metabolism, oxidative stress, and nutrition abnormalities). However, a 2006 systematic review of the available therapies found little if any substantial improvement to tackle the disease.\(^{121}\) (See Appendix 6.14.2 for additional details about ALD pathogenesis.)
Cessation or a marked reduction in alcohol intake has been shown to improve the survival of patients with all stages of ALD.\textsuperscript{122,123} Thus, measures to establish and maintain abstinence are a critical component of the management of patients with ALD. As an alternative, or preferably as an addition, to psychological therapies, some patients may derive benefit from pharmacological therapy. Some patients with AH can progress to cirrhosis even with abstention\textsuperscript{123}, and patients with coexisting AH and cirrhosis have a worse long-term survival than patients with cirrhosis only.\textsuperscript{124} This suggests the need for longer-term treatment trials in patients with AH.

**Figure 6.14.11: Continuous abstinence (per cent) between acamprosate and placebo**

![Continuous abstinence chart]

**Source:** Modified from Pharmacotherapy of Alcohol Dependence: A Review of the Clini... : CNS Drugs [Internet]. Available at http://adisonline.com/cnsdrugs/Fulltext/2004/18080/Pharmacotherapy_of_Alcohol_Dependence__A_Review_of_2.aspx\textsuperscript{89}

Proportion of alcohol-dependent patients remaining continually abstinent in published randomised clinical trials of acamprosate 1998 mg/day in which this variable was measured. The proportion of patients remaining continually abstinent was a primary endpoint in the studies of Chick et al, Paille et al., Tempesta et al, Barrias et al., Sass et al., Geerlings et al., Poldrugo, Pelc et al., Rousseaux et al., Besson et al., Pelc et al., Lhuintre et al. and Ladewig et al. Patient numbers for each study are shown in table II. NS= nonsignificant; *indicates p < 0.05 versus placebo.
In terms of corticosteroids, more than 12 RCTs and meta-analyses on this topic have not been enough to reach a consensus regarding its use.\textsuperscript{125,126} The rationale for steroid use is to decrease the immune and the proinflammatory cytokine response.\textsuperscript{10} Although several similarly designed, well-conducted studies showed that corticosteroids reduced mortality in patients with AH\textsuperscript{127}, a large study failed to show a survival benefit of corticosteroids in patients with moderate and severe AH.\textsuperscript{128} Thus, the efficacy of corticosteroids is controversial. Two potential side effects of steroids used in medium/high dose include poor wound healing and increased susceptibility to infection. This highlights the need for alternative therapies for AH.

### 3.3.1 Oxidative stress and hepatocyte membrane injury

There is some evidence implicating oxidative stress as a key mechanism in alcohol-mediated hepatotoxicity. Reactive oxygen containing species are the superoxide anion, hydrogen peroxide and hydroxyl and hydroxyethyl radicals, the latter arising during ethanol metabolism.\textsuperscript{129} Several recent trials using antioxidant supplementation in AH have shown no survival benefit. Specifically, to reduce hepatic oxygen consumption, investigators have examined the role of propylthiouracil in patients with AH. A 2011 meta-analysis combining the results of six randomized clinical trials demonstrated no significant effects of propylthiouracil versus placebo on all-cause mortality, liver related mortality, or complications of ALD. Occasional serious adverse effects such as leukopenia and generalized bullous eruption were reported.\textsuperscript{53}

Another compound investigated because of its inflammatory properties is pentoxifyline. The first randomized controlled trial of pentoxifyline was reported in 2000 in AH and led to a 40\% reduction in mortality compared to placebo.\textsuperscript{130} A 2009 meta-analysis of five trials found that pentoxifyline reduced mortality compared with control. However, the result was not supported by trial sequential analysis, which adjusts for multiple testing on accumulating data. Moreover, four of the five trials had high risk of bias, risking an overestimated intervention effect. The study concludes that pentoxifyline may have a positive effect on all-cause mortality and due to hepatorenal syndrome. No concussions could be reached about AH and ALD.\textsuperscript{131}

### 3.3.2 Extracorporeal Liver Support (ELS).

A further experimental therapy that may benefit patients with liver failure is ELS. Currently, two detoxification devices are available for clinical use: albumin dialysis (AD, MARS) and fractionated plasma separation (FPS, Prometheus). Albumin dialysis’ primary aim is to support impaired liver function while the liver recovers or the patient undergoes liver transplantation. Both procedures have the ability to remove water-solved and albumin-bound toxins, which contribute to the liver failure’s pathogenesis.\textsuperscript{132} Krisper and colleagues found that FPS achieved significantly higher clearance for all markers, compared to AD,MARS; and unconjugated bilirubin (strongly correlated to albumin-bound toxins) was influenced only by FPS. The previous study however, compared only the technical effectiveness of the two devices, warranting for additional research to be focus on clinical outcomes, treatment intensity, different patient groups, and treatment dose. Both techniques must still be considered experimental. Larger ongoing trials are needed to corroborate increased patient survival.\textsuperscript{132}
3.4 Alcoholic Cirrhosis (AC)

Current treatments for cirrhosis are severely limited. One can remove underlying injurious stimulus (where possible); eradicate existing viruses using interferon in viral hepatitis; and transplant the liver. Short-term viral eradication could lower risk of hepatic decompensating in up to 40 to 70 per cent of patients with HCV genotypes 1, 2 or 3. The high mortality of severe AH is coupled with the relatively young age of many of the patients and this makes it an important area for therapeutic trials. However, the vast majority of patients with ALD in clinical practice have advanced fibrosis or cirrhosis. Patients with AC must abstain, since continued AC leads to hepatitis, driving to hepatic fibrogenesis and decompensation. Unfortunately, as with AH, no adjunctive pharmacotherapies have been consistently shown to improve survival in more than one randomized controlled trial, although some have shown promise.

3.4.1 Antioxidants

Human trials have evaluated the pharmaceutical product silymarin, which is the active component of the herb milk-thistle and has potent antioxidant properties. Results are conflicting.

Evaluation of S-adenosyl-L-methionine (SAMe) acts as both an antioxidant and maintains cell membrane fluidity. It has been evaluated in patients with alcoholic cirrhosis. Using death or liver transplantation as a combined end-point, there was a significant beneficial effect of SAMe treatment in patients with cirrhosis. SAMe participates in the synthesis of glutonate, the main cellular antioxidant, behaving as a methyl donor. Animal experiments have associated alcohol consumption with impaired methionate conservation, therefore, methionine supplementation has been proposed to treat ALD. However, a review of thirteen randomized clinical trials reported no beneficial effects of milk thistle for patients with ALD, highlighting the lack of high-quality evidence to support the intervention. Data from 1992 suggested that 11 to 12 per cent of European hospital-based specialists in gastroenterology/hepatology used sometimes SAMe for AH and cirrhosis. In addition, a review of nine randomized clinical trials could not find evidence supporting or refuting the use of SAMe for individuals suffering from ALD. The study however, warranted for long-term, high quality randomized trials to determine its efficacy.

3.4.2 Propylthiouracil (PTU)

This compound may improve the long-term survival of patients with AC. There has, however, been only one trial reported thus far. Fifteen per cent of European hospital-based specialists in gastroenterology/hepatology considered PTU to treat AH. However, evidence seem to suggest against its utilization for ALD problems. A systematic review from six clinical trials reported no significant effects of PTU versus placebo on all-cause mortality, liver related mortality, or complications of the liver disease among patients with ALD. Severe adverse events were also reported.
3.4.3 Colchicine

This anti-inflammatory drug has been evaluated in the treatment of patients with alcohol and non-alcohol-related cirrhosis because of its anti-fibrotic effects. To date, clinical results have been conflicting. However, latest meta-analysis reported that colchicine should not be used for alcoholic, viral, or cryptogenic liver fibrosis or liver cirrhosis (no significant effects of colchicine versus placebo/no intervention on 15 randomized clinical trials).

3.4.4 Anabolic-androgenic steroids (AAS)

Between 5 and 43 per cent of European hospital-based specialists in gastroenterology/hepatology (depending on the region) considered AAS as a valid therapy to treat ALD (135). The latest published evidence could not demonstrate however, any significant beneficial effect of anabolic-androgenic steroids on mortality, liver complications, and histology among ALD patients.

3.5 Transplantation

ALD is currently the second most common indication for liver transplantation in Europe and the United States. It accounts for approximately 17 to 25 per cent of all transplants performed in the United States and Europe. Figure 12 shows the increased rates of ALD from 1968 through 2008 as indication for liver transplantation in Europe. Transplantation is a highly successful treatment, particularly for end stage cirrhosis, with a 81-84 per cent (one year survival rate) and 72 to 66 per cent (five year survival rate) if recipients remain alcohol-free in the post-transplant period. Without transplantation, five year survival is as low as 23 per cent. However, limited availability of organs, growing lists of patients needing a transplant, cost, issues of compatibility, and comorbid factors mean that not everyone is eligible for transplantation.

At present, most transplant centers require patients to have six months of abstinence and appropriate addiction treatment before they can undergo liver transplantation. Patients with active AH are not candidates for liver transplantation because of their lack of demonstrated abstinence and high perioperative mortality.

Data from 2007 in the United States reported that less than four per cent of patients with alcohol-induced cirrhosis were listed for liver transplantation, even though published evidence have found that ALD patients have similar, if not better survival than those who undergo transplantation because of non-alcohol-induced liver disease. Most studies suggest that alcohol relapse after transplantation occurs in 15% to 30% of patients.

Organ shortage is a major problem and the decision to be an organ donor remains voluntary in most European countries. A recent UK study demonstrated that, when compared to other patient groups, the general public, primary care physicians and even gastroenterologists, all place patients with ALD well down their list of patients most deserving a liver transplant. The perception that patients with ALD have played a significant role in their disease and the widely held belief that, ‘once a drinker always a drinker’ seems likely to be the most important factors contributing to this negative view of ALD patients. Transplantation for ALD remains a complex issue.
Overall, the best treatment outcomes from ALD are linked with two patients’ characteristics:
a) lower cumulative doses of alcohol consumption b) long-term abstinence from alcohol.

Figure 6.14.12. Evolution in the indication for orthotopic liver transplantation in European Liver Transplant Registry (2008), alcoholic liver disease is the second common indication after viral cirrhosis.


4. What is known of the Economic Burden, Feasibility, and Sustainability of the Control Strategy?

4.1 Economic burden

Alcohol significantly affects the lives of many people in Europe through profits from alcohol production and trade as well as employment, salaries or other revenues to distillery and brewery workers, to wine farmers, to waiters and shopkeepers, and to producers of raw materials and other equipment to the alcohol industry and trade. For instance, it has been estimated that in 1990 the production and trade of alcoholic beverages provided directly or indirectly employment to nearly three million people or to about 2.0 per cent of the civilian employment in the 12 member states of the European Communities (EC).26 In 1992, the top six alcohol exporting countries were France, the United Kingdom, Italy, Germany, Spain and the Netherlands.26 ACo is also socially and culturally deeply embedded in the daily lives of most Europeans. However, published literature argue that social and economic burdens resulting from the effects of ACo on the individual, family, work and society outweighs commercial benefits. For example, 2003 data estimated the total tangible cost of alcohol to EU society to be 125 billion euros (equivalent to 1.3 per cent GDP), whereas the intangible cost (value place on pain, suffering, and lost life due to social and health harms caused by alcohol) were estimated to be between 150 and 760 billion euros. Even though these estimates seem large, different areas of human life could not be considered, suggesting that the true cost may be even higher.7 In terms of mortality and morbidity, EU data from 2004
estimated that over 7000 deaths and 200 000 DALYs were caused by harm to others attributable to ACo.30

The precise estimation of the cost of alcohol abuse and its medical and social consequences remains the subject of methodological debate, as the many costs related to alcohol abuse and ALD cannot be measured directly. Indirect costs of liver disease, namely economic loss as a result of premature death, illness, and disability associated with liver disease, are substantial, as liver disease tends to affect people in their most productive phase of life. It has been calculated that the cost of alcoholism in Europe, in terms of lost production and cost of medical services, represents between 2 to 6 per cent of Gross National Product, depending on the country.28 In addition, the economic costs of alcohol-attributable crime in 2003 add up to 33 billion euros.7 In the United States, the total economic burden (direct and indirect costs) imposed by alcohol abuse as a proportion of total health care expenditure is a remarkable 16.6 per cent.142 In terms of ALD, lack of effective treatment to date further increases the disease burden with an estimated total cost reaching 3.8 billion US dollars per annum.35

In terms of treatment options, the approved pharmacotherapy options suggest benefits based on cost-effectiveness analysis. For example, Schadlich and colleagues found that acamprosate therapy led to net savings and improved the patient’s state of health under the German healthcare system.143

In terms of disulfiram, the medication is relatively inexpensive; however, recent guidelines suggest its administration under supervision of a healthcare professional, adding to the cost of the medication itself. In addition, all patients receiving disulfiram require routine laboratory monitoring adding the final cost of the treatment.144 In terms of naltrexone, even though the medication may cost more per dose than disulfiram, it is associated with less need for supervised administration because of less serious side effects; however, high compliance is needed to guarantee the treatment’s effectiveness. A longer-acting dosage form of the drug is currently under investigation to enhance compliance.144

### 4.2 Feasibility and sustainability

Detoxification, with or without pharmacotherapy, is the first step of treatment. The major behavioral approaches currently used in alcoholism treatment include cognitive-behavioral therapy, motivational enhancement therapy, and Alcoholics Anonymous (AA) or related 12-step programs.9 Published literature has compared the effectiveness of these approaches. And most of the evidence did not detect significant differences among the three treatments in patient outcome, although certain treatment methodologies may be most appropriate for patients with certain characteristics.9 Historically, pharmacotherapy with aversive or anti-craving medications has been used as supplement to behavioral treatment approaches.

A wide spectrum of interventions was proven to be effective for decreasing ACo. For example, minimum drinking age, zero tolerance laws, decreasing the availability of alcoholic beverages are inversely related with alcohol abuse among youth and younger adults, by increasing the expected time and legal costs of alcohol use.81 Most countries in the world have at least one of these interventions operating; however, keeping them through time has proven to be difficult and costly. We need more research to better understand the cost effectiveness of such interventions.
The overall picture of alcohol as causing considerable global burden of disease will continue going forward, if the current levels and patterns of ACo remain stable. A definitive “cure” of AUD is not yet possible. Intensive basic and applied research into the genetic, metabolic, and behavioural mechanisms involved need to be better understood (Figure 1).

We also need to improve the quality of care of AUD, which remains low. McGlynn and colleagues found that across the United States, only 11 per cent of individuals suffering from AD had received guideline-recommended therapy. Prevention requires concerted effort with regard to diet, lifestyle, diagnosis, costs and access.

The economic role of the alcoholic drinks industry is considerable. For example, alcohol excise duties in the EU-15 countries amounted to 25 billion euros in 2001. In addition, the number of jobs supported is significant. Even though more research is required to measure the impact of decreasing ACo and job losses, current evidence suggest that declining consumption may not necessarily lead to job losses.

5. Why Does the Disease Burden Persist?

The burden persists for the following reasons:

1. The difficulty in changing large-scale alcohol consumption patterns: Cultural and historic trends of ACo can predict AUD; hence, the incidence and prevalence of AUD in certain regions of the world remain a complex problem to solve.

2. The lack of effective therapies: Pharmacotherapy remains at best a “supportive” option to treat AUD and ALD. The exact pathogenesis of both disorders continues to be a work in progress for scientists and may be a factor for the current low efficacy of the current medications options available.

3. The high rates of alcohol beverages availability: Overall volume of drinking plays a major role in the extent of alcohol problems, both at individual and at population levels. It may be possible to imagine a population with a net gain in health from drinking – a population with a low per capita consumption, with alcohol consumed frequently but only in small amounts – but no such national population has been identified in the real world. On the basis of patterns of consumption in real national populations, an increase in the volume of drinking will result in net losses in terms of years of life lost to death and disability.

4. The effectiveness of prevention interventions is low: By and large, targeted policy options have been more successful when dealing with vulnerable populations (e.g. young people). For example, universal interventions and multi-component prevention programs have shown to be effective among adolescents, however, such interventions aimed to different age groups (such as adults and the elderly) are much more difficult to implement and their short-term effects tend to disappear once the intervention ends. Some evidence suggests that family-based interventions may have small, but persistent and consistent medium and long/term prevention effects.
5. The globalization of the alcohol industry: Producers have an immense power to influence policies at the country level in order to protect their commercial interests, which are frequently in conflict with public health priorities. On the other hand, civil society is not organized enough to act as counterweight to the industry. Civil society has lessons to learn from advocacy groups such as activists against tobacco, and become a stronger public health voice.

6. Physicians and individuals do not consider AUD as a medical condition, hence, a medical treatment is not perceived as a priority. Attitudes changes about the disease are necessary to increase the utilization of current therapies. In addition, the involvement of physicians in the management of AUD is critical to increase the pharmacologic treatment.⁹¹

6. What can be learnt from past/current research into pharmaceutical interventions for this Condition?

6.1 Alcohol Use Disorders (AUD)

Advances in neurobiology support the development of medications to treat alcoholism by modifying the activity of specific chemical messengers (i.e. neurotransmitters) in the brain. These include opioid antagonists, specific glutamate antagonists, selective serotonin reuptake inhibitors and dopamine antagonists, 5-HT₃ receptor antagonists.⁸⁹

The practical effectiveness of these compounds and any pharmacological intervention may be compromised by poor patient compliance and other factors. It is important to investigate whether use of specific medications in combination can further enhance their effectiveness. For example, a 2007 RCT examined the effects of combining naltrexone and fluoxetine for those subjects suffering from AD and major depression (results not published). Additional research is needed to determine how medications interact with different psychosocial factors and treatments. For example, a 2007 RCT funded by NIH examined the effects of combining naltrexone and fluoxetine for those subjects suffering from AD and major depression (results are not available yet).

However, many of these compounds, in addition to reducing alcohol intake, may suppress appetite or have other undesirable effects. Thus, the development of suitable medications with greater selectivity toward excessive alcohol intake remains a major goal. Understanding the neurobiological basis and their corresponding effects of these interventions in human alcoholics, perhaps with new imaging technologies, remains an option to explore further.

6.2 Alcohol Liver Disease (ALD)

The high mortality of AH and cirrhosis, highlights the need for better therapy and our increased understanding of the precise mechanisms of ethanol-induced liver injury and there are now several promising therapeutic modalities in this area. In contrast, little progress has been made towards the development of specific pharmacotherapy for advanced fibrosis and cirrhosis. Potential reasons for the lack of progress in cirrhosis thus far include: (a) a lack of a
clear understanding of disease pathogenesis; (b) problems with compliance in long-term treatment trials; and (c) the confounding effect of drinking behavior during the duration of the trial (d) treatment may not be cost effective, compared to other therapies aimed to prevent AH and cirrhosis. As a result, at present the management of patients with advanced fibrotic ALD is directed primarily at preventing and treating the complications of portal hypertension, liver failure and hepatocellular carcinoma and deciding if and when to consider patients for orthotopic liver transplantation.\textsuperscript{41} Alcohol hepatitis is characterized by death and injury of hepatocytes so that it seems rational to develop therapies to stimulate proliferation of hepatocyte mass. This concept has been examined in patients with AH by treating them with insulin and glucagon, which is thought to stimulate liver regeneration.\textsuperscript{146} However, the results have been discouraging, and cases of severe hypoglycemia have dimmed enthusiasm for this approach. In advanced liver disease such as cirrhosis, the liver is unable to regenerate itself enough. Researchers are looking at various means, including use of adult bone, blood or liver stem cells and growth control proteins (e.g. cyclins, cyclin-dependent kinases) to stimulate growth.\textsuperscript{146}

7. What is the Current “Pipeline” of Products that Are to Be Used for this Particular Condition?

7.1 Alcohol Use Disorders (AUD)

Current available options to treat AUD have modest effects, making it necessary to identify newer treatment options for AD. The following drug classes have been classified as third phase drugs\textsuperscript{91}, showing some efficacy to treat the disease.

7.1.1 Opioid antagonists

An oral form of the antagonist nalmefene (an injectable, marketed as Revex\textsuperscript{®}) for reversing the effects of opioid anaesthetics) has been shown to increase abstinence in a preliminary placebo-controlled, double-blind study of 105 alcoholics.\textsuperscript{89} Nalmefene is also less likely than naltrexone to produce the adverse side effect of liver damage. Consequently, large-scale clinical trials of nalmefene in alcoholic populations would be important but we found none in the USA database of RCT. Further animal and human studies are needed. Nalmefene has a longer half-life (about eight to twelve hours) and possesses a greater protein binding ability than naltrexone. The dose and optimal duration of therapy for nalmefene have not yet been established. Hence, implantable long-term delivery systems are under investigation.\textsuperscript{91}

7.1.2 Serotonergics

Selective serotonin reuptake inhibitors (SSRIs): Serotonin 5-HT1A receptors may be associated with ACo and the development of tolerance, 5-HT2 receptors have been found to contribute to reward, and 5-HT3 receptors are linked to the development of reinforcement. Results of clinical trials using SSRIs have been mixed as most double-blind, placebo-controlled studies using SSRIs have not reduced drinking or any other measures of AD. However, there is good evidence that fluoxetine may reduce heavy drinking in depressed alcoholics.\textsuperscript{147} Sertraline may be efficacious among individuals with late-onset alcoholism.
Update on 2004 Background Paper, BP 6.14 Alcohol Use Disorders

However, results have been disappointing for early-onset alcoholism. Sertraline also enhances naltrexone efficacy for those individuals with MDD.\textsuperscript{148} Ondansetron, an antiemetic, may be a treatment for the same biologically predisposed subtype (type B) that does not respond to SSRIs. Ondansetron, which has functionally opposite effects to SSRIs, blocks serotonin. While further evidence is needed, early studies suggest ondansetron could provide important adjunctive treatment for a particular alcoholic subgroup. Ondansetron has been administered with naltrexone in early-onset alcoholic patients. In an eight-week, double-blind, placebo-controlled trial, the combination was found to significantly reduce drinks per day and per drinking day and had a positive effect on the percentage of days abstinent compared to placebo.\textsuperscript{149}

7.1.3 Dopaminergics

Atypical antipsychotics (aripiprazole, olanzapine, quetiapine) have all demonstrated various degrees of usefulness in reducing ACo or increasing abstinence.\textsuperscript{85} For example, Guardia and colleagues found that alcohol-dependent patients showed good adherence and compliance to olanzapine, but no differences in relapse rate or other drinking variables when comparing olanzapine with placebo-treated patients. Moreover, the study did not find differences over drinking variables.\textsuperscript{150} Aripiprazole did not show an overall advantage over placebo over primary outcomes. Overall, antipsychotics’ adverse effects may not warrant its utilization for treating AD.

7.1.4 GABA targeting

Medications with effects over the glutamate system show promise as treatments for alcohol withdrawal. For example, topiramate may have beneficial effects by facilitating functioning of the neurotransmitter GABA. Johnson and colleagues demonstrate efficacy of the medicine in very heavy drinking alcohol dependent patients.\textsuperscript{151} Individuals also reduced cigarette smoking, which may offer additional benefits to alcohol-dependent smokers. Cognitive dysfunction, abnormal sensations and anorexia has been identified as side effects.\textsuperscript{85} Baclofen, a GABA receptor agonist, reduced symptoms of alcohol withdrawal over alcohol-dependent individuals.\textsuperscript{152} Gabapentin has shown moderate efficacy in early treatment among individuals with high alcohol-withdrawal symptoms\textsuperscript{153}, or individuals with comorbid insomnia.\textsuperscript{154}

7.1.5 Other interventions

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) launched in 2007 the Clinical Investigations Group (NCIG), an effort to accelerate the development and approval of newer pharmaceutical treatment to address AUD. NCIG is currently working on three trials. Quetiapine, a drug used in treating psychiatric disorders, was examined in 224 very heavy-drinking alcohol-dependent individuals. Results from this study have been analyzed and submitted for publication. Data from a trial of levetiracetam XR (Keppra XR\textsuperscript{®}), an anti-seizure drug, are currently being analyzed, and subjects are being recruited for a trial evaluating varenicline (Chantix\textsuperscript{®}), a smoking cessation medication. In addition, NCIG staff are in the process of choosing compound(s) for a fourth trial.\textsuperscript{155}

Table 6.14.7 summarizes the information described above about the experimental “pipeline” for AUD.
Table 6.14.7. Experimental pharmacoterapies in alcohol dependence

<table>
<thead>
<tr>
<th>Drug</th>
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<td>Opioid receptor antagonist</td>
<td>May reduce relapse</td>
<td>Three small studies all promising</td>
</tr>
<tr>
<td>Nalmefene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopaminergic agents</td>
<td>Dopamine receptor antagonists</td>
<td>None</td>
<td>No effect demonstrated in large</td>
</tr>
<tr>
<td>Tiapride, flupenthixol, amisulpride</td>
<td></td>
<td></td>
<td>studies</td>
</tr>
<tr>
<td>Serotonergic agents</td>
<td>Selective inhibition of serotonin reuptake</td>
<td>May reduce alcohol consumption</td>
<td>Act by reducing depressive</td>
</tr>
<tr>
<td>Fluoxetine, citalopram, sertraline</td>
<td></td>
<td></td>
<td>comorbidity</td>
</tr>
<tr>
<td>Buspirone</td>
<td>5-HT₁A receptor agonist</td>
<td>May improve treatment retention</td>
<td>Acts by reducing anxious</td>
</tr>
<tr>
<td>Rilanserin, nefazodone</td>
<td>5-HT₂ receptor agonist</td>
<td>None</td>
<td>No effect demonstrated</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>5-HT₃ receptor agonist</td>
<td>May reduce alcohol consumption</td>
<td>Two pilot studies require</td>
</tr>
<tr>
<td>Agents with unknown mechanisms</td>
<td></td>
<td></td>
<td>confirmation</td>
</tr>
<tr>
<td>Lithium, carbamazepine</td>
<td>Unknown</td>
<td>May reduce alcohol consumption</td>
<td>Unconfirmed in large studies</td>
</tr>
<tr>
<td>Sodium oxybate (γ-hydroxybutyric acid)</td>
<td>Unknown</td>
<td>May increase abstinence rates</td>
<td>One pilot study requires</td>
</tr>
</tbody>
</table>

Source: Pharmacotherapy of Alcohol Dependence: A Review of the Clin... : CNS Drugs [Internet].

7.2 Alcoholic Liver Disease (ALD)

There are a large number of potential interventions that might be used to modulate the course of fibrosis in ALD, particularly in the latter states of hepatitis and cirrhosis (See Chapter 3.2).

There seems to be a mismatch between the potential targets for ALD (particularly in its latter stages as evidence by Table 6.14.8) and the actual number of compounds tested in the regulatory system (Table 6.14.6) as inferred from information on clinical trials.

Clinical trial information probably provides a reasonably up to date and reliable source in this regard. We reviewed information on 2004 USA clinical trials on the NIH website devoted to clinical trials using the search term “alcoholic liver disease”, “liver fibrosis”, or “cirrhosis”. We found are no industry-sponsored clinical trials for interventions designed to eliminate AD in this database. We also repeated the search using another clinical trials database, which includes some UK trials (www.controlled-trials.com) and found similar results. We note the presence of a new EU clinical trials database (https://eudract.ema.europa.eu/eudract-web/index.faces) which came into force on 1 May 2004 wherein all clinical trials on medicinal products for human use that takes place in the 25 EU states must be registered. However, the information submitted will be confidential and only national and EU regulatory authorities as well as the EC will be able to find out what trials are going on.
Table 6.14.8: Possible therapeutic interventions in liver fibrosis in progressive or established fibrosis based on laboratory/academic research and animal models.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Possible Therapeutic intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>• Removal of injurious agent&lt;br&gt;• Interleukin-10 — anti-inflammatory effect&lt;br&gt;• Tumour necrosis factor inhibitors — anti-inflammatory effect&lt;br&gt;• Antioxidants — suppress fibrotic response to oxidative damage</td>
</tr>
<tr>
<td>Stellate cell activation</td>
<td>• Interferon gamma (or interferon alpha) — inhibits activation of hepatic stellate cells&lt;br&gt;• Hepatocyte growth factor — inhibits activation of hepatic stellate cells&lt;br&gt;• Peroxisome proliferator-activated receptor ligand — reduces activation of hepatic stellate cells</td>
</tr>
<tr>
<td>Perpetuation of stellate cell activation</td>
<td>• Transforming growth factor -1 antagonists — reduce matrix synthesis and enhance matrix degradation&lt;br&gt;• Platelet derived growth factor antagonists — reduce proliferation of hepatic stellate cells&lt;br&gt;• Nitric oxide — inhibits proliferation of hepatic stellate cells&lt;br&gt;• Angiotensin-converting-enzyme inhibitors — inhibit proliferation of hepatic stellate cells</td>
</tr>
<tr>
<td>Inhibitors of Stellate cell secretion of collagen rich matrix</td>
<td>• Angiotensin converting enzyme inhibitors — reduce fibrosis&lt;br&gt;• Polyhydroxylase inhibitors — reduce experimental fibrosis&lt;br&gt;• Interferon gamma — reduces fibrosis&lt;br&gt;• Endothelin receptor antagonists — reduce fibrosis and portal hypertension&lt;br&gt;• To enhance or initiate resolution of fibrosis</td>
</tr>
<tr>
<td>Stellate cell apoptosis</td>
<td>• Gilotoxin — causes apoptosis of hepatic stellate cells&lt;br&gt;• Nerve growth factor — causes apoptosis of hepatic stellate cells</td>
</tr>
<tr>
<td>Degradation of collagen rich matrix</td>
<td>• Metalloproteinases — enhance activity of metalloproteinases&lt;br&gt;• Tissue inhibitor of matrix (TIMP) antagonists — enhance activity of metalloproteinases&lt;br&gt;• Transforming growth factor-1 antagonists — downregulate TIMPs and increases activity of metalloproteinases&lt;br&gt;• Relaxin — downregulates TIMPs and increases activity of metalloproteinases</td>
</tr>
</tbody>
</table>

Treatment will remain a challenging task, however, and thus far no drugs are approved as liver antifibrotic agents in humans. Therapies will need to be well tolerated over decades, with good targeting to liver and few adverse effects on other tissues. The liver offers a unique advantage as a target for orally administrated agents, since those with efficient liver “extraction” will have, in principle, agents targeted directly to the liver since systemic distribution will be minimized. Combination therapies may prove synergistic rather than
additive, but agents must first be tested individually to establish safety and ‘proof-of-principle’.

It is uncertain whether antifibrotic therapies will require intermittent or continuous administration.\textsuperscript{146,156} Testing of antifibrotic agents in clinical trials presents unique challenges, since efficacy cannot be simply assessed by a serum test such as viral load, and, moreover, a clinical benefit may only be apparent after a prolonged period of treatment. In contrast, for example, trials of antiviral medications for HCV, can obtain evidence of efficacy within weeks or months by a simple blood test assessing viral load. Additionally, there are no established serum markers that can substitute for obtaining tissue, obligating investigators to perform percutaneous liver biopsies at the onset and completion of therapy, which limits attractiveness to patients. More research is needed to identify biomarkers capable to assess liver fibrosis.

7.3 “Spillovers” from the Hepatitis C pipeline and Other Fibrotic Conditions

Possibly for these reasons, the contrast between the “liver fibrosis” pipeline and the drug pipeline directed to liver diseases resulting from chronic hepatitis infections is telling. The medical need and the potential market for a liver-specific anti-fibrotic agent will be large and this appears to be driven in large part by the market for hepatitis, not ALD.

Most of the impetus for developing useful anti-fibrotic therapies for ALD could, in principle, be developed as “spillover” from research into chronic hepatitis C. Liver fibrosis is a paradigm for wound healing in other tissues in the body such as the lung and kidney as it involves analogous cells and cell mediators. Thus, there is a large “research gap” between academic research into fibrotic conditions and translation into clinical, and even pre-clinical research into anti-fibrotic interventions to treat alcoholic liver disease.

8. What is the Current Status of Institutions and Human Resources Available to Address the Disease?

8.1 Public funding

The level of research into the epidemiology, aetiology and treatment of ALD is not consistent with the burden of alcoholism in both the EU and the US. Much of the research currently undertaken deals with addictions and its psychosocial nature, which although very relevant, often neglects the latter stages of AUD and ALD in terms of treatment options. Overall, there is an imbalance between the severity and magnitude of AUD and ALD and the amount of money spent on research.
8.1.1 European sources of funding for alcoholic liver diseases: selected countries

United Kingdom

The UK Medical Council on Alcohol has a large clinical trial on psycho-social interventions. Basic research on ALD and fibrosis is being funded by the Wellcome Trust.

There are several UK clinical trials devoted to various fibrotic conditions, none of them are for liver fibrosis. The National Health Service has a Phase II clinical trial directed to use of Combivir® for treating primary biliary cirrhosis, the UK Cancer Research Center has a trial on use of pentoxiphylline and alpha-tocopherol to treat radiation-induced fibrosis.

The UK counterpart of the National Institutes of Health, the Medical Research Council (MRC) is sponsoring a clinical trial on use of steroids to treat pulmonary fibrosis. We note the MRC has a research collaboration with the Japanese company Teijin to find novel drug targets for kidney and lung fibrosis, although this has been operative for several years without an apparent “hit” and liver fibrosis in apparently not specifically included in the research.

The Foundation for Liver Research (based in the Royal Free & Union College, London) is supporting development of the above identified liver dialysis (MARS) technology at a level of about 4 million US dollars.

8.1.2 European Union

Within the EU for 2004, the following areas of work have been identified as “priority areas”: health determinants: tobacco; alcohol; drugs; nutrition and physical activity; sexual and reproductive health; mental health; injury prevention; environmental health determinants; socioeconomic determinants of health; health promotion in particular settings; training in public health; disease prevention, in particular cardiovascular diseases, cancer and diabetes. The financial envelope of the public health program for the period 2003-2008 is €312 million. The budget available for 2004 is about €61 million. The European council later renewed the program for 2008-2013 period. It appears that the EU has made alcohol research a priority in terms of public health but how this is to be implemented, and whether pharmacological interventions are part of this priority is far less clear.

The Health and Consumer Protection Directorate of the EC has funded several alcohol-related projects funded under its Health Promotion Program- all directed to psychosocial interventions. Other initiatives are of interest in this regard as well. The WHO supports an Alcohol Control Databank (European Alcohol Information System). The database is designed primarily to track alcohol policies and their implementation. For example, several initiatives show promise. In 2009, the “Alcohol Measures for Public Health Research Alliance” (AMPHORA) was funded to involve researchers and institutions from 14 European countries, and counterparts from all 27 Member States and provide with new scientific evidence for public health measures to reduce alcohol-related harm, through addressing social and cultural determinants, marketing and advertising, taxes and pricing, availability and access, early diagnosis and treatment of disease, interventions in drinking environments and safer untaxed alcohol products (ftp://ftp.cordis.europa.eu/pub/fp7/docs/web-ph-booklet_en.pdf).
8.1.3 United States sources of funding

Public financing

The resources come from federal and state sources. Both public payer programs paid for more than 77% of all substance abuse treatment (including alcohol) in 2003, even though public payers funded only 45% of general health expenditure.\textsuperscript{157} Medicare, a jointly funded program by federal and state resources, which covered 14% of non-elderly Americans in 2007\textsuperscript{158}, vary greatly in terms of eligibility and requirements across states. For example, Tompkins and colleagues found that six states did not offer treatment benefits for substance abuse problems\textsuperscript{157} and a different study found that 74% of 31 states with Medicaid managed-care plans covered outpatient treatment services.\textsuperscript{159} Interestingly, programs funded primarily by public resources tend to offer a more comprehensive service compared to programs primarily funded by private resources.\textsuperscript{160} In terms of research resources, the NIAAA is the lead United States governmental agency at the NIH for alcohol use and abuse. The NIAAA receives about 400 million US dollars each year. The NIAAA is supporting over a dozen clinical protocols with regard to alcohol abuse and its sequelae (Table 6.14.9).

Its extramural programs include one with Germany (which is contributing €9 million for three years) on a project dealing with addiction research, but not therapeutic interventions. In comparison to the total appropriations package for other NIH research centres, the individual share to the NIAAA is small (Figure 6.14.13).

The 2004 NIAAA appropriation is about 4% of the estimated ALD economic burden in the United States (9 billion US dollars in 1998) but a trivial fraction of the direct and indirect economic costs from alcohol abuse. In contrast, the appropriated funding for diabetes research by the federal agency responsible for this (NIDDK) is about 1.5% of the annual United States diabetes economic burden, and that for cancer research (NCI) is about 2.5% of the average annual direct and indirect cost of cancer. Unlike ALD, however, both cancer and diabetes are much better represented in the development pipeline and do not suffer from apparent neglect by the private sector.
### Table 6.14.9: Clinical trials related to alcoholic liver disease, liver fibrosis, alcoholic hepatitis, cirrhosis, fibrosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sponsor</th>
<th>Phase</th>
<th>Treatment</th>
<th>NOTES</th>
<th>Trial Sites[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney fibrosis</td>
<td>NIDDK</td>
<td>II</td>
<td>Pirfenidone</td>
<td>Patients with glomerulosclerosis</td>
<td>1 state (25)</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>NHLBI</td>
<td>II and III</td>
<td>Oral bosentan</td>
<td></td>
<td>International</td>
</tr>
<tr>
<td>Lung scleroderma</td>
<td>NHLBI</td>
<td>III</td>
<td>Cyclophosphamide de azathioprine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood hepatic cirrhosis</td>
<td>NCRR[^c]</td>
<td>I</td>
<td>Colchicine</td>
<td></td>
<td>1 state (15)</td>
</tr>
<tr>
<td>Systemic Sclerosis</td>
<td>Genzyme/ Cambridge Antibody Technologies</td>
<td>I and II</td>
<td>Anti TGF beta 1 monoclonal antibody</td>
<td></td>
<td>4 states</td>
</tr>
<tr>
<td>Nonalcoholic Steatohepatitis (NASH)</td>
<td>NIDDK</td>
<td>II</td>
<td>metformin</td>
<td>NASH associated with diabetes</td>
<td>1 state (30)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>NCRR and NIDDK</td>
<td>III</td>
<td>Methotrexate/ursodiol vs, methotrexate/colchicine</td>
<td></td>
<td>2 states (405[^d])</td>
</tr>
<tr>
<td>Liver Fibrosis</td>
<td>InterMune</td>
<td>II</td>
<td>Interferon gamma 1b</td>
<td>In HCV patients only</td>
<td>(500)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>NIDDK</td>
<td>III</td>
<td>Ursodiol/methotrexate vs. methotrexate</td>
<td></td>
<td>11 states</td>
</tr>
<tr>
<td>Primary biliary fibrosis</td>
<td>NIDDK</td>
<td>I</td>
<td>budesonide</td>
<td></td>
<td>(50)</td>
</tr>
<tr>
<td>NASH</td>
<td>NIDDK</td>
<td>II</td>
<td>Pioglitazone</td>
<td></td>
<td>(60)^[^d]</td>
</tr>
<tr>
<td>OTHERS</td>
<td></td>
<td></td>
<td></td>
<td>North America and EU (600)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney disease in diabetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(120)</td>
</tr>
</tbody>
</table>

[^a]: Proposed or actual enrolment (in parenthesis).
[^b]: National Health, Lung, and Blood Institute
[^c]: National Center for Research Resources
[^d]: Several different phase I, II or III trials combined
8.2 Private sector funding

The pharmaceutical industry worldwide has moved slowly in alcoholism treatment, and resources spent on alcohol-related therapies are quite low, compared to other diseases. Some factors were identified elsewhere that may reduce the interest of the industry to invest more research on the disease; such factors were investment and marketing risk, and health liability.\textsuperscript{91}

With regard to the United States, the dollar amount spent on AUD treatment has been declining since 1986, when private insurance contributed 2.8 billion, or almost 30 per cent of all expenditures, as Figure 6.14.14 shows. From 1986 to 2003, private expenditure decreased by 20\%. However, these estimates may underestimate actual expenditure, since they only account for AUD if they are counted as a primary diagnosis.\textsuperscript{157}
Figure 6.14.14. Distribution of funding of Alcohol and other Substance Disorders by payer for 1986 and 2003.


Out-of-Pocket Financing

Data from 2003 reported an increase of out-of-pocket expenditure by 0.5 billion US dollars, compared to 1986 figures (1.7 billion to 1.3 billion respectively) to treat alcohol-related diseases. However, the annual increase is lower than inflation, suggesting that individual’s contribution actually declined. Two main elements may explain the decrease: the increasing use of Medicaid (which requires lower copayments compared to private schemes) and increased use of public funded treatment (low or no cost sharing).

The patient protection and Affordable Care Act (ACA), signed in 2010, may have positive effects for those individuals suffering from AUD, in terms of access to treatment. The National Association of State Alcohol and Drug Abuse Directors (NASADAD) studied ACA effects on those states that enacted it before the federal regulation (Maine, Massachusetts and Vermont). People living in all three states had increased access to AUD treatment and states achieved cost savings.
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.

9.1.1 Basic research

The burden of alcohol-related mortality and morbidity is due to alcohol-related injuries, malignant cancers, cardiovascular disease and ALD. We need to investigate further proper treatment protocols capable of dealing with co-occurring diseases and AUD. The paucity of such interventions is evident. Little information is available on the utility of combinations of different pharmacological agents to treat AUD. Indeed, the “true” effectiveness of each treatment needs to be established better to run such studies. Unfortunately, this is not the case for most potential drug treatments.

In terms of ALD, stopping drinking has been shown to improve the survival of patients with all stages of ALD. Many kinds of treatment have been tried in patients with AH but few are consistently beneficial. Current treatments for AC are severely limited. For those subjects that could not significantly decrease their ACo and developed ALD, effective antifibrotic treatments are needed urgently. There is need for:

- New therapeutic interventions for liver fibrosis
- New biochemical markers and diagnostics for the variety of alcoholic liver diseases

Alcoholic hepatitis leads to death and injury of liver cells so research has been directed to stimulating proliferation of hepatocytes. Results have been discouraging. Researchers are looking at various means, including use of adult bone, blood or liver stem cells and growth control proteins (e.g. cyclins, cyclin-dependent kinases) to stimulate growth. There is need for:

- More basic research into liver regeneration using stem cells
- More basic research into the co-morbidities of alcoholic liver disease (TB, infections, HCV) and effect of alcohol use on treatment efficacy.

Even though both transplantation and antifibrotic treatment should be investigated more, our attention should be focused to prevent ALD consequences.

9.1.2 Applied research

Pharmacologic treatment alone will not likely be enough to manage AUD. No medication to date has been proven effective in clinical trials without some form of concomitant behavioral therapy. The combination of both approaches needs to be investigated more, improving the odds of achieving meaningful sobriety or decreasing the consequences of continued alcohol abuse.

The distinction between the “alcoholic liver fibrosis” pipeline and the pipeline directed to liver diseases resulting from chronic hepatitis infections is telling. The medical need and the potential market for a liver-specific anti-fibrotic agent will be large and this appears to be driven in large part by the market for hepatitis, not ALD. Most of the impetus for developing
useful anti-fibrotic therapies for ALD could, in principle, be developed as “spillover” from research into chronic hepatic C. Nearly 200 million people worldwide are affected by HCV but, just as in alcohol-derived liver disease, there are no approved therapeutic interventions to delay or reverse liver fibrosis associated with HCV. There is a need for:

- Closing the gap between the targets for anti-fibrotic therapies and the actual number of anti-fibrotic interventions. Public funding should be directed to translating this basic research into the clinic and to improve the inefficiencies in going from animal models to humans.
- Encouraging information “spillover” from research on hepatitis-induced liver fibrosis, lung and biliary fibrosis to research on alcohol-induced liver fibrosis.
- Public funds to support clinical trials specifically on ALD

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

10.1 Systematic data recollection about morbidity

Previous research has explored extensively alcohol-related mortality, however, the paucity of alcohol-related morbidity research is surprising, as 1.5 per cent of all deaths were attributable to alcohol, but 6 per cent of all life years lost to disability were attributable to alcohol. In addition, even developed countries do not gather as much disability data in comparison to mortality data. The latter is easier to quantify and must be collected by law. Developed and developing countries should enhance data recollection allowing refined analysis between alcohol use and disability or quality of life. If such a disability registration existed, investigators could explore which are the main factors that explain the association between alcohol and morbidity. Fewer studies examine alcohol-related morbidity alone or a combination of morbidity and mortality. Rehm and colleagues grouped morbidity and mortality together examined the impact of alcohol on coronary heart disease; in this study, which used data from the National Health and Nutrition Examination Epidemiologic Follow-Up Study, based on a large representative survey of the United States general population, the data did not distinguish between people newly diagnosed with CHD and people who had died of the disorder. Overall, information about alcohol-related morbidity alone is limited because studies identifying morbidity as the endpoint demand substantial resources to assess individual outcomes in an objective and standardized way.

10.2 Data comparability

The robustness and comparability of data is still weak. Even developed countries in the European region do not have standardized definitions to better compare trends and patterns (e.g. cut-off levels for episodic heavy drinking and binge drinking). The problem is also valid for economic evaluations, which do not use a standardized methodology yet. In addition, the amount of repeated and comparative surveys need to be increased, specifically about heavy drinking, drunkenness, context of drinking, unrecorded consumption (smuggling) and AD.
In addition, externalities surrounding alcohol abuse need to be accounted for (similar to passive smoking). For example, the effect of alcohol on the drinker’s peers and family, effects on the victims of violence and traffic injury, and the indirect costs to society. The impact of these issues should be relevant in debates about the public and political acceptability of effective alcohol policy.\textsuperscript{32}

10.3 Alcohol pathogenesis

In terms of the pathogenesis of the disease, the latest findings about gut increased permeability to alcohol (consequence from chronic ACo), which promotes an increase of endotoxin levels in the bloodstream, becomes a promising field to measure its epidemiologic and epigenetic effects. For example, recent NIAAA funded research revealed that alcohol induced alterations in microRNA expression in the cell lining of the gut may cause a reduction of protein levels, leading to increased intestinal permeability, indirectly inducing liver damage.\textsuperscript{10} These findings should help develop targeted pharmaceutical agents to abolish the protein decay. Another promising field for research is related with the source of fibrosis. The latter has been traditionally linked to stellate cells, including hepatocytes themselves. However, additional mediating factors may contribute to the process. For example, transforming growth factor (TGF)-β induces early fibrosis. Inhibition of the TGF-β pathway, in turn, has been found to prevent liver injury.\textsuperscript{162}

10.4 Better understanding of young people’s drinking

Historically, adolescents have been the major focus point for research regarding alcohol consumption patterns, however, strong evidence recognizes young adults (18-25 age group) as the heaviest drinking group age.\textsuperscript{7,69} More research is needed to better understand their motivation, risk factors, and how ACo affects this population segment.

10.5 Social harm

More research is needed to effectively measure all aspects of social harm related to alcohol. Currently, analysis within the family, at the workplace, criminal behavior, sexual behavior and less serious but more common harms are scarce. Validity and reliability of current survey measures need to be revised, and wider conceptual frameworks need to be developed in order to properly measure harm to others from a person’s drinking.\textsuperscript{7}

10.6 Alcohol policy

Systematic investigation is needed to measure the effects of policy changes. For example, the impact of policy changes regarding prices and taxation on alcoholic beverages between countries and regions over time.

10.7 Evidence-based treatment

Approximately only 10 per cent of United States treatment programs have access to medications and evidence-based behavioral treatment. The remaining 90 per cent still relies on a model developed 50 years ago, when scientific understanding of AUD was rudimentary.\textsuperscript{9} The principal weakness of current treatment options is related with the assumption that a relatively brief period of counseling will dramatically affect the prognosis
of a severe chronic illness. Such approach has no scientific basis and is not used for other chronic diseases. More research is needed to understand why the shift from older therapies to newer ones has not occurred yet.

More evidence is needed to determine the effectiveness of many of the interventions to reduce harmful alcohol consumption such as targeted policy option to reduce drinking in adults that are sustainable over time. Also health service research is needed to identify organizational models to effectively coordinate between treatment for AUD and other non-communicable diseases and to scale these up.

10.8 Combination of pharmaceutical options

More RTCs are needed to identify potential combinations of pharmaceutical options capable of offering higher rates of efficacy than individual treatments. For example, one study evaluated the combination of acamprosate and disulfiram. However, the disulfiram arm was not randomized. The results suggested that concomitant administration of disulfiram improves the effectiveness of acamprosate on absolute abstinence and on relapse prevention.89

11. For which of these gaps are there opportunities for pharmaceutical research (possible ways to go forward with regards to public funding?)

11.1 Alcohol pathogenesis

Latest findings described about AUD pathogenesis, offer clear pathways to explore the development of specific substances blocking the alcohol cascade in non-traditional segments. In addition, more research and highly effective compounds are needed to have substantial impact on the main stages of AUD: acute drinking, chronic drinking, and relapse.

In terms of ALD, no safe and effective treatments are currently available. In addition, liver anti-fibrotic therapies are on the world market due in large part of the inability of most drugs to inhibit excessive fibrosis in the liver without simultaneously affecting the production of beneficial and needed fibrotic mechanisms in other parts of the body. Novel therapies to inhibit and reverse fibrosis remain the ultimate goal to treat liver cirrhosis.

11.2 Public and private funding needs to be increased

Commonly, developed economies devote a share of resources to investigate and promote interventions for reducing alcohol abuse and harm. However, that’s not the case for the most part of developing economies. Governments all around the world need to recognize the enormous burden of disease related to alcohol and increasingly explore which context-based variables are driving ACo. Private funding to accelerate the development of newer treatment options should be promoted, with special emphasis to efficacious treatment to deal with relapse.
12. Conclusion

Alcohol, a longstanding public health problem, remains a challenge for health services around the world. An impressive amount of knowledge in neuroscience, genomics, pharmacology, psychology, social sciences, and mathematics has been developed in the last 20 years to help people change their alcohol-related behaviour. Even though several medications options are available to treat AUD or ALD, none could be categorized as ‘highly efficacious’; hence, preventing both maladies still offers the best possible outcomes. The scientific community is working on numerous and novel approaches to improving efficacy, quality, effectiveness, accessibility and cost-effectiveness of treatment. However, treatment needs to better combine the full menu of evidence-based options and evaluate more rigorously the current most common interventions, such as the 12-step program. Therefore, organization and delivery of alcohol services need to be reformed to offer longitudinal and integrated care, improving the communication and collaboration between primary care settings and supportive groups.

Due to the strong cultural affinity for alcohol in Europe, dealing with the sequelae of alcohol abuse will continue to be a significant challenge. The burden of disease is substantial, the health service costs are increasing, and effective therapeutic options are still lacking. Because the biological basis of AD appears to be multifactorial, the future of AUD and ALD may be combination therapy, using pharmacological options acting on different neuronal pathways, such as acamprosate and naltrexone. Additionally, psychotherapy should be used in association with pharmacotherapy due to high rates of comorbidity affecting these patients. Liver transplantation, a very expensive treatment option, has disappointing long-term outcomes. There is a need for basic and applied research on all aspects of this problem. Moreover, blaming the ALD patient for behaviour which induced their disease will not change the reality that these patients consume substantial health service resources and need more effective treatments.

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17 Gilpin NW, Koob GF. Neurobiology of alcohol dependence: focus on motivational mechanisms. Alcohol research & health: the journal of the National Institute on Alcohol Abuse and Alcoholism. 2008;31(3):185.


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Appendices


Figure 2: Proposed mechanism for alcoholic liver disease. Chronic alcohol abuse increases gut permeability resulting in high circulating endotoxin that reaches the liver via portal circulation. Endotoxin (lipopolysaccharide or LPS) is recognized by the Toll-like receptor (TLR)-4 complex on resident macrophages or Kupffer cells in the liver, leading to production of pro-inflammatory cytokines, particularly tumor necrosis factor (TNF-α), and resulting in injury to liver cells (hepatocyte).

Source: Szabo G, Mandrekar P. Focus on: alcohol and the liver. Alcohol Health & Research World. 2010;33(1):87. 10
Appendix 6.14.3

Figure Neurocircuitry schematic illustrating the combination of neuroadaptations in the brain circuitry for the three stages of the addiction cycle that drive drug-seeking behavior in the addicted state. Note the activation of the ventral striatum/dorsal striatum in the binge intoxication stage. During the withdrawal-negative affect stage, the dopamine systems are compromised and brain stress systems such as CRF are activated to reset further the salience of drugs and drug-related stimuli in the context of an aversive dysphoric state. During the preoccupation/anticipation stage, contextual cues via the hippocampus and stimuli cues via the basolateral amygdala converge with frontal cortex activity to drive drug seeking. Other components in the frontal cortex are compromised, producing deficits in executive function.

Source: Koob GF. The potential of neuroscience to inform treatment. Alcohol Research & Health. 2010;33(1/2):144-51.163

### Table: Neurotransmitter Systems in the Brain Involved in Different Stages of the Addiction Cycle and Existing and Potential Pharmacotherapies Targeting Them in the Treatment of Alcohol Dependence

<table>
<thead>
<tr>
<th>Neurotransmitter System</th>
<th>Existing and Potential Pharmacotherapies</th>
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<td>• D₃ receptor antagonists</td>
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<td><strong>γ-Aminobutyric acid</strong></td>
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<td>(GABA) system</td>
<td>• GABA₉ receptor modulator (gabapentin)</td>
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<td><strong>Brain stress system</strong></td>
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<td>• Dynorphin/ opioid receptor antagonists</td>
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<td>Glutamate receptor agonists and antagonists</td>
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<td></td>
<td>• mGluR2 and mGluR3 agonists</td>
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Source: Koob GF. The potential of neuroscience to inform treatment. Alcohol Research & Health. 2010;33(1/2):144-51.¹⁶³
Table: Institute of Medicine (IOM) Recommendations for Implementing Quality Integrated Care for Individuals With Co-Occurring Disorders (CODs).

- Coordination of care and integrated treatment by leadership and all key stakeholders. Development of a shared vision among systems of care (Minoff, 1991; 1997, 2001; Mueser et al., 2003).
- A "no wrong door" policy. Whenever individuals enter a service system, they will find access to care, including "anticipation of comorbidity and formal determination of intent to treat or refer."
- Clear and agreed upon definitions of coordination of care, formally documented between providers and in purchaser agreements. This will help ensure coordination and accountability for outcomes.
- Assertive outreach and patient engagement and retention activities, key to improving outcomes for COD patients.
- Development and adoption of standardized performance indicators across organizations and systems.
- Comprehensive assessment practices across systems of care (e.g., alcohol and other drug treatment programs, mental health departments, primary care, chronic disease programs, and emergency departments). The IOM specifically recommends (1) screening for alcohol misuse by all adults, including pregnant women (U.S. Preventive Services Task Force); (2) screening for a co-occurring mental or substance-use problem at initial presentation with either condition, and (3) screening of entrants into child welfare and juvenile justice systems, because of the high prevalence of CODs among children (IOM, 2006). Assessments on-site when possible, by referral when necessary.
- Interdisciplinary training of staff, to enhance clinical capacity and fluency with diagnostic and treatment placement criteria, and therapeutic techniques, regardless of type of program.
- Comprehensive services across programs and across disorders (e.g., individual and group therapy, family therapy, vocational counseling, assistance with housing and income programs, case managements, etc.).
- All types of disorders treated as "primary." No program, patient, type of disorder, or approach to treatment is considered more important than others.
- Motivational enhancement activities, which studies show are among the most effective components of care (Glarey et al., 2008).
- Availability of long-term services and continuity of care across programs and time. Patients may benefit from a disease management/chronic care rather than an episodic treatment approach.
- "Reduction of negative consequences" or harm-reduction philosophy (Mueser et al., 2003). Improvement in mental health symptoms and functioning should be emphasized as important interim goals.
- Comparable administrative infrastructures, including information technology systems and instruments, electronic medical records, and assessment tools.
- Sharing of patient information, including patient records when possible, and encouragement of patients to consent to releasing information. Programs should require clear guidelines and safeguards around the use, disclosure, and protection of confidential health information.
- Flexible funding across systems to reduce barriers posed by distinct financing mechanisms.
- Co-location of services and clinicians whenever possible (Friedmann et al., 2000a; Hellstein et al., 1996; Sterling and Weisner, 2005).
- Clinical integration of services whenever possible (i.e., dual services provided by the same clinicians, or clinicians in the same programs).
- Program and organizational linkages with other systems involved with the patient (e.g., criminal justice and welfare systems, schools, and employee assistance programs).

Background Paper 6.15
Depression

By Julisca Cesar & Fáraz Chavoushi

April 2013
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<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>CBT</td>
<td>Cognitive behavioral therapy</td>
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<tr>
<td>DALY</td>
<td>Disability-adjusted life year</td>
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<td>EC</td>
<td>European commission</td>
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<td>ECT</td>
<td>Electroconvulsive therapy</td>
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<td>FP6</td>
<td>Sixth EC Framework Programme</td>
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<td>FP7</td>
<td>Seventh EC Framework Programme</td>
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<td>GBD</td>
<td>Global burden of disease</td>
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<td>GDP</td>
<td>Gross domestic product</td>
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<td>HRSD</td>
<td>Hamilton rating scale for depression</td>
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<td>Improving access to psychological therapies programme</td>
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<td>Interpersonal therapy</td>
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<td>Low and/or Middle Income Countries</td>
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<td>Lost productive time</td>
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<td>Monoamine oxidase inhibitors</td>
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<td>Major depressive disorder</td>
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<td>mhGAP IG</td>
<td>Mental health GAP intervention guide</td>
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<td>Serotonin and noradrenaline reuptake Inhibitors</td>
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<td>Selective serotonin reuptake inhibitors</td>
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<td>Transcranial magnetic stimulation</td>
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<td>YLD</td>
<td>Year lived with disability</td>
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Update on 2004 Background Paper, BP 6.15 Depression

1. Introduction

This paper is an update of the background paper for Chapter 6.15 of the 2004 Priority Medicines for Europe and the World.1

(Published at: http://archives.who.int/prioritymeds/report/background/depression.doc.)

This background paper describes demographic trends and the burden of disease of major depression disorder (MDD) for the European Union Member States and the world as a whole, assesses the current treatment options available for MDD as well as the treatments under development and makes recommendations on future research priorities.

The paper demonstrates data and trends derived (mainly) from the recently published 2010 Global Burden of Disease study.2,3 It particularly addresses the epidemiology, the burden of disease, treatment options, and the economic impact of MDD. Furthermore, this background paper describes specific groups within the society that are often misdiagnosed and/or undertreated, or not diagnosed and treated at all.

Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration.4,5 It usually occurs as a result of adverse life events, such as: losses of a significant person, object, relationship or health, but it can also occur due to no apparent cause.4 These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her every day responsibilities.6

Mood disorders are treatable conditions, with each type requiring different treatment approaches and modalities. Antidepressant medications and psychotherapies offer useful treatment approaches and are commonly employed in treating the debilitating effects of depression. If mood disorders like depression are left untreated for long periods of time, the debilitating effects of depression cause unnecessary suffering that intervens with people’s daily-life activities.7

1.1 Definition and classifications

The Oxford English Dictionary defines depression as “a mental condition characterized by severe feelings of hopelessness and inadequacy, typically accompanied by a lack of energy and interest in life.”8 In the medical and social sciences depression is defined in several different ways that will be discussed in this section.

Two frequently used classification systems are the ICD-10 (International Classification of diseases, 10th edition) and the DSM-IV (Diagnostic and statistical manual of mental disorders, fourth edition).9,10 Annex 6.15.1 provides an overview of the classifications used by these two systems.

The ICD has been endorsed by the World Health Organization as a standard diagnostic tool for epidemiology, health management and clinical purposes of all diseases and other health problems. The ICD-10 classification came into use in WHO Member States as from 1994. The ICD-10, classifies ‘mood disorders’ as part of ‘mental and behavioural disorders’. Within the cluster of mood disorders depression is mentioned as a ‘depressive episode’ or a ‘recurrent depressive disorder’. Both definitions are mentioned in Box 6.15.1.9
Box 6.15.1 Definitions based on the ICD-10

Depressive episode:
In typical mild, moderate, or severe depressive episodes, the patient suffers from lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration is reduced, and marked tiredness after even minimum effort is common. Sleep is usually disturbed and appetite diminished. Self-esteem and self-confidence are almost always reduced and, even in the mild form, some ideas of guilt or worthlessness are often present. The lowered mood varies little from day to day, is unresponsive to circumstances and may be accompanied by so-called "somatic" symptoms, such as loss of interest and pleasurable feelings, waking in the morning several hours before the usual time, depression worst in the morning, marked psychomotor retardation, agitation, loss of appetite, weight loss, and loss of libido. Depending upon the number and severity of the symptoms, a depressive episode may be specified as mild, moderate or severe.

Recurrent depressive disorder:
A disorder characterized by repeated episodes of depression as described for depressive episode (see above), without any history of independent episodes of mood elevation and increased energy (mania). There may, however, be brief episodes of mild mood elevation and over-activity (hypomania) immediately after a depressive episode, sometimes precipitated by antidepressant treatment. The more severe forms of recurrent depressive disorder have much in common with earlier concepts such as manic-depressive depression, melancholia, vital depression and endogenous depression. The first episode may occur at any age from childhood to old age, the onset may be either acute or insidious, and the duration varies from a few weeks to many months. The risk that a patient with recurrent depressive disorder will have an episode of mania never disappears completely, however many depressive episodes have been experienced. If such an episode does occur, the diagnosis should be changed to bipolar affective disorder.

The WHO Global Burden of Disease study (2004) that has been used to make the rankings in Chapter and Background Paper five, made use of the ICD-10 classification. The ‘unipolar depressive disorders’ that appear on the rankings include the burden of ‘depressive episodes’ and ‘recurrent depressive disorders’ as defined by the ICD-10.

Unlike the ICD-10, the DSM IV (Diagnostic and Statistical Manual of Mental Disorders – fourth edition) only classifies mental disorders. ‘Mood disorders’ are described as part of ‘clinical disorders’ in the manual. Within the cluster of mood disorders, ‘depressive disorders’ are further specified as a ‘single major depressive disorder’, ‘recurrent major depressive disorder’, ‘dysthymia’ or as a ‘depressive disorder not otherwise specified’. The definitions of these subdivisions are based on the presence of certain symptoms that will be further discussed in section 4.1 which covers the diagnosis of depression.
Despite significant improvements in understanding the biological mechanisms involved in mental disorders, information on genetics, neuroendocrine and functional imaging has not been found valid enough to be included in the diagnostic criteria listed in these international classification reports. The next DSM update, DSM-V, which will be published mid-2013, will have a slightly changed classification and definition of depression. Due to this proposed change, it is expected that there will be more people diagnosed with depression than ever before, which will increase the numbers of cases contributing to the burden of disease worldwide.

The Global Burden of Disease 2010 study, has used its own classification system. In this study, ‘major depressive disorders’ (MDD) are classified as being part of ‘unipolar depressive disorders’ together with dysthymia. In that sense, the Global Burden of Disease 2010 study makes use of a classification more similar to that of the DSM-IV than the ICD-10.

There are multiple variations of depression. A depressive episode involves symptoms such as depressed mood, loss of interest and enjoyment, and increased fatigability. Depending on the number and severity of symptoms, a depressive episode can be categorized as mild, moderate, or severe. An individual with a mild depressive episode will have some difficulty in continuing with ordinary work and social activities, but not to the extent that it significantly poses a barrier to activities of daily living. During a severe depressive episode, on the other hand, it is very unlikely that the sufferer will be able to continue with social, work, or domestic activities, except to a very limited extent.

There are inter-relationships between depression and physical health. For example, cardiovascular disease can lead to depression and vice versa. When present with other chronic conditions, outcomes are usually poorer and health care is considerably more expensive than expected. These facts make it even more important to lower the burden of disease from depression.

Some evidence suggests the need for a different classification, based on clusters with significant comorbidities, common neurophysiopathology, and clinical commonalities. Under this classification, the bipolar conditions would include bipolar depression, rapid mood cycling, dysphoric mania, cyclothymiacs and others. The obsessive cluster would include obsessive-compulsive disorder, obsessive personality and other neurological syndromes with obsessive movement such as Tourette syndrome. The affective cluster would include the stress-related mental conditions, bringing together major depression, dysthymia, general anxiety, panic, post-traumatic stress, adaptation disorders, and evasion-prone personalities.

### 1.2 Natural history

Depression usually starts in early adulthood, with likely recurrences. It affects women more often than men, and unemployed people are also at high risk. An episode may be characterized by sadness, indifference or apathy, or irritability. It is usually associated with change in a number of neurovegetative functions, (such as sleep patterns, appetite and weight, motor agitation or retardation, fatigue, impaired concentration and decision-making) as well as feelings of shame or guilt, and thoughts of death or dying. A small proportion of patients will experience psychotic symptoms. The duration of an untreated crisis ranges from nine months to several years. Approximately eight of ten people experiencing an initial
episode of major depressive disorder will go on to have at least one additional episode during their lifetime. Approximately 10 to 15 per cent will have a subsequent manic episode, at which point the patient is then reclassified as having a bipolar disorder.

The nature of depression is such that affected persons are unlikely to realize that they are depressed and are therefore unlikely to seek help for themselves. They are also less capable of appropriately taking their treatment as directed by health care professionals. In all chronic conditions the concurrence of depression highly affects the quality of care provided by patients themselves and received by others.

1.3 Comorbidities and risk factors

Depression in the physically unwell is common and an important cause of morbidity. People with a physical illness have an increased risk for developing MDD. Surveys in general hospitals indicate that around 10-20% of internal medicine in- and outpatients suffer from so called ‘depressive illnesses’. Similar rates have been found in patients with a chronic physical disease. Reviews and surveys from patients with a specific disorder also demonstrate high prevalence of depression: the prevalence amongst diabetes patients, cancer patients, patients following myocardial infarction and patients with Parkinson disease is 11%, 15%, 20% and 17%, respectively.

Depression is associated with reduced treatment adherence, poor prognosis and increased disability. Depression may increase mortality for many physical diseases. Associations between depression and mortality have been reported across diagnostically mixed groups of physically ill patients, as well as in heart failure, HIV/AIDS, renal disease, cancer and diabetes, and following myocardial infarction and stroke.

In a study conducted in the Netherlands, about half of Dutch persons aged 18-64 years with major depression in the past year also experienced an anxiety disorder. Depression also frequently co-exists with chronic somatic illnesses. Studies indicate that between 50% and 80% of primary care patients with current major depression, dysthyemic disorder, or subthreshold depression also suffer from a chronic somatic condition. Conversely, somatically ill patients common suffer from depression as well. For instance, a large-scale health survey of the adult Canadian population found that the annual prevalence of major depression in persons reporting one or more long-term medical condition was about 9%, more than twice the prevalence among those not reporting a chronic condition (4%).

Other comorbidities include head injury, schizophrenia and other psychotic disorders, substance abuse, Parkinson disease, stroke, acne, multiple sclerosis and migraine. Furthermore, recent research has demonstrated that genetic factors also contribute to the response rate to antidepressants, and therefore these genetic factors might also contribute as risk factors for developing depression or relapses. Most likely, depression is caused by a combination of genetic, psychological, environmental, and biological factors.

Other risk factors for depression are pregnancy, childbirth, (peri)menopause, hormonal factors and menstruation, (low tolerance to) stress, impulsive behavior, alcohol or substance abuse, a family history of depression, alcohol abuse or suicide, sociocultural factors, poverty, severe or chronic medical conditions, insomnia, being a female, intimate partner violence, (childhood) sexual abuse and tobacco use.
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While depression is present in all age groups, the specific issue of depression the young and elderly are further addressed in the next section of this background paper.

Figure 6.15.1a: Burden of disease frequency by age group in the world.

![Distribution by age of DALYs in 2010 for major depressive disorder in the world*](image)


Figure 6.15.1b: Burden of disease frequency by age group in Central Europe.

![Distribution by age of DALYs for major depressive disorder in Central Europe](image)

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Figure 6.15.1c: Burden of disease frequency by age group in Eastern Europe.

Distribution by age of DALYs in 2010 for major depressive disorder in Eastern Europe*


Figure 6.15.1d: Burden of disease frequency by age group in Western Europe.

Distribution by age of DALYs in 2010 for major depressive disorder in Western Europe*

1.4 Depression in young people

Depression is common among adolescents and children, affecting many people before the age of 18. A recent survey among 10,123 adolescents aged 13 to 18 years in the United States, showed that 11.7% of the sample met the criteria of a major depressive disorder or dysthymia as diagnosed with the DSM-IV criteria. These results are in line with other studies that indicate that mood disorders among children and adolescents are more common than is generally believed.44,45,46

Adolescent depression may affect the teen’s socialization, family relations, and performance at school, often with potentially serious long-term consequences. Adolescents with depression are at risk for increased hospitalizations, recurrent depressions, psychosocial impairment, alcohol abuse, and antisocial behaviors as they grow up.47,48

Depression is associated with poor academic achievement, social dysfunction, teenage pregnancy and substance abuse.50 It is also closely linked to attempted and completed suicide.51 This makes depression not only a burden of disease to the patients who are suffering from it, but also for their family, friends and for society as a whole.

Depression in young people may be expressed differently from that in adults, with manifest behavioral disorders (e.g. irritability, verbal aggression and misconduct), substance abuse and/or concurrent psychiatric problems.52

The diagnosis of dysthymic disorder and major depressive disorder are based on similar criteria for children, adolescents, and adults, with two exceptions. First, the DSM (4th edition with text revisions; DSM-FV-TR) has allowed the substitution of irritability for depressed mood in children and adolescents.10 Second, the duration criterion for dysthymic disorder in children and adolescents is one year instead of two.10 Empirical data also suggest that the clinical syndrome of depression is very similar among children, adolescents, and adults although there are some developmental differences. Specifically, hypersomnia shows a developmental trend, with an increased prevalence in depressed adolescents than in children.53 Suicide attempts, especially those involving high lethality, also increase with age.54 Somatic complaints and behavior problems are more common during the developmental period of younger children.55 Depression is also associated with hopelessness and overeating in young people. Although the reasons for the developmental variations in depressive symptoms are not known, maturational effects on emotional and behavioral regulation and cognitive function might contribute to these differences.53

Adolescents with depression have expenditures that are significantly higher compared to children with other mental health conditions and children with no mental health condition.55,56 Children with depression also use more inpatient and emergency services than other children.55 Several different interventions have been shown to be cost effective for treatment or prevention of depression specifically in youth.55,56

It has been estimated that three quarters of young people suffering from depression get no treatment.59 Some studies show that only one third of parents will share their children’s psychosocial concerns with their pediatricians, and only 40% of the pediatricians will respond to these concerns.57 It is estimated in New Zealand that 80% of young people who suffer from depressive symptoms that warrant intervention do not receive treatment.58
1.5 Depression in the elderly

There are growing concerns due to the rise in prevalence of depression among elderly, particularly in Western Europe (Figure 6.15.1d).59 Depression is common in later life, particularly in people with poor physical health. In the acute hospital setting this is associated with poor outcomes, increased length of stay and compromised care.60 These outcomes make depression an even more expensive disease in terms of healthcare costs, especially in the elderly who are very often in a poor physical health state. There is an increase of burden (DALYs) caused by major depressive disorder until the age group of 55-59 years in all regions and in both sexes (Figure 6.15.1a-d).

Somatic and behavioral symptoms of depression are usually so intense that they mask the psychological ones, up to the point that they may seem to suffer “depression without sadness”. The concurrence of several chronic conditions complicates the diagnosis. In these cases depressive symptomatology may reflect the psychological stress of coping with disease, may be caused by the disease process itself or by the medications used to treat it, or may simply coexist in time with the medical diagnosis.61 The elderly are also highly likely to be taking many medications concurrently. Many different classes of drugs that elderly people administer could potentially induce depression.62

When depression is diagnosed in the elderly, this is usually after years of delay. One UK study suggested that 15% of elderly patients whose depressive illness goes untreated will commit suicide.63 The same study showed that most elderly people who commit suicide visited their physician within one month prior to the event, but their symptoms were not recognized or treatment was not adequate.63

2. Epidemiology and burden of depression

In 2010, major depressive disorder (MDD) accounted for a total of 63.2 million (2.5%) DALYs (disability adjusted life years) worldwide, and 8.4 million (3.4%) DALYs in Europe only (Figure 6.15.2).2 These data demonstrate that Europe has a relatively higher burden of disease due to MDD than the rest of the world. A USA based survey of 9 282 participants of 18 years and older showed that 6.7% of the adult population experienced an episode of major depression in a 12-month period.64

Major depressive disorder caused 63 million years lived with disability (YLDs) in 2010, whereas in 1990 it only caused 46 million YLDs, demonstrating a 37% increase over the past two decades.65 MDD was ranked second by global YLDs ranks in both 1990 and 2010.65 Its regional ranking in the three European regions did not differ from the global ranking (second place). However, in some Asian and Latin-American regions it was ranked first in 2010. MDD disorder contributed 8.1% of total YLDs globally.65
Figure 6.15.2: Absolute DALYs caused by depression, by European region and age group.

Figure 6.15.2 shows the total number of DALYs caused by MDD per European region, by age group. These figures demonstrate that the distribution of absolute DALYs on a global level is very different than in all three European regions. This reflects the difference in age distribution in different regions of the world. Where globally the number of DALYs caused by MDD peak at the age group of 20-24 years, in all three European regions the peak occurs at a later age. There are differences between the three European regions as well. Globally, major depressive disorder peaks at the age group 20-29 years, whereas in Central, Eastern and Western Europe it peaks at age groups 30-34 years, 50-54 years and 45-49 years respectively (Figure 6.15.1a-d, 6.15.2 and 6.15.3). Such information may be useful for targeting services.

*Source: Global Burden of Disease Study 2010 (GBD 2010) Results by Cause 1990-2010. Data downloaded from Institute for Health Metrics and Evaluation (IHME).*
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Figure 6.15.3: Absolute DALYs caused by depression in the world, by age group.

![Absolute DALYs caused by MDD in the world, by age group](image)


Figure 6.15.4: Burden of disease for major depressive disorder by age, sex (Male, Female) and region (Western, Central, Eastern Europe and the World).

![Burden of major depressive disorder by age, sex and region*](image)

Women suffer more from MDD than men, both globally and in all European regions (Figure 6.15.4, 6.15.5, 6.15.6). The difference between genders in percentages is 81% and 67% for Europe and the world, respectively. As an example, Figure 6.15.6 shows that women in Eastern Europe have an almost twofold higher burden of disease from depression than men in the same region.
In the general population, depression is often undiagnosed or misdiagnosed and, even more frequently, it is untreated. The following chapters will further address and discuss this issue.66,67

3. Economic aspects of depression

The economic impact of depression on patients and society is well documented. The average annual health costs for depressed patients, including medical, pharmaceutical and disability costs, may be 4.2 times higher than those incurred by the general population.15,68 These patients have more contact with primary care services and secondary care psychiatrists and other specialists, incur more expenses and outpatient charges, than those patients without depression.69 Successful treatment and, as a result of that, cessation of antidepressant medication treatment can result in significant cost savings to the health service.69 The cost of treatment is often completely offset by a reduction in the number of days of absenteeism and productivity lost while not at work.15

Only a few researchers have tried to estimate the economic burden of depression. The most detailed estimation for the United States was published in 2003.70 The total economic burden of depression in the United States was estimated as 83.1 billion US dollars in 2000, of which 26.1 billion US dollars (31%) were direct medical costs, 5.4 billion US dollars (7%) were suicide-related mortality costs and 51.5 billion US dollars (62%) were workplace costs. Despite an increase in treatment of over 50% between 1990 and 2000, the economic burden increased by only 7%, suggesting an increase in the efficiency of the management of depression.70

Instability of treatment with antidepressants is associated with higher comorbidity rates, more urgent care use and higher total, depression- and non-depression-related direct costs.71 A study in 2010 demonstrated that major depressive disorder severity is significantly associated with increased treatment usage/costs, treatment adequacy, unemployment, and disability and with reduced work performance.72 Increased compliance with antidepressants is significantly associated with reduced absenteeism (from workplace) costs.73 The available literature on the impact of depression treatment on worker productivity costs suggests that the gains made in reduced absenteeism and improved productivity at work may offset the costs of depression treatment.73,74,75

In a series of studies depression has been found to be significantly associated with decrements in job performance and at-work productivity.76,77,78,79,80,81 Kessler et al. evaluated work performance of MDD patients with the WHO Health and Work Performance Questionnaire, which assesses self-reported absenteeism and presenteeism (attending work while sick).82 They demonstrated that MDD was associated with 27.2 lost workdays (per worker, per year). Analyzing by type of workday loss (i.e. absenteeism versus presenteeism), absenteeism was associated with 8.7 days for those with MDD, whereas presenteeism was associated with 18.2 days for those with MDD. This suggested that presenteeism may be more problematic than absenteeism.82 Estimates of the impact of these figures on the United States workforce were 225.0 million workdays and 36.6 billion US dollars salary equivalent lost productivity per year for MDD.82
Studies measuring both absenteeism and presenteeism are consistent in finding that presenteeism creates the higher cost burden. This finding holds true both when absenteeism is measured by self-report and when using administrative data.

In another study, Stewart et al. found that USA workers with depression reported significantly more total health-related lost productive time (LPT) than those without depression (5.6 hours/week versus an expected 1.5 hours/week, respectively). Eighty-one per cent of the LPT costs were explained by reduced performance while at work. Major depression accounted for 48% of the LPT among those with depression, again with a majority of the cost explained by reduced performance while at work. Extrapolation of the survey results and self-reported annual incomes of the population of US workers suggested that workers with depression cost employers an estimated 44 billion US dollars per year in LPT, an excess of 31 billion US dollars per year compared with control subjects. However, this estimate did not include labor costs associated with short- and long-term disability.

Compared to the situation of no treatment (natural history), the most cost-effective strategy for averting the burden of (moderate to severe) depression is a combined intervention of antidepressants and psychosocial therapy. The more effective a newer medicine will be in stabilizing a patient, the more cost effective the intervention will be as well. Also, as many antidepressants are (or will become) off patent the cost effectiveness of an intervention will also increase over time.

In a randomized controlled trial in the United States researchers found that - in the long term - a one year collaborative care programme provided by a nurse or psychologist care manager, working in the participant’s primary care clinic to support patient’s regular primary care clinician, reduces the total healthcare costs by more than 3 000 US dollars on average per patient after a four year period.

A retrospective study demonstrated that antidepressant drug adherence was associated with increased comorbid disease medication adherence and reduced total medical costs of patients with diabetes, and coronary artery disease/dyslipidemia, diabetes/coronary artery disease/dyslipidemia, after just one year. These results suggest that antidepressant adherence may be a very important factor in reducing total medical costs even more and making treatments for depression and comorbidities more cost effective.

A study looking at health management programs suggested that telephone counseling, regular follow-ups and educational materials (folders, home videos with education on use of antidepressants) on medication adherence and persistency among patients with newly diagnosed and recurrent depression can succeed in encouraging these patients to stay on antidepressant medication and to reach treatment goals outlined by best practice guidelines.

Some patients are repeatedly referred from primary to secondary care with medically unexplained symptoms (MUS). Some studies aimed to estimate the healthcare costs incurred by such referrals and to compare them with those incurred by other referred patients from the same defined primary care sample. These studies have found that patients who have been repeatedly referred with MUS have high rates of depressive and anxiety disorders, which frequently go untreated. The repeated referral of patients with MUS to secondary
medical care incurs substantial healthcare costs.\footnotemark[80] Better and earlier diagnosis and treatment of depression could therefore offer potential cost savings.

Studies of the cost effectiveness of quality improvement efforts have shed light on the impact of the standard of depression care on healthcare costs, and, to a lesser extent, productivity costs. Quality-adjusted life years (QALYs) are a commonly used metric for comparing treatments and medical technologies on cost-effectiveness. The cost per QALY associated with improved depression care ranges from a minimum of 2 519 US dollars to a maximum of 49 500 US dollars and is similar to other commonly used medical technologies, including smoking cessation programmes, pharmacotherapy for hypertension or hypercholesterolaemia, and treatment of chronic pulmonary disease.\footnotemark[81],\footnotemark[92],\footnotemark[93],\footnotemark[94],\footnotemark[95],\footnotemark[96]

Furthermore, the World Health Organization’s 2006 report (Dollars, DALYs and Decisions: Economic Aspects of the Mental Health System) concluded on the following\footnotemark[86]:

- “Long-term maintenance treatment of depression with antidepressant drugs has a much larger impact on reducing the burden of depression than episodic treatment, and also represents a cost-effective strategy.
- For people with depression or anxiety, psychotherapy is expected to be as cost-effective as newer (generic) antidepressants.
- The most efficient interventions for common mental disorders such as depression and panic disorder can be considered very cost-effective (each DALY averted costs less than one year of average per capita income). In other words, there is just as much of an economic rationale for investing in mental health as there is in other chronic, non-communicable diseases such as diabetes or hypertension.”

Critical gaps in the literature on the cost of depression remain, however. For instance, although we have reasonably sound estimates of the costs of depression, we do not know the economic burden of untreated and/or inappropriately treated versus appropriately treated depression. These research gaps should be addressed.

4. Control strategy

While the global burden of depression poses a substantial public health challenge, not only on the clinical level, but at the social and economic level as well, there are a number of well-defined and evidence-based strategies that can effectively address this burden. It is important to realize however, that although there are many possible treatments for depression; currently there are equally, if not more, barriers to getting treatment.

Last year, for the twentieth edition of the World Mental Health day, ‘depression’ was chosen as the main theme because of its widespread burden and rising importance in all parts of the world. During this day, several recommendations were put forward by the World Federation of Mental Health (WFMH) to encourage action for the improvement of services to those with mental and behavioral disorders, to promote mental health and wellbeing, and to prevent mental disorders.\footnotemark[6] These recommendations were to:

- Provide treatment in primary care
- Make psychotropic medications available
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- Give care in the community
- Educate the public
- Involve communities, families and consumers
- Establish national policies, programs and legislation
- Develop human resources
- Link with other sectors (such as education, labor, welfare, law, and nongovernmental organizations)
- Monitor community mental health
- Support more research

Since this Priority Medicine Report has a focus on pharmaceutical interventions; social, community –based and policy related interventions will not be discussed in much detail.

The World Health Organization recently studied the “treatment gaps” in mental health care and found that worldwide, the median rate of untreated depression is approximately 50 per cent.97 Barriers to effective care include the lack of financial resources, the lack of skilled health care providers in some parts of the world and the social stigma associated with mental disorders.98

When access to health care is not a problem, key interventions to treating for moderate and severe depression are antidepressant medicines and different forms of psychotherapy. Less used interventions are electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS). These different types of treatments, as well as tools for diagnostics and prevention of depression will be discussed in the section below. The main focus of this paper will be on antidepressant medicines, for which the general population, the elderly and children/adolescents will be discussed separately.

4.1 Diagnosis

The starting point for providing effective treatment for depression is the recognition of the problem and a correct diagnosis. The first point of access is usually primary care, but evidence suggests that many cases go unrecognized at the level of the general practitioner.99,100 Diagnostic criteria and methods of classification of depressive disorders have changed substantially over the years. Although operational diagnostic criteria have improved the reliability of diagnosis, classifying a disorder that is heterogeneous and best considered in a number of dimensions remains challenging.

The ICD–10 (International Classification of Diseases, 10th edition) and the DSM–IV (Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, 4th edition) are the two most commonly used tools to diagnose depression as already has been described in section 1.1 and in Annex 6.15.1.10,101 Both have very similar diagnostic features for a ‘clinically important’ severity of depression.102 Nevertheless their thresholds differ.

The ICD–10 requires at least one of the following core symptoms to be present most days, most of the time for at least two weeks101:

1) Depressed mood
2) Anhedonia
3) Loss of interest
The degree of the depression is further determined by the presence of the following symptoms:

1) Disturbed sleep
2) Poor concentration or indecisiveness
3) Low self-confidence
4) Poor or increased appetite
5) Suicidal thoughts or acts
6) Agitation or slowing of movements
7) Guilt or self-blame

The total of these symptoms determines the degree of the depression as follows:
- Not depressed (fewer than four symptoms)
- Mild depression (four symptoms)
- Moderate depression (five to six symptoms)
- Severe depression (seven or more symptoms, with or without psychotic symptoms)

The DSM-IV requires a minimum of five out of the nine following symptoms (which must include depressed mood and/or anhedonia):

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful). 
   Note: in children and adolescents, it can present as an irritable mood.
2. Anhedonia: markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3. Significant weight loss when not dieting or weight gain (e.g. a change of more than five per cent of body weight in a month), or a decrease or an increase in appetite nearly every day. Note: in children, a failure to make expected weight gains should be considered.
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

To make a diagnosis of depression the DSM-IV also requires assessment of three linked, but separate factors:

(a) severity: based on the amount of symptoms present and their interference with daily functioning (further discussed below).
(b) duration: a minimum of two weeks duration of symptoms that includes at least one key symptom is necessary for diagnosis of a depressive episode. Individual symptoms should be present for most of every day.
(c) course: differentiation between a single episode, recidivating episodes, season-bound patterns, post-partum onset and chronic depression.
Classification of the degree of the depression is as follows according to the DSM-IV:

- **Subthreshold depressive symptoms**: fewer than five symptoms of depression
- **Mild depression**: few, if any, symptoms in excess of the five required to make the diagnosis, and the symptoms result in only minor functional impairment
- **Moderate depression**: symptoms or functional impairment are between ‘mild’ and ‘severe’
- **Severe depression**: most symptoms, and the symptoms markedly interfere with functioning. Severe depression can occur with or without psychotic symptoms.

Diagnostics using the three factors listed above (severity, duration and course) only provide a partial description of the individual experience of depression. People with depression vary in the pattern of symptoms they experience, their family history, personalities, premorbid difficulties (for example, sexual abuse), psychological mindedness and relational and social problems – all these factors play an important role in the actual presentation of the depression and the individuals’ response to treatment. It is also common for depressed people to have a comorbid psychiatric diagnosis, such as anxiety, social phobia, panic and various personality disorders. This makes diagnosis and treatment even more complicated.

Making a diagnosis of depression does not automatically imply a specific treatment. The diagnosis should be a starting point in considering the most appropriate way of helping an individual in their particular circumstances. It would not be correct to presume that evidence from randomized clinical trials can be applied directly to clinical practice. Patients presenting in the clinic each have their own unique set of symptoms that require tailored interventions to combat the disease. The NICE clinical guideline states: "Given the current limited knowledge about which factors are associated with better antidepressant or psychotherapy response, most decisions will rely upon clinical judgment and patient preference until there is further research evidence."

### 4.2 Treatment

There are ongoing discussions regarding the effectiveness of the management of common mental health problems in general practice settings. Although evidence based clinical guidelines are available, initiation and adherence to effective treatment are usually poor. There are several models of care that aim to increase access to mental health care through the improved coordination of care between primary and specialist mental health services. One of those models is called the ‘stepped care model’. The stepped care model provides a framework in which to organize the provision of services, and supports patients, caregivers and practitioners in identifying and accessing the most effective interventions (Figure 6.15.7). In stepped care the least intrusive, most effective intervention is provided first; if a person does not benefit from the intervention initially offered, or declines an intervention, they are offered a ‘next step’ intervention.
Figure 6.15.7: Outline of the Stepped Care model

<table>
<thead>
<tr>
<th>Focus of the intervention</th>
<th>Nature of the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 4:</strong> Severe and complex depression; risk to life; severe self-neglect</td>
<td>Medication, high-intensity psychological interventions, electroconvulsive therapy, crisis service, combined treatments, multiprofessional and inpatient care</td>
</tr>
<tr>
<td><strong>STEP 3:</strong> Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression</td>
<td>Medication, high-intensity psychological interventions, combined treatments, collaborative care, and referral for further assessment and interventions</td>
</tr>
<tr>
<td><strong>STEP 2:</strong> Persistent subthreshold depressive symptoms; mild to moderate depression</td>
<td>Low-intensity psychosocial interventions, psychological interventions, medication and referral for further assessment and interventions</td>
</tr>
<tr>
<td><strong>STEP 1:</strong> All known and suspected presentations of depression</td>
<td>Assessment, support, psychoeducation, active monitoring and referral for further assessment and interventions</td>
</tr>
</tbody>
</table>

*Complex depression includes depression that shows an inadequate response to multiple treatments, is complicated by psychotic symptoms, and/or is associated with significant psychiatric comorbidity or psychosocial factors.

*Only for depression where the person also has a chronic physical health problem and associated functional impairment (see ‘Depression in adults with a chronic physical health problem: treatment and management’ [NICE clinical guideline 91]).

Source: adopted from the NICE clinical guideline 2010

There have been several studies providing limited evidence to support the effectiveness of this model, and it has been adopted by the IAPT (Improving Access to Psychological Therapies) programme as the framework for the delivery of the service. The usage of this model is recommended in the NICE guidelines for clinical practice. The WHO mental health Gap Intervention Guide (mhGAP IG) uses a similar treatment model with one key difference; it does not recommend the use of medication for patients with subthreshold depressive symptoms or mild depression.

As shown in Figure 6.15.7, interventions in the stepped care model differ based on the severity of the depression and include self-help, psychoeducation, psychological interventions of different intensities, medication and electroconvulsive therapy. This model is an example of how and at what stage different treatment options take place; the different individual interventions will be further discussed in the next section, starting with antidepressant medications.

### 4.2.1 Antidepressant medicines

Since the introduction of the monoamine oxidase inhibitors (MAOIs) and the first TCA (tricyclic antidepressant), imipramine, in the late 1950s, many new antidepressants have been introduced and approximately 35 different antidepressants are currently available worldwide.
Most of the effects of antidepressants in the body occur at the level of the synapse - the site in the nervous system where neurons communicate with each other or with other types of cells (e.g. muscle cell) by means of neurotransmitters. Some neurotransmitters (e.g. norepinephrine, serotonin and dopamine) are taken back into the nerve ending after release. This process is called *uptake, reuptake* or *transport*. This transport is a mechanism that prevents overstimulation of receptors in the receiving neuron. By blocking the (re-)uptake of these neurotransmitters, or inhibiting the mitochondrial enzyme monoamine oxidase, antidepressants alter the magnitude of the effects of neurotransmitter at these synapses. The loss of sensitivity of the cell to the neurotransmitter is called *desensitization*, while the loss of the receptor protein from the cellular surface is called *down-regulation*.

The specific mechanism of the therapeutic action of antidepressants remains unclear. It is known however, that antidepressants of many types acting by different mechanisms can desensitize or down-regulate certain receptors for neurotransmitters by causing a local abundance of neurotransmitters. This ability of changing communication between neurons is what forms the basis of a hypothesis on their mechanism of action.

Several of the most frequently used antidepressants and their possible mechanism of action are discussed below.

**Monoamine oxidase inhibitors (MAOIs)** act by inhibiting the activity of the enzyme monoamine oxidase, thus preventing the breakdown of monoamine neurotransmitters and thereby increasing their availability. Well known examples of medicines in this class are phenelzine, isocarboxazid and trylcypromine.

There are two isoforms of monoamine oxidase, MAO-A and MAO-B. MAO-A preferentially deaminates serotonin, melatonin, epinephrine, and norepinephrine. MAO-B preferentially deaminates phenylethylamine and trace amines. Dopamine is equally deaminated by both types. Because of potentially lethal dietary and drug interactions, monoamine oxidase inhibitors are usually reserved as a last line of treatment, used only when other classes of antidepressant drugs (for example selective serotonin reuptake inhibitors and tricyclic antidepressants) fail. New research into MAOIs indicate however, that much of the concern over their dangerous dietary side effects might stem from misconceptions and misinformation, and that it is underutilized and misunderstood in the medical profession.

**Tricyclic antidepressants (TCAs)** were first discovered in the early 1950s and were subsequently registered later in the decade. The medicine is named after their chemical structure, which contains three rings of atoms. Examples of medicines from the TCA class are amitriptyline, imipramine and desipramine. The tetracyclic antidepressants, which contain four rings of atoms, are a closely related group of antidepressant compounds. The majority of the TCAs act primarily as serotonin-norepinephrine reuptake inhibitors (SNRIs) by blocking the serotonin transporter (SERT) and the norepinephrine transporter (NET), respectively, which results in an elevation of the synaptic concentrations of these neurotransmitters. In addition to their reuptake inhibition, many TCAs also have high affinity as antagonists at several receptors, which may contribute to their therapeutic efficacy, as well as their side effects.

**Selective serotonin reuptake inhibitors (SSRIs)** were first developed in the 1970s with the aim of targeting a specific site of the neuron, the reuptake protein, while not influencing
other parts of the neuron such as the receptors. SSRIs are believed to increase the extracellular level of the neurotransmitter serotonin by inhibiting its reuptake into the presynaptic cell, increasing the level of serotonin in the synaptic cleft available to bind to the postsynaptic receptor. They have varying degrees of selectivity for the other monoamine transporters, with the more specific SSRIs having only weak affinity for the noradrenaline and dopamine transporter. Examples of SSRIs are escitalopram, fluoxetine, sertraline, paroxetine and fluvoxamine.

**Serotonin and Noradrenaline Reuptake Inhibitors** (SNRIs) were first introduced in 1994. This type of antidepressant acts by inhibiting the reuptake of the neurotransmitters serotonin and norepinephrine. In relation to major depressive disorder, norepinephrine is thought to be related to alertness and energy as well as anxiety, attention, and interest in life; while (a lack of) serotonin is thought to be related to anxiety, obsessions, and compulsions. The inhibition of the reuptake of these neurotransmitters results in an increase in their extracellular concentrations and, therefore, an increase in neurotransmission. Venlafaxine and milnacipran are examples of SNRIs.

**Noradrenergic and specific serotonergic antidepressants** (NaSSAs) are a class of psychiatric drugs used that act by antagonizing the α2-adrenergic receptor and certain serotonin receptors. Antidepressants mianserin and its successor mirtazapine are examples of medicines in this class. By blocking α2-adrenergic autoreceptors and heteroreceptors, NaSSAs enhance adrenergic and serotonergic neurotransmission in the brain involved in mood regulation. In addition, due to their blockade of certain serotonin receptors, serotonin transmission is not facilitated in unwanted areas. This specificity is what is referred to in the name of this class of medicines.

An overview of common antidepressive agents, their drug class, trade names and mechanisms of action can be found in Appendix 6.15.2.

Despite the widespread usage of these classes of medicines to treat MDD, it has been shown that less than 50% of patients experience a clinical response to treatment with the first antidepressant treatment used. With respect to the research that guides clinical practice and underpins evidence-based medicine, a series of meta-analyses have been published in recent years that have found that antidepressants in general have relatively small specific effects as compared with placebo in randomized controlled trials. The authors argue that even though clinical trials may find an overall significant beneficial effect for newer generation antidepressant medications, this effect is below recommended criteria for clinical significance. By the NICE criterion of a three-point or 0.5 standardized mean difference score in Hamilton Rating Scale for Depression (HRSD), differences between drug and placebo are not clinically significant in clinical trials involving either moderately or severely depressed patients. According to Kirsch et al., only clinical trials that enrolled very severely depressed patients (with a pretreatment score of at least 25 HRSD points) were likely to observe a statistically significant effect, large enough to be considered clinically relevant as well.

The relatively small effect sizes that are found in clinical trials have been related to the fact that up to 80% of the antidepressant effect may be duplicated by the placebo effect - that is, 80% of the antidepressant effect is thought to be due to placebo response. Furthermore, side effects of antidepressants may reveal the identity of medication to participants or
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investigators and thus bias the results of conventional trials using inert placebos. Studies using ‘active’ placebos that mimic some of the side effects of antidepressants have revealed that differences between antidepressants and active placebos were small.131 This suggests that unblinding effects may give an overestimation of the efficacy of antidepressants in clinical trials using inert placebos.

Many patients are not able to tolerate available antidepressant medications due to side effects.132 Studies show that as many as 50% of subjects may discontinue antidepressant treatments within a six month period, reporting adverse effects as a main reason for discontinuation.133 Side effects of antidepressants will be further discussed below.

In reply to the studies that question the use of antidepressants in clinical care, critics have argued that the same small mean difference score can result from two different groups of study participants. One could observe a group with very minor (clinically insignificant) benefits of treatment for all patients; or a group where a small portion of patients experiences a large and clinically significant difference on treatment, while the rest of the group did not experiences benefit.134 Both groups could result in the same mean score on overall improvement. Due to the high burden of MDD in all parts of the world, they argue, millions of people can be helped by the available medication, even if the people that benefit are only a small proportion of the total population that suffers from the disease.134 However, much remains to be done on predictors to response.

Methodological issues

These recent studies have shown that there are several statistical and methodological issues that complicate drawing conclusions for clinical practice based on the scientific evidence of antidepressant effectiveness. The effect size refers to a standardized measure of the difference between treatments.135 For a continuous variable such as a score on the Hamilton Depression Rating Scale, the effect size is calculated as the between group difference divided by the pooled standard deviation.136 For categorical outcomes, differences in response or remission rates can be standardized in relative terms such as Odds Ratio (OR) or Relative Risk (RR) or in absolute terms using the Number Needed to Treat statistic (NNT).136 It has been argued that because of an overestimation of the expected effect size, most RCTs on antidepressants do not have the statistical power to discriminate between an effective and an even more effective treatment.137 This makes it hard to determine if a “not statistically different” finding reflects true therapeutic equivalence or if it is a false negative result.137 As mentioned before, these relatively small effect sizes have been related to an increase in placebo response rates.127,130

When expected effect sizes are relatively small, large sample sizes are needed to obtain enough statistical power to detect a significant difference.135 To enroll a large group of study participants in a short time period, data are now combined from large numbers of clinical sites which greatly increases the complexity of a study and its measurements.138 Alternatively, meta-analyses are used to analyze the results of a group of related studies.139 In meta-analyses, differences in study methods can compromise the validity of pooling the results across studies. Examples are whether or not to include different measurement end points (e.g., response at six weeks, response at 12 weeks), studies that are or are not placebo controlled and studies that use different outcome measures (relative risks or mean difference scores). As applies to clinical trials, meta-analyses are susceptible to publication bias and
commercial bias (sponsorship influence of pharmaceutical companies). Ideally, before future clinical trials on depression are performed, a standardized method for measuring antidepressant efficacy should be assessed and end points should be clearly defined and, if possible, standardized as well. Furthermore, research should be conducted to provide evidence on clinically important differences of depression rating scales. In that way, researchers can determine beforehand, what result would have implications for clinical practice, regardless of the statistical significance of their findings. Once the standardized end points and method have been developed and the clinically important differences of depression rating scales have been determined, comparisons between multiple pharmaceutical treatments can be made to assess efficacy amongst different population groups (e.g., age group, gender, race). In order to clearly show the regulatory authorities the benefits in terms of efficacy and safety of a new pharmaceutical compared to the existing available medicines, such studies should ideally be performed during the post marketing authorization period for new antidepressants. A conditional marketing authorization, where the pharmaceutical company has to assess and investigate certain outcomes after having launched the medicine on the market, might be a useful approach for both the regulatory authorities and the pharmaceutical industry to provide real world information on effectiveness and side effects. (see Background Paper 8.2 and 8.4).

Antidepressant medicines for the elderly (See also background paper 7.3)

The pharmacological treatment of depression for the elderly has a number of clinical challenges. First, older patients with depression tend to present with somatic complaints instead of depressed mood. Such a presentation can lead to misdiagnosis and undertreatment of depression. Second, older adults tend to have multiple other medical conditions and are treated with multiple pharmaceuticals, which increases the chance of drug to drug interactions, drug-disease interactions and the risk of experiencing side effects. Third, older adults with depression may be more likely to experience a relapse than younger people do. When taken together, these factors complicate the selection and effective use of antidepressant agents in the elderly.

Another challenge on the research part is the lack of randomized clinical trials looking at this specific patient population, which makes it hard to draw conclusions on treatment efficacy for depression in this group. One of the few Cochrane systematic reviews on antidepressants in the elderly which was conducted in 2001 showed that compared to placebo, the major drug classes of TCAs, SSRIs (only fluoxetine was included in this review) and MAOIs were all effective in the treatment of depression in elderly patients. This old review did not have the evidence to report on the adverse events associated with these classes of drugs, but another review done in 2006 provided some more information. This review looked at the efficacy of SSRIs and TCAs in the treatment of depression in the elderly and compared withdrawal rates in each class. The authors concluded that SSRIs and TCAs were of the same efficacy, but that classical TCAs were associated with higher withdrawal rates due to side effect experience. A recent systematic review conducted in 2012 examined the efficacy of antidepressants in preventing the relapse and recurrence of depression in older people. They concluded that, when comparing antidepressants with placebo, there was no significant difference in outcome at six months follow-up. At 12 months follow-up, both SSRIs and TCAs were more effective than placebo in preventing recurrence and at 24 months the beneficial effect was evident for TCAs only. At 36 months there was no significant difference
for antidepressants overall. Some of these study results are graphically represented in Figure 6.15.8. The corresponding studies are represented in Table 6.15.1.

Figure 6.15.8 Selection of results from Cochrane systematic reviews on antidepressants versus placebo for the elderly (see Table 6.15.1 for study details)

![Graph showing odds ratio and confidence intervals for antidepressants versus placebo for the elderly](image)

* Although this finding is significant, the authors concluded this finding to be based on data with methodological flaws and therefore irrelevant.

<table>
<thead>
<tr>
<th>No.</th>
<th>Reference</th>
<th>No. trials</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wilson K, Mottram PG, Sivananthan A, Nightingale A. Antidepressants versus placebo for the depressed elderly. Cochrane Database of Systematic Reviews 2001, Issue 1.</td>
<td>17 (1327)</td>
<td>Described as elderly, geriatric senile or older adult</td>
</tr>
<tr>
<td>2</td>
<td>Wilkinson P, Izmeth Z. Continuation and maintenance treatments for depression in older people. Cochrane Database of Systematic Reviews 2012, Issue 11. Art.</td>
<td>7 (803)</td>
<td>60+</td>
</tr>
</tbody>
</table>
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The NICE clinical guideline summarizes the available evidence including systematic reviews outside of the Cochrane library. They conclude that there is no difference in the efficacy of the various antidepressants for which studies have been undertaken in older adults.\textsuperscript{107} They also conclude that there is no evidence of differences in acceptability of the medicines.\textsuperscript{104} With regard to augmenting an antidepressant with lithium, elderly patients appear to be more likely to achieve remission without the addition of lithium. These patients are also less likely to leave treatment early.\textsuperscript{104}

The dearth of studies of treatment of depression in the elderly reflects a problem identified in background paper 7.3 related to clinical trials in the elderly.

Antidepressants for treating depression in dementia

Studies suggest that depressive disorder is associated with increased risk of developing cognitive dysfunction and eventually dementia.\textsuperscript{145,146,147} Antidepressants may have protective abilities by increasing the proliferation and survival of newborn neurons and therefore improve memory processes and cognition.\textsuperscript{148,149} Furthermore, one preliminary study suggested that treatment with an SSRI may improve cognitive function and daily living in patients with Alzheimer disease.\textsuperscript{150}

There are very few systematic reviews that summarize all the evidence of clinical trials on the use of antidepressants in dementia because the lack of research in this area makes it difficult to make such a review.\textsuperscript{151} NICE guidelines recommend using the regular protocol for the elderly after making a thorough risk/benefit analysis. Furthermore, the specific use of antidepressant medicines with anticholinergic effects is not recommended because they may adversely affect cognition.\textsuperscript{152} In addition to antidepressants, cognitive behavioural therapy and a range of tailored interventions (such as reminiscence therapy, multisensory stimulation, animal-assisted therapy and exercise) are recommended to be available for people with dementia who have depression.\textsuperscript{104}

Further research in this area is needed before more definite conclusions can be drawn on effectiveness and safety of antidepressants in the treatment of depression in dementia.

Antidepressant medicines for children/adolescents (See also Background Paper 7.1)

The WHO does not recommend the use of antidepressants for the treatment of children 6-12 years of age with depression in non-specialist settings.\textsuperscript{153} For adolescents with a depressive episode in non-specialist settings it is recommended that fluoxetine, but not TCA’s or other SSRI’s, may be considered as a possible treatment. Adolescents on fluoxetine should be monitored closely for suicide ideas and suicidal behavior. For all adolescents on fluoxetine, support and supervision from a mental health specialist should be obtained, if available.\textsuperscript{154}

The National Institute for Health and Clinical Excellence (NICE) is currently updating their guideline ‘Depression in children and young people’ that specifically covers the care of children and adolescents. This updated guidance is due in September 2013.\textsuperscript{155} Their previous guideline (published in 2005) makes recommendations for the identification and treatment of depression in children (5–11 years) and young people (from the age of 12 up to 18) in primary, community and secondary care.\textsuperscript{156} The key recommendation from the 2005 guideline was that “children and young people with moderate to severe depression should be offered,
as a first-line treatment, a specific psychological therapy, and that antidepressant medication should not be offered to a child or young person with moderate to severe depression except in combination with a concurrent psychological therapy. Antidepressant medication should not be used for the initial treatment of children and young people with mild depression”.

For this paper, we summarize evidence found in systematic reviews from the Cochrane Library so as to give an overview of what systematic research has been conducted in this field in the past decades.

The effect of tricyclic antidepressants was reviewed in 2002 and it showed that they are not effective in the treatment of depression in prepubertal children. The effect of this class of medicines in the age group of adolescents was proven to be moderate at best. TCAs are therefore not recommended in the treatment of depression in children and adolescents (Figure 6.15.9 and Table 6.15.2).

Figure 6.15.9: Efficacy of tricyclic antidepressants on recovery and the prevention of relapse by various antidepressants versus placebo in children and adolescents,157,158

*based on limited evidence and with increased risk of side effects and suicide risk {[224 Cox,G.R. 2012]}
With regard to interventions for preventing relapse and recurrence, a systematic review based on limited evidence showed that antidepressants reduce the chance of relapse and recurrence in children and adolescents. However, the majority of these trials that involved antidepressant medication reported adverse events including suicide-related behaviors (Figure 6.15.10 and Table 6.15.2).159

Figure 6.15.10: Newer generation antidepressants versus placebo for depression in children and adolescents.159
The effect of newer generation antidepressants for children and adolescents has been reviewed in 2012.\textsuperscript{159} It was shown that those treated with an antidepressant have lower depression severity scores and higher rates of response/remission than those treated with a placebo. There was however, an increased risk (58\%) of a suicide-related outcome for those treated with antidepressants compared to those that received a placebo.\textsuperscript{159} The authors concluded that due to methodological limitations of their review the results had to be interpreted with caution and that the size and clinical meaningfulness of the significant results were uncertain. They argue that only after a careful risk benefit analysis it should be decided whether or not to give a child an antidepressant and that if an antidepressant is chosen, that fluoxetine might be the medication of first choice.\textsuperscript{159}

The United States National Institute of Mental Health (NIMH) comes to a similar conclusion after funding multiple clinical trials to assess which therapy is best to treat children and adolescents who suffer from depression.\textsuperscript{160} They state that a combination of the antidepressant fluoxetine with cognitive-behavioral therapy offers the most favorable result between benefit and risk for adolescents with major depressive disorder.\textsuperscript{161} Fluoxetine is currently the only antidepressant approved by the FDA for use in treating depression in children ages eight and older.\textsuperscript{160}

**Side effects of antidepressant medicines**

Experiencing side effects is an important reason for discontinuing antidepressant treatment.\textsuperscript{162,163} A 2004 study by Hu and colleagues reported that out of 401 patients treated with a SSRI, 86\% reported one or more side effects after 75 to 105 days follow up.\textsuperscript{164} Of all participants, 55\% reported at least one side effect they considered bothersome, with sexual dysfunction, drowsiness/fatigue, weight gain and insomnia being rated as the worst.\textsuperscript{164} Antidepressant side effects can adversely impact the treatment of MDD by adding to patient suffering and distress, contributing to a delay or failure to attain an effective or optimal antidepressant dose, and increasing the risk of noncompliance with therapy.\textsuperscript{165} A study conducted telephone surveys among 672 patients at three and six months after starting a SSRI for new or recurrent depression and reported that a higher frequency of adverse effects was reported in patients who switched or discontinued their SSRI early (43\%) compared with patients who discontinued their SSRI late (27\%).\textsuperscript{166}

Figure 6.15.11 shows a distribution of the age groups that have reported adverse reactions to antidepressant medicines to the FDA. When reading this graph, it is important to keep in mind that not all side effects to prescription drugs are reported to the FDA and that some of the side effects reported might be due to other reasons that the use of the antidepressant medicine. The numbers here are therefore low in comparison to the actual side effects occurring in the general population. This graph shows that most adverse events have been reported in the age group of 19-45 year old (25\%), followed by 46-65 year old (21\%) and 65 and older (9\%). In 31\% of all reports, the age of the patient reporting the adverse effects was not known.
Figure 6.15.11: Age distribution of adverse reactions to antidepressant drugs that have been reported to the FDA’s Adverse Event Reporting System (MedWatch), between 2004 and 2011.

Source: http://www.cchrint.org/psychdrugdangers/medwatch_psych_drug_adverse_reactions.php

Figure 6.15.12 gives an overview of the side effects of antidepressant drugs that have been reported to the Food and Drug Administration (FDA) between 2004 and 2011.

Figure 6.15.12: Adverse reactions to antidepressant drugs that have been reported to the FDA’s Adverse Event Reporting System (MedWatch), between 2004 and 2011.

Source: http://www.cchrint.org/psychdrugdangers/medwatch_psych_drug_adverse_reactions.php
Hu et al. also showed that side effects of antidepressant medications change over time.\textsuperscript{164} For example, 82\% of patients experienced nausea following two weeks of treatment, but after three months, only 32\% of those patients continued to have this side effect.\textsuperscript{164} In contrast, the percentage of patients who experienced weight gain increased over time (from 29\% during the first two weeks to 59\% in the three month follow-up period).\textsuperscript{164}

A more extensive overview of side effects associated with different classes of antidepressive medicines can be found in Appendix 6.15.3.\textsuperscript{125}

### Side effects in children and adolescents

A study reviewing five specific side effects (headache, nausea or vomiting, agitation, sedation, and sexual dysfunction) among patients diagnosed with depression, who were new users of antidepressants, aimed to measure and compare the prevalence of side effects in adults and adolescents.\textsuperscript{170} Data were drawn from a large national database of integrated medical and pharmacy claims and stratified for adolescents and adults. The authors compared five different drug classes (SNRIs, TCAs, bupropion, phenylpiperazine and tetracyclic antidepressants) with SSRIs and concluded that overall headache (up to 11\%) and nausea or vomiting (up to 4\%) were the most commonly detected side effects.\textsuperscript{170} This finding was the same for both age groups. Figure 6.15.13 is adopted from this study and shows which antidepressants showed more or less side effects compared to SSRIs for both age groups.

Figure 6.15.13 shows that relative to adults receiving SSRIs, adults receiving SNRIs had a significantly higher risk of nausea or vomiting and of having one or more side effects of any type.\textsuperscript{170} Adults receiving bupropion were also significantly less likely to have headaches than adults receiving an SSRI. This finding was the same for adolescents. Adolescents receiving a tetracyclic however, were more likely to have headaches than adolescents receiving an SSRI.\textsuperscript{170} Other trends in side effects can also be seen in the figure, but these effects were not statistically significant.

This study points out the difference in treatment response to antidepressant medicines for the different age groups.

Another side effect that is prevalent especially in children and adolescents is suicidal ideation and behavior.\textsuperscript{171} The relationship between suicidal ideation and antidepressants has mainly been studied in SSRIs. In October 2004, the FDA issued a warning about the increased risk of suicidal thoughts and behavior in children and adolescents being treated with antidepressant medication.\textsuperscript{172} The warning educates users and prescribers on the risk of suicidal thoughts and behavior and encourages clinicians to balance this risk with clinical need and to closely monitor patients, especially at the start of treatment.\textsuperscript{172}
4.2.2 Psychotherapy

A range of psychological and psychosocial interventions for depression have been shown to relieve the symptoms of major depressive disorder and there is growing evidence that psychosocial and psychological therapies can help people recover from depression in the long term. Because this report has a focus on pharmaceutical interventions, psychotherapies will not be discussed in much detail. More information on the different psychotherapeutical interventions can be found in the most recent mhGAP-IG guidelines and in the 2010 NICE guideline.

Of all the different types of psychotherapies, cognitive behavioral therapy (CBT) is by far the most studied. Cognitive behavioral therapy for depression was developed by Aaron T. Beck during the 1950s and was formalized into a treatment in the late 1970s. The cognitive model describes how, when depressed, people focus on negative views of themselves, the world and the future. The therapy takes an educative approach where, through collaboration,
the person with depression learns to recognize his or her negative thinking patterns and to re-evaluate his or her thinking. Meta-analyses have long proven the effectiveness of CBT as an intervention to treat depression.

Other high intensity psychotherapies that have proven to be effective include behavioral activation therapy, problem solving, interpersonal therapy and life review for older adults. Examples of less invasive (low intensity) therapies are: guided self-help, computerized cognitive behavioral therapy, reactivation of the social network and physical activity programmes. According to the stepped care model, displayed in Figure 6.15.7, these low intensity therapies should be applied to patients presenting with persistent sub-threshold depression or mild to moderate depression. Only if patients do not respond to these initial treatments or if patients present with more severe symptoms, will the high intensity interventions be recommended. 

Studies that compared a psychological treatment to a combined treatment consisting of the same psychological treatment with a pharmacological therapy have shown that combined treatments are more effective than psychological treatment alone. The effect of combined treatment over pharmacotherapy alone has been less studied and results of different studies have not been conclusive, although there seems to be an advantage of using combination treatment over pharmacological treatment alone, both in direct outcomes and in reducing drop-out rates.

4.2.3 Electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) a

For those patients who do not respond to psychological and pharmacological approaches, or for patients who need treatment more rapidly, alternative therapeutic options are needed. Electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) are two of those options that will be briefly discussed in this section.

Electroconvulsive therapy has been used as a treatment for depression since 1938. During ECT, an electric current is passed briefly through the brain, via electrodes applied to the scalp, to induce generalized seizure activity. The individual receiving treatment is placed under a general anesthetic and muscle relaxants are given to prevent body spasms. The ECT electrodes can be placed on both sides of the head (bilateral placement) or on one side of the head (unilateral placement).

In the 1950s the popularity of this treatment decreased due to concerns regarding its’ side effects and the availability of new drug treatments. Despite its controversial history, ECT has been used successfully in clinical practice, and it remains a rapid and effective treatment for depressive disorders, particularly when other treatments have failed. Response rates are greater than 80%, with even higher rates observed in those with psychotic depression. The biggest concern in using ECT for the treatment of depression remains the cognitive side effects that cause memory loss up to about six months post-treatment. Some authors have even concluded that due to these side effects and the poor cost-benefit analysis for ECT, its use cannot be scientifically justified.

a The WHO currently has no guidelines on the use of TMS and ECT in the treatment of depression.
The most recent NICE guideline concludes in recommending the use of ECT only for “acute treatment of severe depression that is life threatening and when a rapid response is required or then other treatment have failed” and “not to use ECT routinely for people with moderate depression” but to “consider it if their depression has not responded to multiple drug treatments and psychological treatment.”

Transcranial magnetic stimulation is another popular brain stimulating technique. It uses an electromagnetic coil on the scalp to create an extremely potent but brief magnetic field. This magnetic field enters the surface of the brain (cerebral cortex) without interference from the skin, muscle, and bone. In the brain, the magnetic pulse encounters nerve cells and induces electrical current to flow. Thus, the magnetic field created from electrical energy in the coil passes through the skull and is converted back into electrical energy in the brain. Treatment with TMS does not require anaesthesia and it can be performed on an outpatient basis. The daily sessions of treatment last about 30 minutes and are repeated for two to four weeks or longer.

Transcranial magnetic stimulation therapy received FDA clearance for the treatment of adult patients with MDD who have failed to receive satisfactory improvement from one prior antidepressant medication in 2008. Ever since the legislation of its use as a treatment, the body of TMS literature has suggested that daily TMS (on the left side of the brain in the prefrontal area) for three to six weeks has antidepressant effects that are significantly greater than sham, and that these effects in open label studies are clinically meaningful (30% remission), with low side effects and no drug–drug interactions. This evidence is based both on clinical trials and clinical treatment data.

A 2002 systematic review from the Cochrane Depression, Anxiety and Neurosis Group collected and compared data from randomized controlled trials assessing the therapeutic efficacy and safety of transcranial magnetic stimulation for depression. The researchers concluded that the available data showed no strong evidence for benefit from using TMS to treat depression. However, they did recognize that many of the included studies had small sample sizes and that, therefore, the possibility of a benefit could not be excluded. Articles that have been published since this 2002 Cochrane Review tend to be more positive. A revision of the Cochrane Review would be of great value.

Several studies have looked into the difference between ECT and TMS treatment and the potency of TMS as a replacement of ECT, due to its lower side effect profile. A recent meta-analysis and systematic review concluded that ECT seems to be more effective than high frequency TMS for treating MDD, although both treatments did not differ in terms of dropout rates. The authors suggest that future research with larger clinical trials is needed to draw conclusions on implications for clinical practice.

Future research on TMS should focus on the optimal dose of magnetic stimulation over the optimal time period, something that has not been established yet. Also, providing evidence on the optimal positioning of the coil would be another relevant research priority. Overall, investigation of the neurobiological underpinning of these neurostimulatory treatments, is needed to provide new insight into the neurophysiology of mood regulation.
4.3 Prevention

Given the high costs of depression once it occurs (see section 3) and the promise of initial studies, prevention of depression is an area that should deserve more attention. Although study results have been contradictory, many prevention programmes implemented across the lifespan have provided evidence on the reduction of elevated levels of depressive symptoms.\textsuperscript{200} Effective community approaches to prevent depression focus on several actions surrounding the strengthening of protective factors and the reduction of risk factors.\textsuperscript{6} Examples of strengthening protective factors include school-based programs targeting cognitive, problem-solving and social skills of children and adolescents, exercise programs for the elderly and mobile phone delivery of prevention interventions.\textsuperscript{200, 201, 202} Another opportunity for preventing depressive disorders seems to be in education.\textsuperscript{200} During the last ‘World Mental Health Day’ (October 2012) the WFMH called for “public education and awareness campaigns on mental health in all countries” so as to “reduce stigma and discrimination, increase the use of mental health services and bring mental health and physical health care closer to each other.”

A recent systematic review showed that targeted and universal depression prevention programmes are likely to be effective in reducing symptoms of depression and incidence of depressive disorder.\textsuperscript{203} However, the lack of placebo or attention controls\textsuperscript{b}, the lack of allocation concealment and heterogeneity in findings remain a concern in these studies. Future studies should test efficacy against a credible alternative to address the gap that remains concerning a possible placebo effect. Furthermore, it will be important to measure not only reduction in depression, but also function, and the medium and long term consequences.\textsuperscript{203} In terms of nonspecific risk factors, attention to poverty, exposure to violence, sexual abuse, and family circumstances are needed.\textsuperscript{200} It is also important to focus more research on moderators of intervention effects. It appears that some intervention programs work better for youth, who have a particularly high risk for depression, which are based on individual risk variables and/or family risk. Additional important moderators to consider in future research include sex and exposure to recent stressors.\textsuperscript{200} Given the gender differences in prevalence, and the change in these that occurs in adolescence with a disproportionate increase in prevalence rates for girls, it is likely that girls and boys will respond differently to interventions.\textsuperscript{203}

5. Persistence of the disease

Our poor understanding of the neurophysiology of mental disorders like major depressive disorder (MDD) affects our ability to diagnose in a more efficient way, predict clinical outcomes in patients and our capacity for producing newer highly efficacious and safe antidepressants.\textsuperscript{204} To date there is no evidence for positive diagnostic or predictive MDD biomarkers. A specific biomarker of treatment response for MDD might lead to less misdiagnoses and, would also affect our capacity to delineate MDD from other neurodegenerative disorders.\textsuperscript{204} The development of a neurobiological parameter for a

\textsuperscript{b} treatment that mimics the amount of time and attention received by the treatment group but is thought not to have a specific effect upon the subjects
Update on 2004 Background Paper, BP 6.15 Depression

reliable prediction of the individual patients' responses to different antidepressive drugs would allow immediate, adequate and effective drug treatment, and shorten the disease process, thus preventing chronicity or sustained therapy resistance.\textsuperscript{205} In addition, indirect and direct cost of treatment could be reduced.\textsuperscript{205} However, it is currently unknown if such a biomarker for depression exists. It may be possible that multiple biomarkers are important in the physiopathology of depression. In that case, the ultimate research goal should be to develop a model of the integrative pathophysiology (or pathophysiology's) associated with depression.

However, what is urgently needed, are predictors of treatment response, which allow for a preselection of the best treatment strategy for the individual patient. This kind of prediction should possibly be based on information regarding the respective functions of central serotonergic or noradrenergic pathways. Thus, one promising way to predict response to antidepressants could be based on the identification of neurochemical subtypes of depressed patients.\textsuperscript{205}

There have been proposals for differential predictors but the data on these predictors have been preliminary and need to be further researched.\textsuperscript{204,205} There have also been recent proposals for research strategies by researchers targeting to detect and validate positive MDD biomarkers.\textsuperscript{204} However, these strategies are based on a complex (molecular, neurophysiological and genetic) biological model that includes state of the art knowledge on the pathobiology of MDD.\textsuperscript{204}

Low depression diagnosis and treatment rates are part of the reason why the burden of depression still exists in the community. In an analysis of national survey data (survey was conducted between 2001 and 2005) in the United States, researchers found that diagnosis rates of depression were just 3.8 - 7.2\%.\textsuperscript{206} In Europe the treatment gap is still considerable, 50\% of cases of depression in primary health care settings are unrecognized, although 30\% of consultations with general practitioners are for mental health problems.\textsuperscript{207}

Fewer than 10\% of patients finish a therapeutic course of antidepressive treatment.\textsuperscript{205,208} Poor adherence to pharmacological and psychosocial treatments for depression, especially in the elderly, is an additional barrier to effectively treat patients suffering from depression.\textsuperscript{208} Rates of non-adherence may be as high as 60\% in older adults.\textsuperscript{209} Factors attributed by some researchers for this high non-adherence rate amongst elderly include lack of information and misperceptions about mental illness and its treatment, stigma, lack of family support, cognitive impairment, adverse events, side effects, and a poor physician-patient communication or relationship.\textsuperscript{209}

Furthermore, therapy resistant depression (TRD) is a common clinical problem and challenges both patients and doctors. A large percentage of depressive episodes are associated with some degree of treatment resistance.\textsuperscript{210} Approximately two-third of patients fail to achieve remission after the initial antidepressant therapy.\textsuperscript{211,212} If a patient doesn’t respond to one type of medicine, the chance of remission decreases with the next class of medicine.\textsuperscript{213} Despite consistent advances in the pharmacotherapy of mood disorders in the last decade, high rates of TRD are still a challenging aspect of overall management.\textsuperscript{210}

The low availability of antidepressant drugs, among other pharmaceuticals, is another factor contributing to the persistence of the disease, especially in developing countries.\textsuperscript{214,215} Despite
the existence of cost-effective interventions, including administration of psychotropic medicines, the number of persons who remain untreated for their neuropsychiatric condition is as high as 85% in low- and middle-income countries (LMICs). Results from a recent study demonstrate that overall country development is associated with affordability and that strengthening particular facets of mental health systems might improve availability of antidepressant and other psychotropic medicines.

6. Past and current research on depression

6.1 EC Funded research on depression

Currently, there are over 50 projects funded by the Sixth EC Framework Programme (FP6) and the Seventh EC Framework Programme (FP7), specifically doing research on depression. Nineteen of these projects were funded by FP6, whereas thirty-six projects were funded by FP7. Most of these projects are being conducted in the United Kingdom, Germany and Spain. Thirty-five of the projects are, at the time of writing this report, still being executed, whereas three and seventeen projects have been accepted and completed, respectively (Figure 6.15.14). Research initiatives through European partnerships are important to help reduce the burden of disease and raise awareness of mental disorders.

The complete list of projects that are funded by both FP6 and FP7 can be found in Annex 6.15.2. Most of these projects are focusing on the physiopathology of depression.

Figure 6.15.14: Stages of projects on depression funded by FP6 and FP7.

![Project stages funded by FP6 and FP7](image)

Source: Annex 6.15.2
6.2 Past and current trials

Annex 6.15.3 shows the search strategy that was used to acquire the data in this paragraph. Data was derived from all the research data that is relevant to MDD, from a search that was conducted on the United States Clinical Trial Register. This search produced a total number of 3 122 trials.

Only a minority of these trials, 270 (8.6%), had published their results. From the total amount of trials, 643 (20.5%), 162 (5.2%), 1991 (63.8%) and 101 (3.2%) were conducted with behavioral, device, drug and procedure as an intervention, respectively (Figure 6.15.15). Most of the drug intervention trials had studied escitalopram, duloxetine and quetiapine (100, 82 and 68 trials, respectively). Popular behavioral and procedure interventions were cognitive-behavioral therapy and acupuncture, respectively.

Figure 6.15.16 shows the number of studies on depression per region in the world since the start of FP6 onwards. Most of the studies on depression have been conducted in North America (65%), while only 23% of the trials have been conducted in Europe.

Regarding the age groups of the participants, a majority (94.7%) of the trials enrolled adult participants, while only a minority (4.7% and 0.5%) of the trials had enrolled children and elderly, respectively, as participants (Figure 6.15.17). This demonstrates that elderly and children are underrepresented in depression trials.

Figure 6.15.15: Distribution of interventions among trials on depression.

![Distribution of interventions in depression trials](source: clinicaltrials.gov)
Figure 6.15.16: Geographic map number of studies on depression, per region worldwide.

Source: clinicaltrials.gov\textsuperscript{216}

Figure 6.15.17: Percentages of participants in depression trials per age group.

Source: clinicaltrials.gov\textsuperscript{216}

Approximately half of the trials had less than 100 participants (1541), and just ten per cent of the trials (318) had more than 500 participants enrolled. Table 6.15.3 below shows the number of trials on depression that has been started, per year since 2003.
### Table 6.15.3: Numbers of trials on depression per year.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
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<tr>
<td>2004</td>
<td>253</td>
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<tr>
<td>2010</td>
<td>324</td>
</tr>
<tr>
<td>2011</td>
<td>327</td>
</tr>
<tr>
<td>2012</td>
<td>289</td>
</tr>
</tbody>
</table>

Source: clinicaltrials.gov

### 6.3 Pharmaceutical pipeline

The development of psychiatric drugs is considered high risk due to high trial failure rate and high costs associated with a research programme, especially in the current global economic climate. Many pharmaceutical companies have changed their pipelines to remove R&D into medications to treat MDD as well as other mental disorders. Both GlaxoSmithKline and AstraZeneca have announced their intention to scale back drug discovery research for some psychiatric disorders, including depression. The resulting decrease in new medicines that are in development for MDD is in contrast with the rise of the global burden of disease that increased over the past two decades (please see Section 2 of this background paper).

The most active compounds that are currently in the pharmaceutical industry’s pipeline are sigma-1 receptor modulators, triple reuptake inhibitors (TRI), NMDA antagonists, vasopressin receptor antagonists and melatonin targets (Table 6.15.4). Appendix 6.15.1 contains a list of medicines that are in the pipeline since 2009.

### Table 6.15.4: Number of new pharmaceuticals being investigated per drug class since 2009

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Number of active compounds being researched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoamine</td>
<td>31</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>4</td>
</tr>
<tr>
<td>Amino acid neurotransmitters</td>
<td>12</td>
</tr>
<tr>
<td>Neuropeptides</td>
<td>13</td>
</tr>
<tr>
<td>Neurotrophic</td>
<td>3</td>
</tr>
<tr>
<td>Cytokines</td>
<td>5</td>
</tr>
<tr>
<td>Other mechanisms</td>
<td>3</td>
</tr>
</tbody>
</table>

7. Research gaps

As explained in Section 6, the amount of pharmaceutical research that is done on (new) antidepressants is voluminous, but might shrink in the near future since some major pharmaceutical companies have announced a scale back of their research for some psychiatric disorders, like depression.\textsuperscript{217} Also, the focus on augmentation therapies with antidepressants has been increased, probably in an effort to achieve an increased and/or more rapid antidepressant response.\textsuperscript{218}

Raising awareness, reducing stigma, and reducing the discriminatory attitudes may be powerful tools to decrease the burden of disease.\textsuperscript{219} These interventions might help to achieve earlier detection and/or diagnoses of MDD. Therefore, it may be useful to investigate what the best way is to address these issues to the public in order to make them aware.

NICE has published research recommendations in their 2009 guidelines on depression, and identified multiple research gaps.\textsuperscript{(4,102)} These recommendations can be found in summary in Box 6.15.2. For more background information about these recommendations please see Annex 6.15.4.

These research gaps, which have been identified by the NICE, are supported by the authors of this report, but some of these mentioned gaps, however, go beyond pharmaceuticals.

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**Box 6.15.2 Gaps identified by NICE 20094**

- “Defining the best pharmacological treatment strategy for people with depression who have had an inadequate initial response to an antidepressant.

- What the efficacy is of short-term psychodynamic psychotherapy compared with cognitive-behavioral therapy (CBT) and antidepressants, in well-defined depression of moderate to severe severity.

- Determining the cost effectiveness of combined antidepressants and CBT compared with sequenced medication followed by CBT and vice versa for moderate to severe depression.

- The efficacy of antidepressants and placebo compared with CBT for persistent subthreshold depressive symptoms.

- Determining the efficacy of counseling compared with low-intensity cognitive behavioral interventions and treatment as usual in the treatment of persistent subthreshold depressive symptoms and mild depression.

- The efficacy of CBT and antidepressants compared with behavioral activation in the treatment of moderate to severe depression.

- The cost effectiveness and efficacy of different systems for the organization of care for people with depression.

- Determining the cost effectiveness and efficacy of CBT, interpersonal therapy (IPT) and antidepressants in prevention of relapse in people with moderate to severe recurrent depression.”

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6.15-43
There has been very little research on the efficacy of different therapies including medicines and psychotherapies for depression in children, adolescents and the elderly. The research that has been performed on these age groups to date has mainly been looking at efficacy of pharmaceuticals in the short term. To fill in these gaps, more research needs to be conducted on these specific age groups to identify the best treatment strategy for these population groups. Also, the efficacy on the long term has to be clarified in order to demonstrate the optimal treatment for depression in children, adolescents and the elderly (also see chapter 7.1 and 7.3).

Another way of reducing the high non-adherence rates related to currently available antidepressants, and to potentially also reduce the number and severity of their side effects, is the development and usage of antidepressant depot preparations. The major advantage of pharmaceutical depot preparations over oral medication is the facilitation of compliance in medication taking by patients.220 A number of delivery systems have been developed for other diseases to address suboptimal therapy outcomes by enhancing drug delivery, assuring efficacy of treatment, reducing side effects, improving compliance and drug targeting specific locations resulting in a higher efficiency.220, 221 Such versatile delivery systems offer the advantage of a very high loading and controlled release of various drug for an extended period of time compared with plain delivery system. New formulations of antidepressants may offer advantages over older formulations in terms of convenience, side effect profiles, efficacy, and/or a fast onset of action.220 Depot neuroleptics have been widely introduced for long-term treatment of schizophrenia. The question as to whether depot antidepressants should be developed for the treatment of chronic depression and for the prophylaxis of recurrent depression exists. This approach seems to be indicated in patients showing poor compliance to oral antidepressive medication and in patients suffering from secondary depression and who are already receiving depot antipsychotics, but it is also indicated in subgroups of patients who, for social, cultural or personality reasons, have problems with regard to a regular and long-term intake of oral medication.220 Before the development of depot antidepressants is initiated, the ethical and technical issues relating to this form of medication should be addressed.

Pharmacogenetic studies have demonstrated a panel of candidate genes and their possible association to antidepressant response and adverse drug reactions (see also chapter 8.4).38, 40 The studies suggest that genetic variation may contribute to variability in medication response, with an impact on both efficacy and adverse drug reactions (ADRs). These genetic variations may also account for the persistence of MDD.38 While the field of psychiatric pharmacogenetics is rapidly developing, and it is thought that genetic patient information will likely revolutionize clinical practice in the very near future, most of the pharmacogenetic findings for antidepressants have thus far been inconclusive and controversial.222 The main problem with current pharmacogenetic studies is the lack of standardization, making it difficult to distinguish between positive and negative findings in the same candidate gene.222

Future clinical research, conducted in a more standardized manner with bigger samples, may produce findings concerning the exact impact of genetic variations, that improve therapeutic strategies in terms of personalizing therapy, or it may even give the pharmaceutical industry the potential of developing new, safer and more effective drugs that are based on completely new mechanisms of action.
Furthermore, it is uncertain if there are any gender differences in response and adverse drug event rates after taking antidepressant pharmaceuticals. Some pharmacodynamic and pharmacokinetic studies suggest that there are differences, but the clinical effect of these pharmacodynamic and pharmacokinetic differences between genders and age groups is currently unknown and multiple studies have shown different results regarding the response rates and the number and severity of adverse drug reactions.

In conclusion, future research on the abovementioned gaps may demonstrate:
- Currently unknown biomarkers or biological pathways of MDD that can be targeted pharmaceutically;
- The optimal treatment strategy for different stages of depression for different population groups;
- The cost effectiveness of each treatment for MDD, including inter-treatment and different combination therapy comparisons;
- The (long term) effectiveness of different treatment strategies for children, adolescents and the elderly who suffer from depression;
- Differing responses, adverse reactions and adherence patterns related to genetic or other factors;
- The disaggregated effect of treatment modality between psychotherapy and pharmaceutical therapy;
- Determinants of response to different therapies between age groups and genders;
- The relation and correlation between statistically significant effects and the actual clinical effectiveness of different treatment strategies;
- Optimized and standardized method and end points for measuring antidepressant efficacy; and
- Evidence on clinically important differences of depression rating scales that have implications on clinical practice.

8. Conclusions

Depression causes a large burden of disease worldwide and is a leading cause of high health care costs. Europe accounts for more than 13% of the total DALYs caused by MDD worldwide. The proportion of the burden of disease for major depressive disorder in all three European regions is higher than the global burden proportion. This demonstrates that Europe has a relatively higher burden of disease due to MDD than the rest of the world. In terms of years lived with disability (YLDs), MDD increased globally with 37% in just two decades between 1990 and 2010. MDD is ranked second by global and European YLDs ranking.

Effective prevention of major depressive disorder has the potential to reduce its enormous burden and high costs considerably. MDD is a common disorder, widely distributed in the population, and usually associated with substantial symptom severity and role impairment. While the recent increase in treatment is encouraging, inadequate treatment is a serious concern. Emphasis on screening and expansion of treatment needs to be accompanied by a parallel emphasis on treatment quality improvement. Despite modest advances in evidence-
based care, adherence to treatment guidelines and algorithms remains low. Issues related to side effects are inadequately addressed by both physicians and patients.

Multiple factors contribute to low levels of treatment effectiveness. Stigma remains a potent factor in patients acknowledging that they have depression and need help. Similarly, stigma may lead to reluctance on the physician’s part to openly address the issue of depression with his/her patients. Lack of access to mental health services along with stigma contribute to a low detection rate. There is also a perceived lack of competency and capacity to handle issues, such as suicidality, that a patient with depression may present with. An early detection and diagnosis will increase the chance that depressed patients will receive adequate treatment as soon as possible, which in turn increases their chance to achieve a state of remission.

In the context of rising health care costs and the ever-increasing competitive business environment, the impact of depression in the workplace has become an issue for society and employers. The impact depression has on whether an employee is absent from work or not is well known. It is of equal concern to employers that depression reduces work efficiency from depressed employees and thus increases costs. Given the increasing awareness of both the direct and indirect costs of depression in the workplace, employers have started to demand more accountability from both health plans and providers.

Depression results in substantial costs to society because of its prevalence, impact on functioning, early age of onset and chronic or recurrent nature. A wide range of effective treatments for depression are available, yet rigorously tested clinical models to improve depression care have not been widely adopted by healthcare systems, and substantial gaps exist in access to quality care. Some of the patient, healthcare provider, practice and payer-level barriers to improving depression are financial. However, critical gaps in the literature on the cost of depression, especially in Europe, remain. For instance, although we have reasonable estimates of the costs of depression, mainly from studies that have been conducted in the United States, we do not know the economic burden of untreated and/or inappropriately treated versus appropriately treated depression. These research gaps should be addressed.

One of the most common of the challenges to be addressed across Europe is resource insufficiency: not enough financial resources are made available for mental disorders like MDD. This is clearly a major issue for countries where the percentage of GDP devoted to health care is low, or where the percentage going to mental health is limited. If few funds are allocated to depression and mental health in general, there is clearly limited scope for building an effective, accessible system of services and treatments for patients. But regardless of a country’s GDP, attitudes can put up a barrier to the allocation of resources to mental health. The public may have prioritized immediate life-threatening conditions over other health concerns, especially underestimating depression as an important mental health disorder.

Furthermore, it is most likely the case that multiple biomarkers are important in the physiopathology of depression. In that case, the ultimate research goal should be to develop a (clinical) model of the integrative pathophysiology, where multiple biomarkers and biological pathways, that are associated with major depressive disorder, are involved.
Genetic factors are most likely to also be involved in the development and progression of MDD.

The question of whether depot antidepressants should be developed for the treatment or prophylaxis of recurrent and/or long-term depression was also addressed in the background paper. New (depot) formulations of depression might offer advantages over older formulations in terms of convenience, side effect profiles, efficacy, and/or a fast onset of action. As discussed in Section 5 of this background paper, the global availability of the essential antidepressants is also an important factor regarding the persistence of the disease, especially in LMIC.

Furthermore, the characterization of specific patient groups that suffer from side effects or that are non-adherent has not yet been performed despite the numerous studies that have been conducted on antidepressants in the past two or three decades. The currently available data lacks important information so that those who suffer most from adverse drug reactions and/or those who are not adherent to their pharmaceutical therapies can be characterized and targeted for further research, including how care is provided.

Also, where needed, the integration of a health system which is focused on the (early) detection or diagnosis in the primary care is highly desirable. The integration of such health care in the primary care will most likely increase the chance that depressed patients will receive adequate treatment as soon as possible, which in turn increases their chance to achieve a state of remission and, therefore, also reduces the overall burden of depression. Multiple researchers have also concluded that some general practitioners and other doctors are not capable or well-trained enough to detect depression, especially when comorbidities exist.

Currently, research on depression and antidepressants, mainly in adults, is abundant. Specific age groups, however, have not been studied enough and the effectiveness of different treatment strategies for these patients is still not well known. Studies on depression in children, adolescents and the elderly represent a minority of the total amount of studies that have been conducted so far. In order to improve the treatment of depression in terms of efficacy, effectiveness, safety and adherence, more (comparative) research on different treatment strategies are needed, specifically aimed for these subgroups of patients.

References


Update on 2004 Background Paper, BP 6.15 Depression


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Berlim MT, Van den Eynde F, Daskalakis ZJ. A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression. Psychol Med 2012 Dec 3:1-10.


Berlim MT, Van den Eynde F, Daskalakis ZJ. Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (RTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. Depress Anxiety 2013 Jan 24.


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216 clinicaltrials.gov


Annexes

Annex 6.15.1: Overview of ICD-10 and DSM-IV classifications of mood disorders

<table>
<thead>
<tr>
<th>DSM-IV</th>
<th>Classification of psychiatric diagnoses only</th>
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<td></td>
<td><em>Axis I</em>: All diagnostic categories except mental retardation and personality disorder</td>
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<td></td>
<td>► Mood disorders</td>
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<tr>
<td></td>
<td>1) episodes</td>
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<tr>
<td></td>
<td>2) depressive disorders</td>
</tr>
<tr>
<td></td>
<td>- single major depressive disorder</td>
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<tr>
<td></td>
<td>- recurrent major depressive disorder</td>
</tr>
<tr>
<td></td>
<td>- dysthymia</td>
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<td></td>
<td>- depressive disorder NOS (not otherwise specified)</td>
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<tr>
<td></td>
<td>3) bipolar disorders</td>
</tr>
<tr>
<td></td>
<td>4) other mood disorders</td>
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|        | *Axis II*: Personality disorders and mental retardation |
|        | *Axis III*: General medical condition; acute medical conditions and physical disorders |
|        | *Axis IV*: Psychosocial and environmental factors contributing to the disorder |
|        | *Axis V*: Global Assessment of Functioning or Children's Global Assessment Scale for children and teens under the age of 18 |

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<th>ICD-10</th>
<th>Classification of all medical diagnoses</th>
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<td>► Mental and behavioral disorders</td>
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<td>➢ Mood disorders</td>
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<td></td>
<td>1) Manic episode</td>
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<td>2) Bipolar affective disorder</td>
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<td>3) Depressive episode</td>
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<td>4) Recurrent depressive disorder</td>
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<td>5) Persistent mood disorder</td>
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<td>➢ dysthymia</td>
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<td>6) Other mood disorder</td>
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<td>7) Unspecified mood disorder</td>
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Sources:
Annex 6.15.2: EC Sixth and Seventh Framework Projects focusing on depression

Searched on cordis.europa.eu for “depression” under the FP6 and FP7 programmes. The search was conducted on 25-01-2013.

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<thead>
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<td>GENDEP</td>
<td>Genome-based therapeutic drugs for depression (gendep)</td>
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<td>NEWMOOD</td>
<td>New molecules in mood disorders: a genomic, neurobiological and systems approach in animal models and human disorder</td>
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<td>EPCRC</td>
<td>Improved treatment of pain, depression and fatigue through translation research</td>
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<td>SCVDD2B</td>
<td>Serotonin, Cardiovascular disease and depression: Contribution of Serotonin 2B Receptors</td>
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<td>MOODNOP</td>
<td>Nociceptin/orphanin FQ-NOP receptor signaling and mood regulation: behavioural, pharmacological and neurochemical studies</td>
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<td>SPAR</td>
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<td>FEMALE NEUROGENESIS</td>
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### Memory

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<td>Physiological basis of learning and memory processes in the brain</td>
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<td>A sequential high throughput ion channel screening system for drug discovery in neurological and psychiatric disorders</td>
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<td>GWAS BMI T2D AND DEP</td>
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<td>A new logic to control signaling pathways in the mouse brain: The role of MAPK in emotional behavior</td>
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Annex 6.15.3: Search strategy for data on past and current research related to MDD

A search was conducted on The U.S. Clinical Trial Register website (www.clinicaltrials.gov) on 25/01/2013, for all clinical trials that contained the terms ‘depression’, ‘depressive disorder’ or ‘major depressive disorder’ between 01/01/2003 and 25/01/2013. This search strategy produced a total number of 3122 trials. Because not all trials contain the same complete data, calculations have only been made where possible and any number or percentage that is shown here is calculated relatively to the available data from The U.S. Clinical Trial Register.
Annex 6.15.4: NICE 2009 depression guidelines: Recommendations for research gaps


- “Defining the best pharmacological treatment strategy for people with depression who have had an inadequate initial response to an antidepressant. Inadequate response to a first antidepressant is a frequent problem but the best way of sequencing treatments is not clear from the available evidence.

- What the efficacy is of short-term psychodynamic psychotherapy compared with cognitive-behavioral therapy (CBT) and antidepressants, in well-defined depression of moderate to severe severity. Psychological treatments are an important therapeutic option and/or alternative to CBT and antidepressants for people with depression. CBT has the best evidence base for efficacy but it is not effective for everyone. The availability of alternatives drawing from a different theoretical model is therefore important.

- Determining the cost effectiveness of combined antidepressants and CBT compared with sequenced medication follow by CBT and vice versa for moderate to severe depression. There is a reasonable evidence base for the superior effectiveness of combined antidepressants and CBT over either treatment alone in moderate to severe depression. However the practicality, acceptability and cost effectiveness of combined treatment over a sequenced approach is less well-established.

- The efficacy of antidepressants and placebo compared with CBT for persistent sub-threshold depressive symptoms. Persistent sub-threshold depressive symptoms are increasingly recognised as affecting a considerable number of people and causing significant suffering, but the best way to treat it is not known. There are studies of the efficacy of antidepressants for dysthymia (persistent sub-threshold depressive symptoms that have lasted for at least two years) but there is a lack of evidence for CBT.

- Determining the efficacy of counseling compared with low-intensity cognitive behavioral interventions and treatment as usual in the treatment of persistent sub-threshold depressive symptoms and mild depression. Psychological treatments are an important therapeutic option for people with sub-threshold symptoms and mild depression. Low-intensity cognitive and behavioural interventions have the best evidence base for efficacy but the evidence is limited and longer-term outcomes are uncertain, as are the outcomes for counseling. It is therefore important to establish whether either of these interventions is an effective alternative to treatment as usual.

- The efficacy of CBT and antidepressants compared with behavioral activation in the treatment of moderate to severe depression. Psychological treatments are an
important therapeutic option for people with depression. Behavioural activation is a promising treatment but does not have the substantial evidence base that CBT has. The availability of alternatives drawing from a different theoretical model is important because outcomes are modest even with the best supported treatments. It is therefore important to establish whether behavioural activation is an effective alternative to CBT and one that should be provided.

- **The cost effectiveness and efficacy of different systems for the organization of care for people with depression.** The best structures for the delivery of effective care for depression are unfortunately poorly understood.

- **Determining the cost effectiveness and efficacy of CBT, interpersonal therapy (IPT) and antidepressants in prevention of relapse in people with moderate to severe recurrent depression.** Psychological and pharmacological treatments are important therapeutic options for people with depression, but evidence on the prevention of relapse (especially for psychological interventions) is limited. All of these treatments have shown promise in reducing relapse but the relapse rate remains high.”
Appendices

Appendix 6.15.1: Active compounds in the pharmaceutical pipeline since 2009.

Source tables: Expert Opin. Emerging Drugs (2012) 17(3);285-294

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<tr>
<th>Drug class</th>
<th>Agents in development</th>
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<th>Phase</th>
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<td>Desvenlafaxine</td>
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<td>IV</td>
<td>Approved in US 2008, Canada 2009</td>
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<td></td>
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<td></td>
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<td>Application withdrawn from European Medicines Agency (EMA)</td>
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<td>Confirmatory studies of minimal impact on CYP450 enzymes</td>
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<td>EMSAM (Transdermal selegiline)</td>
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<td>Approved in Europe 2009, increased global availability</td>
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<td>5HT2C antagonist</td>
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<td>Geprone</td>
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<td>a supplemental filing</td>
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<td>Currently undergoing trials to treat sexual dysfunction [30-32]</td>
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<td>Vilazodone (Viibryd)</td>
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<tr>
<td>LuAA21004 (vortioxetine)</td>
<td>SERT inhibition, SHT1A agonist,</td>
<td>III</td>
<td>Phase III trials ongoing with vortioxetine, expected completion in</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5HT1B/5HT3/5HT7 antagonist</td>
<td></td>
<td></td>
<td>the first quarter of 2012, with NDA filing later in 2012</td>
</tr>
<tr>
<td>LuAA24530 (Tedatixetine)</td>
<td>SERT inhibition, SHT2/5HT2C antagonism</td>
<td>III</td>
<td>Positive Phase II trials</td>
<td></td>
</tr>
<tr>
<td>DOV 216,308</td>
<td>SHT/NE/DA reuptake inhibition</td>
<td>II</td>
<td></td>
<td>Phase III trials with tedatixetine pending</td>
</tr>
<tr>
<td>DOV 21,947 (EB-1010, amitifadine)</td>
<td>SHT/NE/DA reuptake inhibition</td>
<td>II</td>
<td></td>
<td>Licensed to Merck &amp;Co., undisclosed development plans</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Now EB-1010 (amitifadine) by Euthymics Bioscience, positive small RCT</td>
</tr>
<tr>
<td>GSK 372475</td>
<td>SHT/NE/DA reuptake inhibition</td>
<td>II</td>
<td></td>
<td>Failed: February 2009 published failure of 2 MDD clinical trials</td>
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<tr>
<td>SEP 225289</td>
<td>SHT/NE/DA reuptake inhibition</td>
<td>II</td>
<td></td>
<td>Failed: July 2009 announced failed Phase II study vs placebo and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>venlafaxine</td>
</tr>
<tr>
<td>Amibegron (SR 58611)</td>
<td></td>
<td>B3 adrenergic agonist</td>
<td>II</td>
<td>Discontinued: July 2008, no reason given</td>
</tr>
<tr>
<td>Levomepromazine (FZ695)</td>
<td>Enanitomer of milapramine</td>
<td>III</td>
<td></td>
<td>Positive Phase II results, not yet published</td>
</tr>
<tr>
<td>LY2216684 (edvetroxetine)</td>
<td></td>
<td>NRI</td>
<td>III</td>
<td>Positive Phase II results</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recruiting for Phase III trials</td>
</tr>
<tr>
<td>SEP 227162</td>
<td></td>
<td>SNRI</td>
<td>I</td>
<td>Discontinued: In May 2010 announced discontinuation due to</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>DA agonist</td>
<td></td>
<td>IV</td>
<td>reprioritization of portfolio</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lawsuit against BI regarding risk of compulsive behavior found in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>favor of plaintiff (US), class action suit ongoing in Canada [37]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Generic pramipexine available in Canada and US since 2006/2010,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>respectively</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No indication that additional NDA will be filed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No ongoing sponsored trials, only IIT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Generic available in US and Canada since 2008/2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No current ongoing trials</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>DA agonist</td>
<td></td>
<td>IV</td>
<td>Failed first two Phase III flexible dose studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Results from two fixed-dose studies should be available in first</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>half of 2012</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Mecamylamine (TC-5214)</td>
<td>Nicotinic acetylcholine receptor</td>
<td>III</td>
<td>Current Phase II fixed-dose finding study ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>antagonist</td>
<td></td>
<td>Positive replication trial in 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 ongoing trials spearheaded by NIMH and Massachusetts General Hospital</td>
</tr>
</tbody>
</table>
### Update on 2004 Background Paper, BP 6.15 Depression

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Agents in development</th>
<th>Mechanisms</th>
<th>Phase</th>
<th>Update</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acids and neurotransmitters</td>
<td>Ketamine</td>
<td>NMDA antagonist</td>
<td>II</td>
<td>S ongoing RCTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive data; adverse effects and route of administration still limit its use</td>
</tr>
<tr>
<td></td>
<td>Memantine</td>
<td>NMDA antagonist</td>
<td>II</td>
<td>Despite failed RCT, currently ongoing trials RCT as augmentation</td>
</tr>
<tr>
<td></td>
<td>Riluzole</td>
<td>NMDA antagonist</td>
<td>II</td>
<td>Ongoing clinical trials in MDD (approved for ALS) Patient expires in 2013, so unclear whether additional drug filing will be submitted</td>
</tr>
<tr>
<td></td>
<td>MK-0657</td>
<td>NMDA NR2 antagonist</td>
<td>II</td>
<td>Study discontinued due to poor recruitment (n = 5) Undear whether Merck will continue development</td>
</tr>
<tr>
<td></td>
<td>Truxoprodil (CP 101,606)</td>
<td>NMDA NR2 antagonist</td>
<td>II</td>
<td>Discontinued: positive trial results, but evidence of psychomimetic properties</td>
</tr>
<tr>
<td></td>
<td>AZD6765</td>
<td>NMDA antagonist</td>
<td>II</td>
<td>Ongoing Phase II trial in TRD Previous Phase II trial data completed by 2011 not available</td>
</tr>
<tr>
<td></td>
<td>Org24448 (farampator)</td>
<td>AMPA potentiator</td>
<td>II</td>
<td>Completed Phase II trial in 2008 headed by NIMH, but No trial data made available</td>
</tr>
<tr>
<td>Neuropeptides</td>
<td>Saredustant (Si 48968)</td>
<td>NK2 antagonist</td>
<td>III</td>
<td>No ongoing clinical trials, although unclear whether this drug is still in development preclinically, or who owns the rights after successive mergers</td>
</tr>
<tr>
<td></td>
<td>Orexiptant GW679769</td>
<td>NK1 antagonist</td>
<td>II</td>
<td>Discontinued: did not separate from placebo or comparator</td>
</tr>
<tr>
<td></td>
<td>BMS 562086 (pexacelfont)</td>
<td>CRF1 antagonist</td>
<td>II</td>
<td>Terminated: Phase II trials terminated to 'allow assessment of isolated events of seizure' [24] Significantly separated from placebo on depression score at endpoint</td>
</tr>
<tr>
<td></td>
<td>JNU-18038683</td>
<td>CRF1 antagonist</td>
<td>II</td>
<td>Discontinued: did not separate from placebo</td>
</tr>
<tr>
<td></td>
<td>Milipristone (Korlym formerly Corlum)</td>
<td>GR antagonist</td>
<td>III</td>
<td>Failed: did not meet endpoint in three psychotic depression trials Ongoing Phase III trial in psychotic depression</td>
</tr>
<tr>
<td>Neurotrophic</td>
<td>GR205171</td>
<td>GR antagonist</td>
<td>II</td>
<td>Discontinued: drug did not meet endpoint in PTSD trial</td>
</tr>
<tr>
<td></td>
<td>Rolipram</td>
<td>PDE-4 inhibitor</td>
<td>II</td>
<td>No ongoing development program in MDD</td>
</tr>
<tr>
<td></td>
<td>BCI-540</td>
<td>Hippocampal neurogenesis</td>
<td>II</td>
<td>Positive Phase II trial on anxiety at TID dosing</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Infliximab</td>
<td>TNFα antagonist</td>
<td>IV</td>
<td>Completed trial in June 2011, results not available yet</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td>TNFα antagonist</td>
<td>N/A</td>
<td>No current ongoing trials</td>
</tr>
<tr>
<td></td>
<td>Cimicoxib</td>
<td>COX-2 inhibitor</td>
<td>II</td>
<td>Positive effects on depression observed in patients with Psoriasis and rheumatoid arthritis No trials in an MDD sample</td>
</tr>
<tr>
<td></td>
<td>Losmapinod (GW856553X)</td>
<td>P38a kinase inhibitor</td>
<td>II</td>
<td>Results from Phase II trial not available till 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Discontinued: trial terminated due to negative results in a proof-of-concept rheumatoid arthritis study Summary of results show no difference between losmapinod and placebo</td>
</tr>
</tbody>
</table>
# Update on 2004 Background Paper, BP 6.15 Depression

<table>
<thead>
<tr>
<th>Drug: Monoamines</th>
<th>Mechanism</th>
<th>Phase</th>
<th>Company</th>
<th>Indication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-820836</td>
<td>DA/NE/S-HT reuptake inhibitor</td>
<td>II</td>
<td>BMS</td>
<td>TRD</td>
<td>Clinical trials ongoing</td>
</tr>
<tr>
<td>Cariprazine (RGH-188)</td>
<td>D2/D3 receptor antagonist</td>
<td>II</td>
<td>Forest</td>
<td>MDD adjunct, BP depression, mania, SCZ</td>
<td>Failed: Phase II study of adjunctive cariprazine; however, high-dose arm showed signal</td>
</tr>
<tr>
<td>CPI-300 (Forfivo XL)</td>
<td>High-strength formulation of bupropion (450 mg) Presumed noradrenergic and/or dopaminergic mechanisms</td>
<td>IV</td>
<td>IntelGenx</td>
<td>MDD</td>
<td>Ongoing adjunctive trial in MDD FDA approved in Nov. 2011</td>
</tr>
<tr>
<td>DOV 102, 677</td>
<td>DA/NE/S-HT reuptake inhibitor</td>
<td>I</td>
<td>Merck</td>
<td>MDD, alcoholism</td>
<td>Unclar whether Merck is still developing this drug</td>
</tr>
<tr>
<td>DSP-1053</td>
<td>Modulates 5HT1A receptors/SSRI</td>
<td>I</td>
<td>Dainippon Sumitomo Pharma</td>
<td>MDD</td>
<td>Began Phase I trial in the US May 2011 Expect early onset of action Studies expected to be completed in 2013</td>
</tr>
<tr>
<td>LSDexamfetamine (SPD489)</td>
<td>Prodrug for dextroamphetamine; inactive on its own</td>
<td>III</td>
<td>Shire</td>
<td>MDD adjunct</td>
<td></td>
</tr>
<tr>
<td>Oleptro</td>
<td>Trazodone XR Dual serotonin agonist and serotonin reuptake inhibitor</td>
<td>IV</td>
<td>Labopharm</td>
<td>MDD</td>
<td>Approved in US February 2010 and Canada January 2011</td>
</tr>
<tr>
<td>OPC-34712</td>
<td>D2 partial agonist</td>
<td>III</td>
<td>Otsuka</td>
<td>MDD adjunct, SCZ</td>
<td>Three ongoing Phase III clinical trials expected to be complete in 2013/2014 Early in development</td>
</tr>
<tr>
<td>RG7166</td>
<td>DA/NE/S-HT reuptake inhibitor</td>
<td>I</td>
<td>Roche</td>
<td>MDD</td>
<td>Positive proof-of-concept study Ongoing Phase II study, no longer recruiting</td>
</tr>
<tr>
<td>SEP 228432</td>
<td>DA/NE/S-HT reuptake inhibitor</td>
<td>I</td>
<td>Sunovion</td>
<td>MDD, pain</td>
<td>Citalopram + pipamperone not superior to citalopram alone Ongoing Phase III trial to be completed by end of 2012</td>
</tr>
<tr>
<td>Serdaxin (RX-10100)</td>
<td>Serotonin and dopamine enhancer (increases release), β-lactamase inhibitor</td>
<td>II</td>
<td>Rexahn Pharma</td>
<td>MDD, erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td>PNB01 (pipamperone)</td>
<td>At low doses: highly selective 5HT2A and D4 receptor antagonist</td>
<td>III</td>
<td>PharmaNeuroBoost</td>
<td>MDD adjunct, SCZ</td>
<td></td>
</tr>
<tr>
<td>TyRima (CX157)</td>
<td>Reversible MAO-A inhibitor</td>
<td>II</td>
<td>CeNeRx BioPharma</td>
<td>MDD, TRD, anxiety</td>
<td>MDD trial completed in Sept 2009 TRD trial currently enrolling</td>
</tr>
<tr>
<td>Tasmelteon (VEC-162)</td>
<td>Agonism of melatonin 1a (MT1R) and 1b (MT2R) receptors</td>
<td>II/III</td>
<td>Vanda Pharma</td>
<td>MDD</td>
<td>FDA approved in 2010 for use in blind individuals with a sleep-wake disorder MAGELLAN study – currently recruiting; expected completion date: 2013 Assessing measures of circadian and sexual function</td>
</tr>
</tbody>
</table>
## Update on 2004 Background Paper, BP 6.15 Depression

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Phase</th>
<th>Company</th>
<th>Indication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acids GLYX-13</td>
<td>NMDA modulator</td>
<td>I &amp; II</td>
<td>Naurex</td>
<td>TRD</td>
<td>Intravenous GLYX-13 RCT ongoing in TRD sample</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Estimated study completion date Feb 2012</td>
</tr>
<tr>
<td>RG7090</td>
<td>mGluR5 antagonist</td>
<td>II</td>
<td>Roche</td>
<td>TRD</td>
<td>No listed trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unclear where this drug is in development</td>
</tr>
<tr>
<td>RG1578</td>
<td>mGluR2 antagonist</td>
<td>I</td>
<td>Roche</td>
<td>MDD</td>
<td>Early in development</td>
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<tr>
<td>AZD2066</td>
<td>mGluR5 antagonist</td>
<td>II</td>
<td>AstraZeneca</td>
<td>MDD, pain</td>
<td>Discontinued in 2011</td>
</tr>
<tr>
<td>R228060 (YKP10A)</td>
<td>Phenylalanine derivative, non-amphetaminic stimulant</td>
<td>II</td>
<td>Johnson &amp; Johnson</td>
<td>MDD</td>
<td>Trial vs placebo and paroxetine completed in 2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unclear what results were or whether this drug is still in development</td>
</tr>
<tr>
<td>Neuropeptides ALKS 5461</td>
<td>Nonaddictive opioid modulator and buprenorphine</td>
<td>II</td>
<td>Alkermes</td>
<td>MDD</td>
<td>Study sample history of nonresponse with 1 - 2 meds</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>January 2012 reported positive results from small Phase VII RCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completed safety trial in September 2011</td>
</tr>
<tr>
<td>ABT-436</td>
<td>V1b antagonist</td>
<td>I</td>
<td>Abbott</td>
<td>MDD</td>
<td>Discontinued: Phase II study terminated due to poor efficacy results from interim analysis in 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No safety concerns</td>
</tr>
<tr>
<td>CP-316,311</td>
<td>Selective CRH1 receptor antagonist</td>
<td>II</td>
<td>Pfizer</td>
<td>MDD</td>
<td>Discontinued: Phase III trial failed against placebo and paroxetine in 2006</td>
</tr>
<tr>
<td>MK0869 (aprepitant)</td>
<td>NK1 receptor antagonist</td>
<td>III</td>
<td>Merck</td>
<td>MDD</td>
<td>No listed trials, although report of Phase II trial ongoing in Europe</td>
</tr>
<tr>
<td>SA4503 (cutamesine)</td>
<td>Selective sigma 1 receptor antagonist</td>
<td>II</td>
<td>M's Science Corp.</td>
<td>MDD, ischemic stroke, Alzheimer's, multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Discontinued: failed to meet endpoint in Phase II trial</td>
</tr>
<tr>
<td>SSR125543</td>
<td>CRF1 antagonist</td>
<td>II</td>
<td>Sanofi</td>
<td>MDD</td>
<td>Discontinued in 2008</td>
</tr>
</tbody>
</table>
## Update on 2004 Background Paper, BP 6.15 Depression

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Phase</th>
<th>Company</th>
<th>Indication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurotrophic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCI-952</td>
<td>Fixed dose melatonin and buspirone</td>
<td>II</td>
<td>Brain Cells</td>
<td>MDD</td>
<td>Drug being outlicensed</td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Antidiabetic, anti-inflammatory</td>
<td>II/VIII</td>
<td>Takeda</td>
<td>MDD, bipolar disorder, Parkinson’s disease</td>
<td>FDA approved to treat diabetes Positive Phase II results in small RCT for MDD with abdominal obesity</td>
</tr>
<tr>
<td><strong>Acetylcholine</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>BCI-224 (subcomeline)</td>
<td>Nonselective muscarinic partial antagonist</td>
<td>II</td>
<td>Brain cells</td>
<td>MDD adjunct</td>
<td>Phase II trials have not commenced Drug shown to be neurogenic Discontinued: interim analysis in 2011 showed lack of efficacy</td>
</tr>
<tr>
<td>CP-601,927</td>
<td>Nicotine receptor partial agonist</td>
<td>II</td>
<td>Pfizer</td>
<td>MDD adjunct</td>
<td></td>
</tr>
<tr>
<td><strong>Other mechanisms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JNJ26489112</td>
<td>Glucose-lowering sulfamide; unclear</td>
<td>II</td>
<td>Johnson &amp; Johnson</td>
<td>TRD</td>
<td>Trial ongoing vs venlafaxine XR; estimated study completion date in 2012 Previous trial results not available Current trial for patients with previous nonresponse to meds not recruiting yet Discontinued: failed to meet endpoint in MDD Phase II trial</td>
</tr>
<tr>
<td>RO4995819</td>
<td>Undisclosed</td>
<td>II</td>
<td>Hoffmann-La Roche</td>
<td>MDD adjunct</td>
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<tr>
<td>SSR411298</td>
<td>Fatty acid amino hydrolase inhibitor</td>
<td>II</td>
<td>Sanofi-Aventis</td>
<td>MDD, anxiety</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix 6.15.2: Common antidepressive agents, their trade name, drug class and mechanism of action.

Source: Joffe, R.T. \(^ {125} \)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trade Name</th>
<th>Drug Class</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Elavil</td>
<td>TCA</td>
<td>5-HT and NE reuptake inhibition</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Wellbutrin IR, Wellbutrin SR, Wellbutrin XL</td>
<td>NDRI</td>
<td>NE and DA reuptake inhibition</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celexa</td>
<td>SSRI</td>
<td>5-HT reuptake inhibition</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Anafranil</td>
<td>TCA</td>
<td>5-HT and NE reuptake inhibition</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Norpramine, Pertofran</td>
<td>TCA</td>
<td>NE reuptake inhibition</td>
</tr>
<tr>
<td>Doxepine</td>
<td>Sinequan</td>
<td>TCA</td>
<td>5-HT and NE reuptake inhibition</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lexapro</td>
<td>SSRI</td>
<td>5-HT reuptake inhibition</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac</td>
<td>SSRI</td>
<td>5-HT reuptake inhibition</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Luvox</td>
<td>SSRI</td>
<td>5-HT reuptake inhibition</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tofranil</td>
<td>TCA</td>
<td>5-HT and NE reuptake inhibition</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>Ludomil</td>
<td>TCA</td>
<td>NE reuptake inhibition</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Remeron</td>
<td>SARI</td>
<td>α₂ and 5-HT, antagonist, NE and 5-HT, release</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Serzone</td>
<td>SARI</td>
<td>5-HT reuptake inhibition and antagonist</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Aventyl, Pamelor</td>
<td>TCA</td>
<td>5-HT and NE reuptake inhibition</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil, Paxil CR</td>
<td>SSRI</td>
<td>5-HT reuptake inhibition</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>Nardil</td>
<td>Nonreversible MAOI</td>
<td>MAO-A and B inhibitor</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>Vivactil</td>
<td>TCA</td>
<td>5-HT and NE reuptake inhibition</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft</td>
<td>SSRI</td>
<td>5-HT reuptake inhibition</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Desyrel</td>
<td>SARI</td>
<td>5-HT and antagonist</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>Surmontil</td>
<td>TCA</td>
<td>5-HT and NE reuptake inhibition</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Effexor, Effexor XR</td>
<td>SNRI</td>
<td>5-HT and NE reuptake inhibition</td>
</tr>
</tbody>
</table>

TCA = tricyclic antidepressant; 5-HT = serotonin; NE = norepinephrine; IR = immediate release; SR = sustained release; XL/XR = extended release; NDRI = norepinephrine dopamine reuptake inhibitor; DA = dopamine; SSRI = selective serotonin reuptake inhibitor; SARI = serotonin 2A antagonist/reuptake inhibitor; CR = controlled release; MAOI = monoamine oxidase inhibitor; MAO-A and B = monoamine oxidase types A and B; SNRI = selective norepinephrine reuptake inhibitor.
# Appendix 6.15.3: Common antidepressive agents and associated side effects.

Source: Joffe, R.T. 125

<table>
<thead>
<tr>
<th>Agent</th>
<th>Anti-Cholinergic*</th>
<th>Anti-Histaminergic†</th>
<th>Anti-α-Adrenergic§</th>
<th>Serotonergic‡</th>
<th>Dopaminergic*</th>
<th>Adrenergic*</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>Lower seizure threshold</td>
</tr>
<tr>
<td>Citalopram</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+++++</td>
<td>0</td>
<td>++</td>
<td>Discontinuation symptoms</td>
</tr>
<tr>
<td>Desipramine</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Doxepine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>+</td>
<td>Discontinuation symptoms</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td>Discontinuation symptoms</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td>Discontinuation symptoms</td>
</tr>
<tr>
<td>Imipramine</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>0</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>0</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>Liver damage</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td>Discontinuation symptoms</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td>Dietary restriction</td>
</tr>
<tr>
<td>Sertraline</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>++</td>
<td>Discontinuation symptoms</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>Dietary restriction</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>++</td>
<td>Increased BP at higher dose</td>
</tr>
</tbody>
</table>

* Dry mouth, blurred vision, sweating, tachycardia, constipation, urinary retention
† Drowsiness, weight gain
§ Sedation, dizziness, postural hypotension, reflex tachycardia
‡ Headache, nervousness/agitation, akathisia, sweating, anorexia, weight loss/gain, gastrointestinal symptoms, sexual dysfunction
§ Restlessness, insomnia, agitation/anxiety
¶ Tremors, tachycardia, sweating, sleep disturbance, sexual dysfunction
Side Effects: +++=substantial; ++=marked; +++=moderate; ++=minimal; 0=none.
BP=blood pressure.
Background Paper 6.16
Postpartum Haemorrhage

By By Paul Ashigbie, B. Pharm. MPH
January 2013
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Abbreviations

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<th>Definition</th>
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<tr>
<td>ACOC</td>
<td>American College of Obstetricians and Gynecologists</td>
</tr>
<tr>
<td>AMTSL</td>
<td>Active Management of the Third Stage of Labor</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>DALYs</td>
<td>Disability Adjusted Life Years</td>
</tr>
<tr>
<td>EML</td>
<td>Essential Medicines List</td>
</tr>
<tr>
<td>FIGO</td>
<td>International Federation of Gynecologists and Obstetricians</td>
</tr>
<tr>
<td>ICM</td>
<td>International Confederation of Midwives</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LMICs</td>
<td>Low and Middle Income Countries</td>
</tr>
<tr>
<td>MDG</td>
<td>Millennium Development Goals</td>
</tr>
<tr>
<td>PATH</td>
<td>Program for Appropriate Technology</td>
</tr>
<tr>
<td>PPH</td>
<td>Postpartum Haemorrhage</td>
</tr>
<tr>
<td>RCOG</td>
<td>Royal College of Obstetricians and Gynecologists</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>RR</td>
<td>Risk Ratio</td>
</tr>
<tr>
<td>rVIIa</td>
<td>Recombinant Factor VIIa</td>
</tr>
<tr>
<td>TTI</td>
<td>Temperature-Time Indicator</td>
</tr>
<tr>
<td>USFDA</td>
<td>United States Food and Drugs Administration</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Executive summary

Introduction
This paper is an update of the 2004 background paper on postpartum haemorrhage (PPH) (http://archives.who.int/prioritymeds/report/index.htm) for the Priority Medicines for Europe and the World report. The paper discusses causes and the burden of PPH, which is the leading cause of maternal mortality, assesses the current treatment options available for PPH, as well as the treatments under development and makes recommendations on future research opportunities.

The burden of postpartum haemorrhage
The World Health Organization (WHO) defines PPH as “blood loss greater than or equal to 500 ml within 24 hours after birth”, and severe primary PPH as “blood loss greater than or equal to 1000 ml within 24 hours.” Postpartum haemorrhage is the leading cause of maternal mortality, accounting for about 35% of all maternal deaths. About 14 million women around the world suffer from PPH every year (26 women every minute). The vast majority of these deaths occur in low and middle-income countries (LMICs). Yet, recent studies have shown increasing incidence of PPH in developed countries as well.

Diagnosis and Management of PPH
The most common symptoms of PPH include uncontrolled bleeding, decreased blood pressure, increased heart rate, decreased red blood cell count, and swelling and pain in tissues in the vaginal and perineal area. Postpartum haemorrhage can be managed by medical, non-medical and surgical interventions. The WHO and other professional bodies recommend active management of the third stage of labor (AMTSL) for all vaginal births. Active management of the third stage of labor involves a prophylactic administration of uterotonics before delivery of the placenta in addition to other non-pharmacological interventions, such as late cord clamping and controlled cord traction of the umbilical cord (in settings where skilled birth attendants are available).

Medicines for managing PPH (uterotonic medicines)
In 2004, oxytocin with or without supplemental ergometrine, ergometrine alone, 15-methyl prostaglandin F\textsubscript{2a} and misoprostol were the uterotonics of choice in AMSTL. In addition to the above medicines, the 2009 and 2012 WHO guidelines for managing PPH mentioned carbetocin, recombinant factor VIIa and tranexamic acid as possible therapeutic interventions for PPH.

Oxytocin and ergometrine are unstable at room temperature and thus require special temperature and light storage conditions to remain effective. Additionally, both medicines must be administered parenterally, requiring trained personnel to administer them. Compared to oxytocin ergometrine has more severe side effects: hypertension, coronary vasospasms, increased systemic vascular resistance, pulmonary edema, intracranial haemorrhage and seizures, and retinal detachment. For these reasons, ergometrine was removed from the WHO Model List of Essential Medicines, making oxytocin is the most
effective intervention for the prevention or treatment of PPH and therefore the recommended first line treatment. Some studies are on-going to produce heat stable oxytocin formulations.\textsuperscript{13,14} One example is Uniject, an oxytocin device to ensure safer and accurate dosage of oxytocin, has been developed with a temperature – time – indicator (TTI) to monitor the quality of the product in transit and storage.\textsuperscript{15} However, this technology is yet to be deployed on a large scale.

As of 2004 there was lack of clarity on the effectiveness of misoprostol in AMTSL. Recent studies indicate that where other agents are not available, misoprostol may be effective in preventing and treating PPH without the side effects associated with other uterotonic drugs.\textsuperscript{16} Furthermore, misoprostol is relatively stable at room temperature, has a long shelf life, and can be given orally – all of which are advantages over currently available uterotonic drugs.\textsuperscript{16,17} According to the 2012 WHO guidelines, misoprostol may be used in situations where the use of oxytocin is not possible.\textsuperscript{1}

Tranexamic acid is an antifibrinolytic agent used in surgery to reduce blood loss. Based on research studies, the WHO recommended that tranexamic acid may be offered as a treatment for PPH as a fourth alternative or if the bleeding may be partly due to trauma.\textsuperscript{1,9}

**Non-medical interventions for management of PPH**

The 2012 WHO recommendations for the management of PPH recommends the following non pharmacological interventions for managing PPH: uterine massage, bimanual uterine compression, intrauterine balloon or condom tamponade, external aortic compression, uterine artery embolization, and non-pneumatic anti-shock garments.\textsuperscript{1,9}

**Opportunities for further research**

While substantial progress has been towards improving on the existing interventions for managing PPH, more research studies are needed to make these improvements and ultimately available for therapeutic use. Areas in which further research studies are needed include: the development of a heat stable oxytocin; scaling up the use of oxytocin-Uniject with the TTI in low resource settings, in tandem with adequate post marketing pharmacovigilance; establishing the standard, safe and effective dose of sublingual misoprostol for treating PPH; exploring the potential of tranexamic acid in treating PPH; exploring the possible benefits of carbetocin in treating PPH in women with pre-eclampsia; and operational research to determine the effectiveness of these interventions at the community level.\textsuperscript{1,16,18,19,20}

**Conclusion**

Postpartum haemorrhage still remains the leading cause of maternal mortality. Though the burden of PPH is highest in developing countries, the incidence of PPH is increasing in developed nations. Current preventive and treatment interventions are inadequate and inequitably distributed. More research is needed to develop new interventions in order to improve on existing interventions and also to ensure that existing and new technologies can be used and are equitably available in rural areas.
1. Introduction

This paper is an update of the 2004 background paper on postpartum haemorrhage (PPH) (http://archives.who.int/prioritymeds/report/index.htm) for the Priority Medicines for Europe and the World report. The paper discusses causes and the burden of PPH, assesses the current treatment options available for PPH as well as the treatments under development, and makes recommendations on future research opportunities. This revised paper serves as a background paper on PPH for the second edition of the Priority Medicines for Europe and the World Report of 2013. While maternal mortality accounted for about 287 000 deaths in 2010, these deaths disproportionately impact the life and health of the affected families.

2. Definition and etiology of PPH

Postpartum haemorrhage (PPH) can be classified as primary (early) or secondary (late). Primary PPH, the most common and severe, occurs within the first 24 hours after delivery. Secondary PPH occurs 24 hours to 12 weeks after delivery. Most cases of morbidity and mortality due to PPH are the result of primary PPH, while secondary PPH results from retained placental fragments, subinvolution of the placental site, infection, and coagulation defects (bleeding diatheses) which cause abnormal excessive bleeding. The World Health Organization (WHO) defines PPH as “blood loss greater than or equal to 500 ml within 24 hours after birth”, and severe PPH as “blood loss greater than or equal to 1 000 ml within 24 hours”. This is the most common definition of PPH as the definition for PPH may not be uniform across countries. For example, the United States and Canada define PPH as blood loss of 500 ml for a vaginal delivery and 1 000 ml for a caesarean birth, while in Australia PPH refers to blood loss of 500 ml for a vaginal delivery and 750 ml for a caesarean delivery. The usefulness in measuring blood loss in managing PPH is not clear. Firstly, it is difficult to accurately estimate blood loss routinely. Secondly, blood loss less than 500 ml in women who are already anaemic may be serious and may require treatment interventions. It has also been shown that many women lose enough blood in otherwise normal deliveries to meet the diagnostic criteria for PPH. The 2009 WHO guidelines for the management of PPH conclude that there is not enough evidence to recommend quantification of blood loss over clinical estimation of PPH.

Bleeding during and after the third stage of labor may result from uterine atony (failure of the uterus to contract properly after delivery), trauma (cervical, vaginal, or perineal lacerations), retained or adherent placental tissue, clotting disorders, and inverted or ruptured uterus. About 75 to 90% of PPH cases are caused by uterine atony.

The risk factors for PPH are listed in Table 6.16.1. Though some women are at greater risk for postpartum haemorrhage compared to others, two out of three women with PPH had no risk factors before delivery. Postpartum haemorrhage often comes unexpectedly and caregivers must promptly diagnose and treat it.
Table 6.16.1 Risk Factors for Uterine Atony

<table>
<thead>
<tr>
<th>Risk factors for postpartum haemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged labor</td>
</tr>
<tr>
<td>Retained placenta products</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
</tr>
<tr>
<td>Oxytocin used in labor</td>
</tr>
<tr>
<td>Preeclampsia/eclampsia</td>
</tr>
<tr>
<td>Multiple gestation</td>
</tr>
<tr>
<td>Hydroamnios</td>
</tr>
<tr>
<td>Halogenated anesthesia</td>
</tr>
<tr>
<td>Previous episode of uterine atony</td>
</tr>
<tr>
<td>Increasing maternal</td>
</tr>
<tr>
<td>Obesity and raised Body Mass Index</td>
</tr>
<tr>
<td>Caesarian delivery and induction of labor</td>
</tr>
</tbody>
</table>


3. The burden of PPH

Haemorrhage is the leading cause of maternal mortality, accounting for about 35% of all maternal deaths. About 14 million women around the world suffer from PPH every year translating to 26 women every minute. Though maternal deaths and maternal mortality ratio (MMR) have decreased globally from 543 000 and 400 per 100 000 live births to 287 000 and 210 per 100 000 live births respectively between 1990 and 2010, developing countries continue to experience very higher numbers of maternal deaths. In 2010, the MMR in developing countries was 240 per 100 000 (284 000 maternal deaths) compared to 16 (2 200 maternal deaths) in developed countries. Thirty-five countries have been noted as either making insufficient progress or not making any progress at all towards achieving the Fifth Millennium Development Goal (MDG5), which aims to reduce maternal mortality rate by 75% from 2000 to 2015. To reduce MMR and achieve MDG 5, it is important to drastically reduce PPH, the leading cause of maternal mortality.

Table 6.16.2 summarizes the statistics on the global burden of PPH. The incidence of PPH among countries ranges from 0.55% to 17.5% of deliveries with 60% of all maternal deaths occurring during the postpartum period of which 45% in the first 24 hours after delivery. According to the 2005 World Health Report which focused on maternal and child health, the incidence of PPH was 10.5% of live births with about 13.8 million PPH cases per year. The case fatality rate of PPH was 1% with a DALY (Disability Adjusted Life Years) of 4.4 million. Table 6.16.1 above shows the major obstetric complications and their contributions to maternal deaths.
Update on 2004 Background Paper, BP 6.16 Postpartum Haemorrhage

Table 6.16.2: Estimated incidence of major obstetric complications and their main maternal sequelae

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence (% of live births)</th>
<th>Cases</th>
<th>Case fatality rate</th>
<th>Maternal deaths (2000)</th>
<th>Main sequelae</th>
<th>DALYs lost (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPH</td>
<td>10.5</td>
<td>13,795,000</td>
<td>1.0</td>
<td>132,000</td>
<td>Severe anemia</td>
<td>4,418</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4.4</td>
<td>5,768,000</td>
<td>1.3</td>
<td>79,000</td>
<td>Infertility</td>
<td>6,901</td>
</tr>
<tr>
<td>Pre-eclampsia/eclampsia</td>
<td>3.2</td>
<td>4,152,000</td>
<td>1.7</td>
<td>63,000</td>
<td>Eclampsia</td>
<td>2,231</td>
</tr>
<tr>
<td>Obstructed labor</td>
<td>4.6</td>
<td>6,038,000</td>
<td>0.7</td>
<td>42,000</td>
<td>Urinary incontinence, Fistula</td>
<td>2,951</td>
</tr>
<tr>
<td>Abortion</td>
<td>14.8</td>
<td>19,340,000</td>
<td>0.3</td>
<td>63,000</td>
<td>Infertility</td>
<td></td>
</tr>
</tbody>
</table>


About 99% of deaths from PPH occur in low and middle income countries (LMICs) compared with 1% in industrialized nations. The risk of maternal mortality from haemorrhage is 100 per 100,000 live births in developing countries accounting for one-third of all maternal deaths in Africa and Asia. The risk of maternal mortality in developed countries is 1 per 100,000 live births, or 100 times less compared to the risk in LMICs. Women who survive severe PPH are more likely to die in the year following PPH. Kaye et al. conducted a systematic review of the magnitude and case fatality ratio for severe maternal morbidity in sub-Saharan Africa between 1995 and 2010 using twelve studies with sample sizes ranging from 557 to 23,026 participants. The review found that the incidence of haemorrhage ranged from 0.06% to 3.05%, while the case fatality ratio for haemorrhage ranged from 2.8% to 27.3%.

While PPH seems to be most devastating in developing countries, recent studies have shown increasing incidence of PPH in developed countries. A population based retrospective cohort study among 650,000 childbirth hospitalizations between 1999 and 2009 in Ireland showed that the overall rate of PPH increased from 1.5% to about 4% during that time period. Atonic PPH increased from 1% to 3.4%. Another review by the International Postpartum Haemorrhage Collaborative Group found an increase in the incidence and the severity of adverse outcomes of PPH in Australia, Canada, the UK, and the United States. The increase in incidence of PPH in Australia, Canada and the USA were mainly limited to atonic PPH. These findings are consistent with findings from a population-based study in the USA by Callaghan et al. The study showed that PPH increased 26% between 1994 and 2006 from about 2% (n = 85,954) to almost 3% (n = 124,708; p< 0.001) primarily due to an increase in uterine atony. This increase observed in PPH could not be explained by changes in rates of cesarean delivery, vaginal birth after cesarean delivery, maternal age, multiple birth, hypertension, or diabetes mellitus. The risk of death from obstetric haemorrhage in the USA has remained at 7.7 per 100,000 deliveries, with haemorrhage as the lethal cause in 13%-30% of all cases.
4. **Diagnosis and Management of PPH**

The symptoms and signs of PPH may vary from woman to woman including uncontrolled bleeding, decreased blood pressure, increased heart rate, decreased red blood cell count (hematocrit), and swelling and pain in tissues in the vaginal and perineal area.

Postpartum haemorrhage is managed by medical, non-medical and surgical interventions. There are two approaches to the clinical management of the third stage labor (the period from the birth of the child until the placenta is delivered): expectant and active management. Expectant management involves allowing the placenta to deliver spontaneously or aiding by gravity, maternal effort or nipple stimulation. Uterotonic agents are given only if there is excessive bleeding, and the cord is clamped later. Active management of third stage of labor involves a prophylactic administration of uterotonic before delivery of the placenta, late cord clamping, and controlled cord traction (in settings where skilled birth attendants are available). These procedures enable the uterus to contract immediately, decreasing the amount of time necessary to deliver the placenta. More recently, Begley et al. discussed a third method of clinical management of the third stage of labor called the mixed management (also known as ‘combined’ or ‘piecemeal’ management). This consists of the use of some of the components of both active and expectant management.

In a paper by Prendiville et al. in 2000 the advantages of AMSTL were described as substantially decreasing the following signs and symptoms:

- Incidence of PPH due to an atonic uterus by about 60%
- Length of the third stage of labor
- Need for additional drugs to treat excessive bleeding by about 70%
- Need for a blood transfusion
- Need for surgical intervention
- Incidence of anaemia and other problems associated with excessive blood loss

The Prendiville study has since been withdrawn. However, a 2011 systemic review of Cochrane Pregnancy and Childbirth Group Trials Register by Begley et al confirmed most of the above advantages of AMSTL. The review which compared the effectiveness of active and expectant management of third stage labor in women expecting vaginal delivery in hospitals yielded seven randomized and quasi-randomized controlled trials (RCTs), six in high-income countries and one in low-income countries, all involving 8247 women. Four studies compared active with expectant management, while three compared active management with a mixed management. The findings of this review are:

1. Among women at mixed levels of risk of bleeding, active management showed a reduction in the average risk of maternal primary haemorrhage of more than 1000 ml at time of birth (risk ratio (RR): 0.34, 95% confidence interval (CI): 0.14 to 0.87). The risk of maternal hemoglobin falling below 9 g/dl after birth was also reduced (average RR 0.50, 95% CI: 0.30 to 0.83, two studies, 1 572 women).

2. There were significant decreases in primary blood loss greater than 500 ml and mean maternal blood loss at birth, as well as the need for maternal blood transfusion and the use of uterotonics during the third stage or within the first 24 hours or both.
Update on 2004 Background Paper, BP 6.16 Postpartum Haemorrhage

3. Significant increases in maternal diastolic blood pressure, vomiting after birth, after-pains, and use of analgesia from birth up to discharge from the labor ward were observed with active management. Also, the number of women returning to hospital with bleeding increased.

4. There was a decrease in the baby’s birth weight with active management, which the authors attributed to lower blood volume as a result of interference with placental transfusion due to early cord clamping.

5. There was no significant difference in the length of the third stage of labor compared to AMTSL and expectant management.

6. Among women at low risk of excessive bleeding, there were similar findings, except that at 24 to 72 hours, there was no significant difference between groups for severe haemorrhage or maternal haemorrhage less than 9 g/dl.

7. The authors could not draw any firm conclusions about the differences in outcome between mixed management and active management of the third stage of labor.

The WHO, International Federation of Gynecologists and Obstetricians (FIGO) and the International Confederation of Midwives (ICM) recommend that skilled birth attendants provide AMTSL for all vaginal births. Where skilled birth attendants are not available to provide all of the components of AMTSL, FIGO and ICM recommend that oxytocin (10 IU) or misoprostol (400-600 µg orally) should be given by a trained health worker. Oxytocin is preferred to other uterotonic drugs because it is effective 2–3 minutes after injection with relatively minimal secondary effects. It is important to note that although AMTSL reduces postpartum blood loss, about 3 to 16.5% of women will still go on to experience PPH and will require treatment.

5. Medicines for managing PPH

Active management using standard uterotonic drugs can reduce both PPH incidence and maternal mortality by 40%. In 2004, oxytocin with or without supplemental ergometrine (methergine), ergometrine alone, 15-methyl prostaglandin F2 α, and misoprostol were the uterotonics of choice in AMTSL. In addition to the above medicines, the 2009 and the 2012 WHO guidelines for managing PPH mentioned carbetocin, recombinant factor VIIa and traxenamic acid as possible therapeutic interventions for PPH.

The following sections discuss the effectiveness and limitations of each of these medicines as well as recent research studies to overcome their limitations.

5.1 Oxytocin

Oxytocin is a hormone used to help start or continue labor and to control bleeding after delivery. It is also sometimes used to help milk secretion in breast feeding. Other indications for oxytocin include diabetes insipidus and vasodilatory shock.
Oxytocin is therapeutically available in the following dosage forms:

- **Nasal** solution which is indicated for increasing milk production in breast feeding (not indicated for PPH)
- **Parenteral** injection which is indicated for preventing and treating PPH. There is limited evidence on the comparative effectiveness of intravenous (IV) and intramuscular (IM) oxytocin. In a systemic review of the December 2011 Cochrane Pregnancy and Childbirth Group’s Trials Register by Oladapo et al., no RCTs were found on the comparative effectiveness and safety of IV and IM oxytocin in the prevention of PPH after vaginal delivery.

Administering oxytocin immediately after childbirth is the single most important intervention used to prevent PPH. Women given oxytocin lose less blood, resulting in a decreased incidence of PPH and anaemia. Oxytocin also allows for a faster delivery of placenta minimizing the need for manual removal of the placenta and the associated pain and risks of infections. The timing of oxytocin administration is critical; it is most effective when administered within one minute after the birth of the baby. Waiting to give oxytocin until after the placenta is delivered may increase the woman’s risk of uncontrolled bleeding.

Despite the usefulness of oxytocin in both preventing and treating PPH, the medicine has some limitations. First as a neuropeptide, oxytocin is unstable at room temperature when kept for more than three months. Parenteral and solid formulations degrade rapidly during storage under tropical conditions (of temperature above 30°C) and high humidity. A WHO study published in 1994 evaluated the stability of oral formulations of oxytocics in tropical climates. The medicines (oral ergometrine, oral methylergometrine, buccal oxytocin and buccal desamino-oxytocin) were exposed to artificially-regulated tropical conditions of temperature ranging between 6-40°C and relative humidity between 20-85%. None of the oral oxytocics including oxytocin were found to be stable under the simulated conditions. Oxytocin thus requires special temperature and light storage conditions to remain effective. Additionally, oxytocin preparations must be administered parenterally to prevent PPH. This requires trained personnel. In many settings, lack of trained personnel undermines the potential for implementing the active management of third-stage labor using oxytocin.

Moreover, there are some adverse reactions associated with the use of oxytocin. Oxytocin causes contractions of the uterus. In women who are unusually sensitive to its effects, these contractions may become too strong. In rare cases, this may lead to tearing of the uterus. Oxytocin has been reported to cause irregular heartbeat and increase bleeding after delivery in some women. It has also been reported to cause jaundice in some newborn infants. Other side effects include: confusion, convulsions (seizures), difficulty in breathing; dizziness, fast or irregular heartbeat, headache (continuing or severe), hives, severe pelvic or abdominal pain, skin rash or itching, vaginal bleeding (increased or continuing), weakness, rapid weight gain, nausea, and vomiting. However, some of these side effects are rare and do not happen when oxytocin is used for PPH prevention and treatment.

The expertise and extensive monitoring required to administer oxytocin parenterally, the adverse effects associated with the medicine, and the specific storage requirements of oxytocic agents are barriers to the effective use of these drugs in many countries. Some studies are on-going to produce heat stable oxytocin formulations. The oxytocin-Uniject, a device to ensure safer and accurate dosage of oxytocin has also been developed with a
Temperature Time Indicator (TTI) to monitor the quality of the product in transit and storage. These strategies are discussed in detail below.\textsuperscript{15,34}

**The development of heat stable oxytocin**

Avanti et al. demonstrated that divalent metal ions Calcium (Ca\textsuperscript{2+}), Magnesium (Mg\textsuperscript{2+}), or Zinc (Zn\textsuperscript{2+}) in combination with a citrate buffer greatly improved the stability of oxytocin in aqueous solutions.\textsuperscript{14} Their study showed the recovery and remaining percentage of oxytocin increased by 80\% in the presence of 50 mM Ca\textsuperscript{2+} and 90\% in the presence of 50 mM Mg\textsuperscript{2+} when these preparations were kept for six months at 40\textdegree C. Zinc ions were found to have higher impact on improving the stability of oxytocin at lower concentrations compared to Mg\textsuperscript{2+} and Ca\textsuperscript{2+} ions. A 10 mM Zn\textsuperscript{2+} ions in citrate buffer exerted the same effect on oxytocin stability as combinations of citrate buffer and 50 mM magnesium ions, indicating that zinc ion is a better stabilizer of oxytocin.

Avanti et al. are conducting follow-up studies to identify various degradation products and understand the degradation pathways of oxytocin.\textsuperscript{13} The aim of these follow-up studies is to develop oxytocin formulations that will be stable (yield greater than 90\% recovery) after one year. Though some progress has been made towards a heat stable oxytocin formulation, the fact still remains that there is currently no heat stable oxytocin formulation for therapeutic use. Further research is needed to make these discoveries useful to patients.

**Oxytocin in Uniject**

Intramuscular or intravenous oxytocin is the preferred uterotonic for AMTSL, in order to prevent postpartum haemorrhage.\textsuperscript{1,7} However, in many low-resource settings, safe injection is not always possible due to the need for injection skills and training, lack of sterile equipment, and difficulty measuring the correct dose of oxytocin. To overcome these barriers to safe injection, the Program for Appropriate Technology in Health (PATH) developed the Uniject device for safer oxytocin administration.\textsuperscript{15} The device comes as a single dose, individually packed prefilled, non-refillable, sterile injection, which is easy to use, with a fixed needle that can be "activated" for use after opening the sterile packet. The Uniject device is not new to public health interventions. It has been used to administer tetanus toxoid to pregnant women in Bolivia, Indonesia, and Mali and to deliver Cyclofem (a monthly injectable contraceptive) to women in Brazil.\textsuperscript{3,35,36,37}

The oxytocin-Uniject has the following advantages:\textsuperscript{3}:

- Routine prophylactic use in deliveries by skilled birth attendants
- Improved injection safety
- Improved dose accuracy and convenience
- Selected or emergency use by specially trained providers at community level to prevent or treat PPH
- Potential use in areas with high rates of postpartum haemorrhage and areas with limited access to referral care.

The 2004 background paper used studies conducted in Indonesia to illustrate the above advantages of the oxytocin-Uniject.\textsuperscript{38} The experiences of 140 midwives who attended 2 200 home births using prophylactic oxytocin in Uniject were compared with the midwives’ previous experiences with oxytocin in standard syringes. The authors found that unsafe
reuse of syringes was reduced from 33% to zero once the midwives were supplied with the Uniject. Dosage accuracy increased slightly, and the Uniject was found by mothers to be less painful than regular syringe injections. Additionally, 98% of midwives preferred the Uniject and were willing to pay a small additional amount (over standard syringes) for the convenience of using it.

Since 2004 the oxytocin-Uniject has been produced with a time temperature exposure indicator device (TTI). PATH, in conjunction with BIOL Pharmaceuticals, incorporated the TTI technology in which one of small colored stickers placed on the medicine becomes darker in relation to the cumulative exposure of the medicine to heat.\textsuperscript{15} Like the Uniject technology, the TTI technology is not new to public health interventions. It has been used as an efficient way of monitoring the stability of vaccines as they move out of the cold chain. Stability studies on the oxytocin-Uniject conducted by PATH and BIOL have shown similarities between the different lengths of time the oxytocin remained fully potent at different storage temperatures and the existing TTI developed for the most stable group of vaccines.\textsuperscript{15}

The Uniject with TTI is expected to ensure that only effective oxytocin is administered, improving the overall quality assurance of programs, to improve the ability of programs to flexibly transport and store oxytocin (oxytocin could move in and out of cold chain, cool chain, room temperature, and allow for longer “out of cold chain” periods compared with other approaches). A pilot study on the effectiveness of the oxytocin-Uniject with TTI was carried out from August 2007 to January 2008 in 45 sites in Mali.\textsuperscript{39} In addition to documenting the experience with the TTI in the desert heat of Mali, the study also sought to evaluate the feasibility and safety of the oxytocin-Uniject, its acceptability to providers, pharmacy managers, and management staff, and its impact on the coverage of AMTSL in the Malian context. The safety of the Uniject was evaluated in terms of two outcomes: selected obstetric complications (ruptured uterus, retained placenta, PPH, and uterine inversion) and needle-stick injuries. The results of the study showed no unusual safety problems associated with the use of the Uniject. Other specific observations from the study include the following:

**Safety:** Only five of the 140 (4%) providers interviewed had needle-stick injuries with the oxytocin-Uniject device. The rates of retained placenta and PPH were not significantly different when oxytocin in ampoules or oxytocin in the Uniject device was used. However, the rates of retained placenta and PPH were significantly lower when AMTSL was applied using the oxytocin-Uniject device with TTI compared to vaginal births without AMTSL. Rates of uterine rupture remained constant and occurred only in women referred from peripheral facilities and were not associated with introduction of the oxytocin-Uniject device with TTI. One case of uterine inversion was diagnosed in a referral health center in Bamako in a woman who presented at the health center after home delivery.

**Feasibility:** About 77% (108/140) felt the training they received was adequate to prepare them to use the oxytocin-Uniject device while 97% of providers (136/140) felt competent to manipulate the oxytocin-Uniject devices after training activities. Only 127 (91%) of the providers trained actually gave an injection with the oxytocin-Uniject device. Of these, 92% (117/127) felt confident after only one injection, and about 8% (10/127) felt confident after two or more injections. Through formal or informal training, providers quickly learned how to use the Uniject device, interpret the TTI and determine if oxytocin had been exposed to high temperatures over a period of time that would compromise its effectiveness.
Impact on AMTSL coverage: AMTSL coverage was already high and the introduction of the oxytocin-Uniject device with TTI did not increase coverage significantly.

Acceptability: Providers preferred the oxytocin-Uniject device with TTI to a standard or auto-disable syringe. About 99% (139/140) of providers indicated they preferred the oxytocin-Uniject while 68% of health care facility managers felt there were no disadvantages to use of the oxytocin-Uniject device. However, 17% (7) of managers felt that storage of the units was a disadvantage and 5% (2) noted that the need to cut the foil wrapper with a sharp object was a disadvantage.

A community based cluster randomized trial is currently on-going to assess the effectiveness, safety, and feasibility of expanding the use of prophylactic intramuscular oxytocin in Uniject with TTI in peripheral health care providers at home births in four rural districts in Ghana. The intervention group consists of community health officers randomized to provide an injection of oxytocin 10 IU via the Uniject injection system within one minute of delivery of the baby to women who request their presence at home at the onset of labor. The primary outcomes of this study is to determine if administration of prophylactic oxytocin via Uniject by this cadre will reduce the risk of postpartum haemorrhage by 50% compared to deliveries which do not receive the prophylactic intervention. For the purpose of this study, postpartum haemorrhage will be examined under the following definitions: blood loss of at least 500 ml; treatment for bleeding and/or blood loss of at least 500 ml; hospital referral for bleeding and/or treatment for bleeding; and hospital referral for bleeding and/or blood loss of at least 500 ml. Secondary outcomes included safety (adverse maternal and fetal outcomes) and feasibility of the intervention (logistical concerns regarding assistance at home births and the storage and handling of oxytocin). The results of this trial are expected in mid-2013.

It is evident from the above discussions, that much progress has been made towards the improving the management of PPH with the use of the oxytocin-Uniject. However, this technology is yet to be deployed on a large scale. Scaling up this technology should be associated with extensive evaluation and pharmacovigilance.

5.2 Carbetocin

Carbetocin is a synthetic oxytocin agonist with longer duration of action compared to oxytocin. It has an average lifespan four times that of oxytocin and a pharmacological effect that lasts for two hours. Carbetocin binds to oxytocin receptors on the smooth muscles of the uterus, resulting in rhythmic contractions of the uterus and increased uterine tone. It has a better gastrointestinal and cardiovascular side effects profile compared to oxytocin, synthometrine and other ergot alkaloids. Carbetocin has not been approved by the United States Food and Drugs Administration (USFDA) for use in vaginal births. However, it is currently indicated for prevention of uterine atony after delivery by caesarean section in spinal or epidural anesthesia in 23 countries. Carbetocin remains more expensive than oxytocin, and the 2009 WHO guidelines on managing PPH conclude that there is no evidence of significant advantage of carbetocin over oxytocin.
5.3 Ergometrine

According to WHO recommendations, in the case of treatment failure or unavailability of oxytocin, the second line treatment of choice are ergometrine or ergometrine and oxytocin fixed dose combination. Ergometrine and methylergometrine are more unstable at room temperature compared to oxytocin. It is also photosensitive and thus requires special temperature and light storage conditions to remain effective. A skilled personnel is required to administer ergometrine. However, compared to oxytocin ergometrine has more severe side effects, which includes hypertension, coronary vasospasms, increased systemic vascular resistance, pulmonary edema, intracranial haemorrhage and seizures, and retinal detachment. These side effects make ergometrine inferior to oxytocin and for this reason ergometrine has been removed from the WHO EML.

5.4 Misoprostol

Prostaglandins are effective in controlling haemorrhage but most have disadvantages of being more expensive and having increased side effects. One notable exception is misoprostol, which has a uterotonic property for use in active management of the third stage of labor. Misoprostol is an inexpensive (less than US$ 1 per dose) prostaglandin E1 analogue and has been suggested as an alternative for routine management of the third stage of labor. Studies to date indicate that where other agents are not available, misoprostol may be effective in reducing the incidence of PPH without the side effects associated with other uterotonic drugs. Though misoprostol is relatively stable at room temperature and has a long shelf life, it is sensitive to moisture and may degrade in areas of high humidity. Misoprostol can be given orally, which has a big advantage over oxytocin and ergometrine. According to the WHO misoprostol may be considered third line treatment (after oxytocin and ergometrine) because of its slightly lower potency, which is partly offset by its ease of administration and low cost. An additional practical problem is that misoprostol can be (mis)used for carrying out abortions and is therefore not marketed or approved in many countries.

*Adverse effects of misoprostol:* A number of adverse effects are associated with misoprostol including frequent transient fever and shivering, which are dose and route dependent. Other adverse effects of misoprostol include nausea, vomiting, and diarrhoea. Though lower doses have lower side effects, there is not enough evidence on the efficacy of lower doses of misoprostol. Breastfeeding is not contraindicated when misoprostol is used for PPH prevention.

5.4.1 Misoprostol in the prevention of PPH

In 2004 there was lack of clarity on the effectiveness of misoprostol in AMTSL as the results of trials conducted in the late 1990s and early 2000s were discordant on the benefits of misoprostol in the prevention of PPH. Over the past decade however, the efficacy of misoprostol for PPH prevention has been well documented. The evidence-based misoprostol regimen for prophylaxis against PPH is a single 600 μg dose administered orally to women immediately after vaginal delivery of the baby (or babies, in the case of multiple births). There is also substantial evidence in support of the beneficial effects of oral misoprostol for PPH prevention in the community level. This evidence is summarized below.
Derman et al. demonstrated the effectiveness of misoprostol in preventing haemorrhage in a placebo-controlled trial in 2002-2005. A total of 1,620 women in four primary-health centers in rural India were randomized to receive oral misoprostol (n=812) or a placebo (n=808) after delivery. The drug was administered by auxiliary nurse midwives, who took care of the deliveries and measured blood loss. The intervention group received a single oral dose of 600 μg misoprostol administered after the delivery of the baby and within five minutes of clamping and cutting the umbilical cord. Compared to the placebo, oral misoprostol significantly reduced the rate of acute PPH (12% versus 6.4%, p<0.0001; RR = 0.53, 95% CI: 0.39 to 0.74). Oral misoprostol also significantly reduced the rate of acute severe postpartum haemorrhage (1.2% to 0.2%, p<0.0001; RR = 0.20, 95% CI: 0.04 to 0.91). For every 18 women treated, one case of postpartum haemorrhage was prevented. However, women in the misoprostol group experienced higher rate of transitory symptoms of chills and fever compared to women in the control group.

In another randomized placebo controlled trial in Pakistan in 2006-2008, Mobeen et al studied whether misoprostol reduced the incidence of PPH (blood loss of 500 ml or more) in a total of 1,119 women giving birth at home. A total of 534 women were randomized to receive 600 μg oral misoprostol after delivery while 585 received a placebo. Oral misoprostol was associated with a significant reduction in the rate of PPH (16.5 versus 21.9%; RR = 0.76, 95% CI: 0.59 to 0.97). Compared to a placebo, significantly fewer women who received misoprostol had a drop in hemoglobin less than 3 g/dl (5.1 versus 9.6%; RR = 0.53, 95% CI: 0.34 to 0.83). In this study, cord traction was carried out according to provider preference, in contrast to the Derman study in which there was no controlled cord traction.

Sublingual misoprostol has also been shown to reduce the incidence of severe PPH. Hoj et al conducted a randomized double blind placebo controlled trial in a primary health center in Bissau, Guinea-Bissau, involving 661 women undergoing vaginal delivery. The women were randomized to sublingual misoprostol 600 μg or a placebo also administered sublingually immediately after delivery. The results of this study showed no statistically significant difference in incidence of postpartum haemorrhage (defined as blood loss of more than 500 ml) between the two groups, RR = 0.89 (95% CI: 0.76 to 1.04). Mean blood loss was 10.5% lower in the misoprostol group compared to the placebo group. The rates of severe postpartum haemorrhage of 1000 ml or 1500 ml were respectively 17% (56) and 8% (25) in the placebo group and 11% (37) and 2% (7) in the misoprostol group. Significantly fewer women in the misoprostol group experienced blood loss of 1000 ml or more (RR = 0.66, 95% CI: 0.45 to 0.98) or more than 1500 ml (RR = 0.28, 95% CI: 0.12 to 0.64). There was also less decrease in hemoglobin concentration in the misoprostol group, the mean difference between the two groups being 0.16 mmol/l.

A meta-analysis of the findings of these three studies showed that compared to a placebo, misoprostol resulted in 24% and 41% reductions in the incidence of PPH and severe PPH respectively. However, these trials lack the power to detect an association between the reductions in PPH observed and a reduced risk of maternal death.

In 2011 the 18th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines recommended the addition of 600 μg dose of oral misoprostol to the WHO Model List of Essential Medicines for the prevention of PPH. In addition to WHO, FIGO, and ICM, the Royal College of Obstetricians and Gynaecologists (RCOG) also supports the use of
misoprostol for PPH prevention and recommend that misoprostol can be used to prevent PPH where oxytocin is not available or where birth attendants’ skills are limited.\textsuperscript{16}

### 5.4.2 Misoprostol in the treatment of PPH

An expert panel set up by FIGO recommended that misoprostol can be used for the primary treatment of PPH in the absence of standard uterotonics.\textsuperscript{16} This recommendation was based on published results from seven case reports and three RCTs on the use of misoprostol in treating PPH. Following this recommendation, two large-scale double-blind placebo-controlled randomized trials that compared 800 μg of sublingual misoprostol with 40IU of intravenous oxytocin were conducted. These non-inferiority trials showed PPH due to suspected uterine atony in 9 out of 10 women was controlled successfully within 20 minutes of treatment with either drug.\textsuperscript{16,52,53} Though adverse effects such as shivering and fever were significantly more common in the misoprostol group compared with the oxytocin group, the authors concluded that in settings in which use of oxytocin is not feasible, misoprostol might be a suitable first line treatment alternative for postpartum haemorrhage. Details of these trials are outlined in Annex 1.

There is little evidence to support the benefits of adjunct treatment of PPH with misoprostol and oxytocin. Two RCTs, one undertaken by Hofmeyr et al. in 2002-2003 and the other by Walraven et al. in 2002-2003 showed that compared to a placebo, adjunct administration of misoprostol with standard PPH treatment using oxytocin led to a significant reduction in blood loss greater than or equal to 500 ml.\textsuperscript{54,55} However both studies had small sample sizes (238 and 160 respectively) and had limited power to only detect large differences.\textsuperscript{16,56} However, a recently conducted large multi-center double-blind placebo controlled trial showed no clinical advantage of adjunct use of 600 μg misoprostol (given sublingually) with standard treatment.\textsuperscript{16,57}

The sublingual route is recommended for treating PPH because of the following reasons\textsuperscript{16}:

- The sublingual route is the only treatment route tested in RCTs. Though published studies and case reports on the treatment of PPH using misoprostol have reported on rectal or sublingual route, no double-blind RCT has evaluated the efficacy of administering misoprostol via the rectal route. This was also noted in the 2004 report.
- The sublingual route has the advantage of rapid onset of action compared to the rectal route.
- Compared to other routes, the sublingual route is easy to administer, has the fastest absorption, highest serum levels, greatest bioavailability, and more sustained effect.

In addition to FIGO, the WHO, and RCOG, the American College of Obstetricians and Gynecologists (ACOG) acknowledge that misoprostol is effective in treating PPH and recommend that it be used for treatment in situations where standard uterotonics are unavailable or unfeasible to use. Questions still remain on whether the same therapeutic efficacy of 800 μg misoprostol can be achieved with a lower dose (600 μg) to minimize adverse effects. However, Raghavan et al. argued that while a reduced dose might benefit only a small number of special populations, unjustifiably huge resources would be needed to compare the efficacy of 600 μg and 800 μg misoprostol.\textsuperscript{16} According to the 2009 WHO guidelines on managing PPH, a further review of the safety and effective doses and dosage forms of misoprostol was going to be commissioned by the WHO.\textsuperscript{1}
5.5 Tranexamic acid

Tranexamic acid is an antifibrinolytic agent used in surgery to reduce blood loss. A systematic review of randomized controlled trials of antifibrinolytic agents in elective surgery showed that tranexamic acid reduced the risk of blood transfusion by 39%.\textsuperscript{44} Another Cochrane review showed that tranexamic acid reduced heavy menstrual bleeding without side effects.\textsuperscript{45} According to the WHO, tranexamic acid may be offered as a treatment for PPH if: (i) administration of oxytocin, followed by second-line treatment options and prostaglandins, has failed to stop the bleeding; or (ii) it is thought that the bleeding may be partly due to trauma.\textsuperscript{9} The usefulness of tranexamic acid in PPH treatment is worth exploring through further research studies.\textsuperscript{46}

Gungorduk et al. in 2011 conducted a double-blind RCT to estimate the effects of adding intravenous tranexamic acid to the standard AMTSL in reducing vaginal blood loss.\textsuperscript{58} About 288 women were given intravenous tranexamic acid infusion in addition to standard AMTSL (prophylactic oxytocin 10 IU within two minutes of birth, early clamping of the umbilical cord, and controlled cord traction) while 226 women in the control group received 5% glucose in addition to standard AMTSL. The study results showed significantly lower mean blood loss at the third and fourth stages of labor in the intervention group than that in the placebo group (261.5 ml versus 349.98 ml respectively; p < 0.001). The frequency of PPH greater than 500 ml was also significantly lower in the intervention group (4.1.8%) compared with the controls (15.6.8%; RR = 3.76; 95% CI: 1.27 to 11.15; p = 0.01). The authors concluded that tranexamic acid with standard AMTSL reduced postpartum blood loss with no serious side effects associated with the tranexamic acid.

Peitsidis and Kadir carried out a systematic review of PubMed, Embase, CINAHL, Scopus, Cochrane, and DARE for available evidence on the use, efficacy and safety of tranexamic acid in the management of haemorrhage during pregnancy and for prevention and treatment of PPH.\textsuperscript{58, 59} The authors found 34 articles (five RCTs, seven observational studies, and twenty-two case reports) published from 1976 to 2010. The combined effect of tranexamic acid compared with placebo was estimated to be a difference of 32.5 ml reduction in blood loss (95% CI: -4.1 to 69.13; p = 0.08). Though pulmonary embolism was reported in two cases the involvement of tranexamic acid in could neither be confirmed nor excluded. In conclusion, the authors suggested tranexamic acid is safe and effective in the prevention and management of bleeding during pregnancy and called for more investigation and larger clinical trials to confirm these findings.

A review of the February 2011 Cochrane Pregnancy and Childbirth Group’s Trials Register by Novikoval and Hofmeyr searched for evidence on the effectiveness of tranexamic acid in PPH from completed and ongoing RCTs and yielded two RCTs.\textsuperscript{60} From a meta-analysis of these two RCTs, which involved a total of 453 women, the reviewers found that blood loss greater than 400 ml was less frequent in women who received 1g or 0.5gm IV tranexamic acid after vaginal birth or caesarean section (RR 0.51; 95% CI: 0.36 to 0.72).

5.6 Recombinant factor VIIa

According to the WHO the evidence to recommend the use of recombinant factor VIIa (rVIIa) for the treatment of PPH is weak.\textsuperscript{19} Additionally rVIIa is very expensive, cumbersome to administer and is associated with life threatening side effects. The WHO recommends the
use of rVIIa to be for the treatment of PPH to be limited to women with specific haematological indications.\textsuperscript{1,9}

6. Non-pharmacological management of PPH

The 2012 WHO recommendations for the management of PPH recommends the following non pharmacological interventions for managing PPH.\textsuperscript{9}

\textit{Uterine massage}: A safe and inexpensive intervention to be initiated once PPH has been diagnosed.

\textit{Bimanual uterine compression}: Could be offered as a temporary measure in the treatment of PPH due to uterine atony after vaginal delivery.

\textit{Intrauterine balloon or condom tamponade}: May be used in the treatment of PPH due to uterine atony when other uterotonics fail or if uterotonics are not available. Possible infection is the risk associated with this intervention. The WHO identifies the use of uterine balloon or condom tamponade in the treatment of PPH as a research priority.\textsuperscript{1}

\textit{External aortic compression}: May be provided as a temporary measure to slow down blood loss in treatment of PPH due to uterine atony after vaginal delivery, until appropriate care is available.

\textit{Uterine artery embolization}: May be offered as a treatment for PPH due to uterine atony if other measures have failed and resources are available.

\textit{Non-pneumatic anti-shock garments}: Recommended as a temporary measure until appropriate care is available.

The WHO recommends more research into the effects of uterine massage and intrauterine balloon or condom tamponade in the prevention and treatment of PPH respectively.\textsuperscript{9}

6.1 Surgical interventions

For patients who do not respond to treatment with uterotonics and other non-pharmacological interventions such as uterine massage or who have existing lacerations, large haematomas or a ruptured uterus surgical interventions are required.\textsuperscript{1,9,61} If radiological intervention is available arterial embolization may be done on haemodynamically stable patients as an alternative to surgery.\textsuperscript{63,62}
7. Comparative Trials

7.1 Comparative studies from before 2004

Four Cochrane reviews were published in 2004, and one RCT comparing intra-rectal misoprostol 600 μg with conventional oxytocics. The findings from these trials are summarized.

i). The use of ergometrine-oxytocin in active management of PPH shows a small, but statistically significant reduction in the risk of PPH compared to oxytocin alone for a blood loss of 500 ml. No difference was observed between the two interventions for blood loss more than 1000 ml. The side effects observed for ergometrine-oxytocin were statistically significant compared to oxytocin alone. These included elevated blood pressure, vomiting, and nausea (Cochrane Review 2004).63

ii). Rectal misoprostol, when compared to ergometrine-oxytocin injection, was found to have a statistically significant reduction in the number of women who continued to bleed and those who required medical co-interventions to control the bleeding. No significant differences were observed regarding surgical interventions to control intractable haemorrhage including hysterectomy, internal iliac artery ligation and/or uterine packing. The reviewers concluded that 800 μg rectal misoprostol may be a useful as a first line drug for the treatment of PPH (Cochrane Review 2004).64

iii). Oral misoprostol 600 μg is less effective than conventional injectable uterotonics in reducing blood loss greater than 1000 ml (Cochrane Review 2004).

iv). Compared to conventional injectable uterotonics, prostaglandins reduced blood loss in the third stage of labor but are associated with more side effects (Cochrane review 2004).65

v). Active management, when compared with expectant management was associated with reduced risks of maternal blood loss, postpartum haemorrhage of more than 500 ml and prolonged third stage of labor. Active management is, however, associated with an increased risk of side effects such as nausea, vomiting, and hypertension, where ergometrine is used.66

vi). An RCT conducted in 2002 in Turkey, compared intra-rectal misoprostol 600 μg and oxytocin-methylergometrine. The incidence of PPH was 9.8% in the misoprostol group compared to 3.5% in the oxytocin-methylergometrine group in the management of third stage labour. Rectal misoprostol was comparable to IV oxytocin alone, but less effective than oxytocin plus methylergometrine.67

7.2 Recent comparative trials on managing PPH

Annex 1 shows the details of recent clinical trials comparing the various interventions for managing PPH. Evidence from these studies are summarized below:

i) For women with risk factors for uterine atony, rectal misoprostol (600 μg) is as effective as oxytocin infusion (20IU) as an adjunct to AMTSL for prevention of postpartum haemorrhage.68
ii) Sublingual powdered formulation of misoprostol (400 μg) may be superior to IV oxytocin (10IU) in preventing postpartum blood loss. Chaudhuri et al. also showed that 400 μg sublingual misoprostol was equivalent to 10 units of oxytocin IV in the prevention of PPH after vaginal birth in women with low-risk of PPH.

iii) Sublingual misoprostol (800 μg) may be non-inferior to oxytocin IV (40IU) in the treatment of women with primary PPH who had or had not been exposed to prophylactic oxytocin. The authors of these studies concluded that misoprostol may be used as first line treatment for PPH in settings where the use of oxytocin is not feasible.

iv) Compared to rectal misoprostol 400 μg, intramuscular injection of oxytocin 10IU, and intramuscular injection (0.5 mg ergometrine + 5IU oxytocin), intravenous injection of methylergometrine 0.2 mg was found to be the most effective in reducing the duration of third stage of labor, the amount of blood loss and the incidence of PPH (p = 0.000096, 0.000017 and 0.03 respectively). No significant differences were found in pre-delivery and post-delivery hemoglobin concentration amongst the four groups (p = 0.061). The authors of this study suggested misoprostol should be reserved for use in low resource settings and where other uterotonic drugs were not available.

v) Carbetocin was as effective as oxytocin in the prevention of postpartum haemorrhage in women with severe preeclampsia. The safety profiles of the two drugs were found to be similar. However, carbetocin does not have a major haemodynamic effect in women with severe preeclampsia and the volume per dose for its administration is lower than that of oxytocin. This may be a good option for the management of third stage labor in women with hypertensive disorders during pregnancy.

vi) Carbetocin and a combination of oxytocin and ergometrine have similar efficacy in preventing PPH in women who deliver vaginally. However the former has a better safety profile. The combination of oxytocin and ergometrine was more commonly associated with nausea and vomiting tremor, sweating, retching and uterine pain.

A Cochrane Review by Su et al. compared the effectiveness of carbetocin with conventional uterotonic agents in preventing PPH. This review focused on RCTs which compared carbetocin with other uterotonic agents, carbetocin with a placebo or carbetocin with no prophylactic treatment against PPH. The authors identified 11 studies involving 2635 women from the Cochrane Pregnancy and Childbirth Group’s Trials Register (1 March 2011), the Cochrane Central Register of Controlled Trials (The Cochrane Library 2011, Issue 1 of 4), MEDLINE (1966 to 1 March 2011) and EMBASE (1974 to 1 March 2011).

From the review findings, six trials compared 100 μg carbetocin with oxytocin. Carbetocin was administered as intravenous dosage across the trials, while oxytocin was administered intravenously at varied dosages. Four trials compared intramuscular carbetocin and an intramuscular combination of oxytocin and ergometrine for women undergoing vaginal deliveries. Three of the trials were on women with no risk factor for PPH, while one trial was on women with risk factors for PPH. One trial compared the use of intravenous carbetocin with placebo. Use of carbetocin was associated with a significant reduction in the need for therapeutic uterotonics (RR= 0.62; 95% CI: 0.44 to 0.88; four trials with a total of 1 173 women who underwent caesarean session) compared to oxytocin. Carbetocin was associated with a reduced need for uterine massage following both caesarean delivery (RR = 0.54; 95% CI: 0.37
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to 0.79; two trials, 739 women) and vaginal delivery (RR = 0.70; 95% CI: 0.51 to 0.94; one trial, 160 women) compared to oxytocin.

There was a lower mean blood loss in women who received carbetocin compared to a (mean difference -48.84 ml; 95% CI -94.82 to -2.85; four trials, 1030 women). The need for additional uterotonic agents was not statistically significant between the two groups. However, the risk of adverse effects such as nausea and vomiting were significantly lower in the carbetocin group: nausea (RR = 0.24; 95% CI 0.15 to 0.40; four trials, 1030 women); vomiting (RR = 0.21; 95% CI 0.11 to 0.39; four trials, 1030 women). The incidence of postpartum hypertension was significantly higher in women who received a combination of oxytocin and ergometrine compared to those who received carbetocin. There was no difference in the risk of heavy bleeding between patients given IV oxytocin and IV carbetocin. However, women who received oxytocin were more likely to require additional uterotonics following caesarean sections.

8. Summary of changes since 2004

Notable changes have taken place in the research and management of PPH since 2004.

1. TI Pharma Hot Medicines Consortium has made substantial breakthroughs in developing a heat stable oxytocin, the number one recommended intervention for preventing and treating PPH. Though this progress is promising and worth noting, further research studies are needed to make a heat stable oxytocin available for therapeutic use.

2. There is now more evidence supporting the acceptability, effectiveness, feasibility of use, and safety of the oxytocin-Unject at the hospital and community level. The challenges of expertise in dose measurement and injection skills required to administer oxytocin in ampoules have been technically resolved by the oxytocin-Unject device.

3. A major concern regarding the use of oxytocin-Unject identified in the 2004 report was that in the case of an interrupted cold chain delivery and storage system, the quality of the oxytocin in the Unject device could not be assured. This challenge has also been overcome by the development of the Unject with time-temperature exposure indicator. This technology has been successfully piloted in Mali and is currently undergoing an community randomized trial in Ghana.

4. In 2004 there was lack of clarity on the effectiveness of misoprostol in AMTSL. However, over the past decade the efficacy of misoprostol for PPH prevention has been well documented at both the hospital and community level. The evidence-based misoprostol regimen for PPH prevention is a single 600μg dose administered orally to women immediately after vaginal delivery of the last baby.

5. The effectiveness of sublingual misoprostol in treating PPH has now been established. However, there is still lack of clarity on the most appropriate dose that will be safe and effective to minimize adverse effects. The 2012 WHO recommendations for managing PPH identified as a research priority the determination of the minimum effective dose of misoprostol for treating PPH.

6. In 2004 oxytocin and ergometrine were the only medicines for PPH on the WHO EML. In 2011 ergometrine was removed and oral misoprostol was added to the EML.
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7. Tranexamic acid and carbetocin have recently been suggested as alternative interventions.\(^6\) According to the WHO, tranexamic acid may be offered as a treatment for PPH if first, second, and third line treatments have failed to stop the bleeding or the bleeding is partly due to trauma.\(^1\) The usefulness of tranexamic acid in PPH treatment is worth exploring through further research. On the other hand, carbetocin does not have a strong advantage over its analogue oxytocin, except perhaps in women with (pre) eclampsia.

8. The WHO no longer recommends early cord clamping as part of AMTSL, unless the baby suffers asphyxia and needs to be moved quickly to resuscitation.

9. Need for further research

**Medicine development**

1. The TI Hot Pharma Consortium’s initiative to develop a heat stable oxytocin is promising and should be further pursued. The development of a therapeutically effective heat stable oxytocin will solve the current challenges of cold storage for oxytocin. The thermostable oxytocin should be packaged in Unijets to provide it with an additional advantage of ease of use in low resource settings.

2. There is the need for studies to determine a standard, safe, and effective dose of oral and sublingual misoprostol for preventing and treating PPH.\(^6\),\(^9\)

3. Research is needed to discover new and easy to use treatments for PPH in cases where prophylactic measures fail.

**Clinical studies**

4. Further research is needed to explore the potential of tranexamic acid in treating PPH. Trials comparing the safety and efficacy of tranexamic acid and tranexamic acid in addition to existing uterotonics would be helpful.

5. The usefulness of carbetocin instead of oxytocin in treating PPH in women with pre-eclampsia should also be explored. Carbetocin does not have a major hemodynamic effect in women with severe preeclampsia and the volume per dose for its administration is lower than that of oxytocin.\(^2\)

**Health systems research**

6. The use of oxytocin-Uniject with the TTI should be scaled up especially in low resource settings in tandem with adequate post marketing pharmacovigilance studies.

7. A system of collecting or estimating routine data on the incidence of PPH and severe PPH should be established.

8. There is evidence that sublingual misoprostol is beneficial in the treatment of PPH, especially where there is no access to oxytocin. However evidence is currently limited on the effectiveness of its use by less skilled or lay caregivers at the community level.\(^9\) Operational research is needed to determine if the benefits of advanced community distribution of misoprostol to pregnant women and to lower cadre health workers at the community level outweigh the potential disadvantages. The WHO identifies a study on the effectiveness of antenatal distribution of misoprostol to pregnant women for self-
administration during the third stage of labour in settings where the use of injectable uterotonics is not possible as a key research priority.

9. Regulatory barriers that prevent lower cadre health workers from administering oxytocin or misoprostol should be removed especially in low resource settings.

Finally, research is needed to discover new, patient-friendly and easy-to-use medicines for preventing and treating PPH. According to a 2012 commissioners report of the United Nation Commission on Life-saving Commodities for Women and Children, if current interventions for the management of PPH are improved (development of a thermo-stable oxytocin formulation, the promotion of the oxytocin-Uniject with a TTI technology and the development of a non-parenteral inhalation or intranasal spray oxytocin, etc.) and equitable access is achieved, about 15,000 maternal deaths would be avoided in the next five years.\textsuperscript{74}

10. Why the burden of PPH still persists

Much progress has been made in terms of research into finding solutions to the burden of PPH. However this progress has not completely stemmed the tide against women dying due to haemorrhage during child birth. One reason for this is the fact that there is no “silver bullet” for the prevention or treatment of PPH. Between 3 to 16.5\% of women will go on to experience PPH even after AMTSL with existing interventions.\textsuperscript{16} Oxytocin, the current gold standard for the prevention and treatment of PPH has serious limitations because of its instability in tropical climates and the need for trained personnel for administration. Until the use of the oxytocin-Uniject becomes widespread, the expertise required to administer the medicine will still be a barrier to its use in low resource settings. Until a heat stable formulation of oxytocin is developed, the quality of oxytocin if available in low resource settings cannot be guaranteed because of lack of cold chain storage.

The new interventions that have been suggested, for example the use of tranexamic acid and balloon or condom tamponade in the treatment of PPH still require further research to qualify their use.

Maternal mortality due to haemorrhage is preventable with timely medical treatment. However, delays in allowing pregnant women the access to timely medical treatment result in high maternal mortality. Factors that contribute to delay in deciding to seek care include the actors involved in decision-making (individual, spouse, relatives, family), the status of women, illness characteristics, distance from the health facility, financial and opportunity costs, previous experience with the health care system, and perceived quality of care. Factors contributing to delay in reaching a health facility include physical accessibility, such as the distribution of facilities, travel time from home to facility, availability and cost of transportation, and condition of roads. Factors responsible for delays in receiving adequate care while patient is at the health facility include adequacy of the referral system, shortages of supplies, equipment, and the competence of available personnel. The non-availability or lack of access to appropriate technologies, such as oxytocin-Uniject, heat stable oxytocin or oxytocin packaged with the TTI technology contributes to the delay in patients receiving appropriate care at health facilities. The current technologies available are beyond the training and the skills of lower cadre health workers who most often work at the community
11. Conclusion

Postpartum haemorrhage still remains the leading cause of maternal mortality. Though the burden of PPH is highest in developing countries, the incidence of PPH is on the increase in developed nations. Current preventive and treatment interventions are inadequate and inequitably distributed. While much has been done to improve on the existing interventions including the development of heat stable oxytocin and the development of the oxytocin-Uniject with a TTI technology, these improvements are either not yet therapeutically available for use or are not yet deployed on a large scale. More research is needed develop new interventions, improve on existing interventions, and to ensure that the existing technologies as well as those to be developed are equitably distributed to reduce the burden of PPH.

References


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6.16 Postpartum Haemorrhage


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### Annex

**Annex 6.16.1: Recent comparative studies on uterotoincs**

<table>
<thead>
<tr>
<th>Study design / Year</th>
<th>Setting of study</th>
<th>Study population</th>
<th>Interventions compared</th>
<th>Results</th>
<th>Adverse effects</th>
<th>Conclusion</th>
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</thead>
</table>
| **Misoprostol (rectal) versus oxytocin (infusion) for the prevention of PPH** | Double blind RCT/2009 | University Teaching Hospital in Nigeria | 264 pregnant women with identifiable risk factors for uterine atony in Nigeria | Rectal misoprostol (600 mg; n = 132) after routine AMTSL versus Oxytocin infusion (20 IU in 500 ml; n = 132) after routine AMTSL | 1. No significant difference in the mean intrapartum blood loss between the two groups: 387.28 +/- 203.09 versus 386.73 +/- 298.51, (p= 0.07).  
2. Postpartum hematocrit drop was significantly less in the misoprostol group. 1.0 ± 2.036 versus 2.915 ± 3.103, (p<0.001)  
3. No difference between the two arms in the requirement for additional intervention for uterine atony: 7 (5.6%) versus 6 (4.7%) 0.74 (p = 0.74). | Shivering, pyrexia and vomiting are more frequent with misoprostol, though usually self-limited. | Rectal misoprostol is as effective as oxytocin infusion as an adjunct for prevention of postpartum haemorrhage in women with risk factors for uterine atony |
| **Misoprostol (powdered sublingual) versus oxytocin (IM) for the prevention of PPH** | Double blind RCT / 2007 to 2008 | A teaching hospital in Belgaum India | 652 women with a singleton pregnancy at >28 weeks of gestation, with cephalic presentation, anticipating vaginal delivery and with hemoglobin > 8 g/dl upon presentation | 400 μg powdered sublingual misoprostol (n=321) versus 10IU intramuscular oxytocin (n=331) | 1. Mean blood loss with sublingual misoprostol and oxytocin IM were 192 ± 124 ml and 366 ± 136 ml respectively, (p< 0.001)  
2. The incidence of PPH was 3.1% with misoprostol and 9.1% with oxytocin (p= 0.002).  
3. Proportion of women with hemoglobin decline greater than 10% in the misoprostol and oxytocin groups were 9.7% and 45.6% respectively (p< 0.001) | Nausea, vomiting, shivering and fever were significantly greater in the misoprostol group than in the oxytocin group | Sublingual misoprostol is more effective than intramuscular oxytocin in reducing PPH, with only transient side effects being greater in the misoprostol group |
## Misoprostol (sublingual) versus oxytocin (IM) for the prevention of PPH

<table>
<thead>
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<th>Study design / Year</th>
<th>Setting of study</th>
<th>Study population</th>
<th>Interventions compared</th>
<th>Results</th>
<th>Adverse effects</th>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>Double blind RCT / 2009 to 2010</td>
<td>Hospital in Kolkata, India</td>
<td>530 women without risk of PPH</td>
<td>400 μg of misoprostol given sublingually within one minute of delivery (n=265) versus 10 units of oxytocin IM within one minute of delivery (n=265)</td>
<td>1. Incidence of PPH and postpartum blood loss in the misoprostol group were similar to those in the oxytocin group (6% versus 5.7%, p=0.85 and 153 ml versus 146 ml, p=0.36 respectively). 2. No significant differences between the two arms regarding drop in hemoglobin level in 24 hours, the need for additional uterotonic drug, and the need for blood transfusion</td>
<td>Shivering and pyrexia were more common in the misoprostol than in the oxytocin group</td>
<td>The efficacy of 400 μg of misoprostol administered sublingually was equivalent to that of 10 units of oxytocin given intramuscularly for prevention of PPH in low-risk vaginal delivery.</td>
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## Misoprostol (sublingual) versus oxytocin (IM) for the treatment of PPH

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<tr>
<th>Study design / Year</th>
<th>Setting of study</th>
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<th>Adverse effects</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Double blind non-inferiority trial / 2005 to 2008</td>
<td>Four hospitals in Ecuador, Egypt, and Vietnam</td>
<td>978 women not exposed to prophylactic oxytocin diagnosed with primary PPH</td>
<td>800 μg misoprostol (n=488) versus 40 IU intravenous oxytocin (n=490) (Clinical equivalence of misoprostol defined as the upper bound of the 9.5% CI falling below margin of 6%)</td>
<td>1. Active bleeding was controlled within 20 minutes for 440 (90%) women given misoprostol and 468 (96%) of women given oxytocin (RR = 0.94, 95% CI 0.91–0.98; crude difference 5.3%, 95% CI 2.6–8.6). 2. Additional blood loss of 300 ml or greater after treatment occurred for 147 (30%) of women receiving misoprostol and 83 (17%) receiving oxytocin (RR 1.78, 95% CI 1.40–2.26).</td>
<td>Shivering and fever were significantly more common with misoprostol than with oxytocin.</td>
<td>In women who had not received oxytocin prophylaxis, misoprostol is clinically equivalent to oxytocin in treating post-partum bleeding suspected to be due to uterine atony.</td>
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## Misoprostol (sublingual) versus oxytocin (IM) for the treatment of PPH

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<th>Conclusion</th>
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</table>
| Double blind non-inferiority trial / 2005 to 2008 | Five hospitals in Burkina Faso, Egypt, Turkey, and Vietnam | 809 women exposed to prophylactic oxytocin diagnosed with PPH | 800 μg misoprostol (n = 407) versus 40IU intravenous oxytocin (n=402) (Clinical equivalence of misoprostol defined as the upper bound of the 9.5% CI falling below margin of 6%.) | 1. Active bleeding was controlled within 20 minutes after initial treatment for 363 (89%) women given misoprostol and 360 (90%) given oxytocin (RR = 0.99, 95% CI 0.95–1.04; crude difference 0.4%, 95% CI ~3.9 to 4.6).  
2. Additional blood loss of 300ml or greater after treatment occurred for 139 (34%) women receiving misoprostol and 123 (31%) receiving oxytocin (RR = 1.12, 95% CI 0.92–1.37). | Shivering and fever were significantly more common among women who used misoprostol compared to women who used oxytocin | In women who had received oxytocin prophylaxis, misoprostol is clinically equivalent to oxytocin in treating post-partum bleeding suspected to be due to uterine atony. |

## Carbetocin versus oxytocin in the prevention of PPH

<table>
<thead>
<tr>
<th>Study design / Year</th>
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<th>Study population</th>
<th>Interventions compared</th>
<th>Results</th>
<th>Adverse effects</th>
<th>Conclusion</th>
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</table>
| Double blind RCT / 2010 | Hospital | 60 women with singleton pregnancies of more than 28 weeks' gestation who were admitted to hospital with severe preeclampsia | Carbetocin 100 μg + Ringer’s lactate solution 10ml injected directly into the vein over two minutes versus Oxytocin 20 U diluted in 1000 ml of Ringer’s lactate solution, administered intravenously at a rate of 125 ml/hour | 1. No significant differences in mean arterial pressure and heart rate between the groups (both before and after drug was given)  
2. No differences between the carbetocin and oxytocin groups in hemoglobin concentration, rates of oliguria after delivery  
3. No difference between the two groups in the need for additional uterotonics | Carbetocin had a safety profile similar to that of oxytocin, and it was not associated with the development of oliguria or hypertension | Carbetocin is as effective as oxytocin in preventing postpartum bleeding in women with severe preeclampsia, with no alterations in hemodynamic status and with few side effects |
### Carbetocin versus combination of oxytocin and ergometrine (combinatio n of oxytocin and ergometrine)\(^2\)

<table>
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<th>Study design / Year</th>
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<th>Interventions compared</th>
<th>Results</th>
<th>Adverse effects</th>
<th>Conclusion</th>
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| Double blind RCT / 2005 to 2008 | Referral hospital in Singapore | 370 pregnant women who had no contraindication for vaginal delivery | One ampoule of combination of oxytocin and ergometrine (5 iu of oxytocin and 500 microgram of ergometrine) intramuscularly (n=185) versus 100 microgram carbetocin intramuscularly (n=185) | 1. 14% and 17% of women in the carbetocin group and combination of oxytocin and ergometrine group respectively had postpartum haemorrhage requiring additional uterotonics (\(p = 0.384\)).
2. The proportion of women in each group who had postpartum haemorrhage were the same (1.6%) and the estimated blood loss was similar between the two groups | Compared to the carbetocin group, women who had combination of oxytocin and ergometrine were four times more likely to experience nausea and vomiting. Tremor, sweating, retching and uterine pain were also more common with combination of oxytocin and ergometrine | Carbetocin and combination of oxytocin and ergometrine thus seems to have the same efficacy. However the former has a better safety profile |

### Misoprostol (rectal) versus oxytocin (IM) versus methylergometrine (IV) versus ergometrine + oxytocin (IM)\(^3\)

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<th>Study design / Year</th>
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<th>Study population</th>
<th>Interventions compared</th>
<th>Results</th>
<th>Adverse effects</th>
<th>Conclusion</th>
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| Prospective non RCT / 2007 to 2008 | Hospital in Baroda India | 200 women with singleton pregnancy, between 37 and 42 week of gestation, anticipated vaginal delivery, vertical lie, no high risk factors for PPH | AMTSL with tablet misoprostol 400μg rectal versus AMTSL with IM oxytocin 10 IU versus AMTSL with IV methyl ergometrine 0.2 mg versus AMTSL with injection combination of oxytocin and ergometrine (methyl ergometrine 0.5 mg + oxytocin 5 IU) | 1. Methylergometrine to be the most effective in reducing the duration of third stage of labor, the amount of blood loss and the incidence of PPH (\(p = 0.000096, 0.000017\) and 0.03 respectively).
2. Compared to the other medicines, women given misoprostol had the highest need for additional oxytocics and blood transfusion (\(p = 0.037\) and 0.009 respectively).
3. No significant differences were found in pre-delivery and post-delivery hemoglobin concentration amongst the four groups (\(p = 0.061\)) | Shivering and pyrexia in significantly higher in the misoprostol group, while nausea, vomiting and headache were more associated with methylergometrine and ergometrine–oxytocin. | Compared to the other four medicines, methylergometrine has the best uterotonic property, Authors suggested misoprostol be reserved for use in only low resource settings and where other uterotonic drugs were not available |

Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper
by Warren Kaplan and Samira Asma

Background Paper 6.17
Tobacco use cessation therapies

By Ileana B. Heredia Pi, National Institute of Public Health, Mexico and
Veronika J. Wirtz, Boston University
Update on 2004 Background Paper, BP 6.17 Smoking Cessation

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Executive summary

Smoking is considered the single most important cause of preventable morbidity and premature mortality worldwide. Tobacco addiction caused about 100 million deaths during the 20th century, each year 5.4 million people die from this cause, and if resolute and urgent action is not taken by 2030 the epidemic will cause between 8 and 10 million deaths each year, of which over 80% occur in low- and middle-income countries (LMIC).

Stopping smoking is very difficult; often require repeated intervention and/or multiple attempts to quit. Nowadays, there are numerous effective medications available for tobacco dependence. In general, seven first-line medications (five nicotine and two non-nicotine) are recommended and reliably increase long-term smoking abstinence rates. Based on this evidence, clinicians should encourage their use in patients attempting to quit smoking except when medical contraindication exists or with specific populations (i.e. pregnant women, smokeless tobacco users, light smokers, and adolescents) for which there is insufficient evidence of effectiveness.

The research currently available suggests that abstinence rates can be increased by combining different forms of nicotine replacement therapy (NRT) or simultaneous administration of NRT and non-nicotinic compounds. However, more research is needed in this area, as well as a better definition of the criteria which need to be fulfilled to use some of the therapeutic modalities in combination. Additionally, evidence suggests that smokers who relapse sometimes during their cessation attempt are at high risk of future relapses, so that rescue interventions for smokers are necessary.

More research is needed on the cost-effectiveness of pharmacotherapy for smoking cessation in LMIC to inform decision makers about the need for the development of lower costs therapeutic options for their countries.
Major changes in the area of smoking cessation between 2004 and 2012

a) Strategies and guidelines of international organizations such as World Health Organization (WHO)
   - MPOWER initiative was launched as a tool for countries to successfully implement the Framework Convention on Tobacco Control (FCTC).
   - The WHO Model List of Essential Medicines application and granting of NRT for smoking cessation and the management of tobacco dependence in adult smokers.
   - Definition of "best buy" interventions by WHO including four key elements of the FCTC (increase the tax on tobacco products, comprehensive legal framework to ensure tobacco smoke free public places, information and warning about the harms of tobacco, and the ban on advertising, promotion and sponsorship)
   - In 2009, NRT products were included in the WHO Model List of Essential Medicines.

b) Newly available treatment options for smoking cessation
   - Introduction of new treatment alternatives to the market as selective partial agonists of nicotinic receptors (varenicline) and nicotinic antagonist (mecamylamine).
   - Medicines obtained new indication for their use in the treatment for tobacco addiction: antidepressants (bupropion, nortriptyline), antihypertensives (clonidine), opioid antagonists (naltrexone),
   - New definition of a first-line treatment for the management of patients who wish to stop smoking (NRT, bupropion or varenicline) and second-line treatment (clonidine and nortriptyline).
   - Start of using different treatment options in combination (i.e., patches with other forms of NRT). Additionally, further research is required about other combinations as nortriptyline and NRT, varenicline and bupropion, varenicline and NRT, etc.).
   - New clinical trials conducted in specific populations such as pregnant women and adolescents. More research is needed in this area.

c) Evidence on the cost-effectiveness of interventions
   - Increasing number for pharmacoeconomic studies that comparatively evaluate different treatment options, particularly in low income countries.
   - Most studies were carried out in high-income and upper middle income countries. There is a lack of studies of the cost-effectiveness of treatment options including combinations of pharmacotherapy, individual and group counseling in low middle income and low income countries.

d) Research and development of new treatments
   - Negative NicVAX vaccine study outcomes in two phase III clinical trials conducted by Nabi Biopharmaceuticals.
   - Numerous treatments are currently in development: vaccine (TA-NIC, NIC002, Niccine), antidepressants (EVT 302), partial agonists selective nicotinic
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receptors (cytisine), opioid antagonists (nalmefone), selective antagonists of the cannabinoid receptor type 1 (taranabant).
1. **Introduction**

Smoking is one of the public health problems with the greatest impact on morbidity and mortality globally. Estimates projecting future consequences of using tobacco products show a worrying picture especially for developing countries with the highest proportion of deaths related to tobacco consumption in the coming years coming from these countries. However, high income countries also face serious challenges in relation to the control of the tobacco epidemic. For the European Region, these challenges include the high prevalence of tobacco consumption among women, much higher than those in other regions such as Asia, Africa and the Middle East. The growing trend of women consuming tobacco products has narrowed the gap between the genders, which could be interpreted as a “feminization” of the addiction to tobacco in these countries.

The World Health Organization (WHO) has targeted priority areas to combat the tobacco epidemic, one of which is to support the smoker in their attempt to quit smoking. The cessation support covers a broad spectrum of actions or interventions offered to smokers who want to make a serious attempt to quit ranging from medical advice (offered in any health services received by the smoker, regardless of reason that leads to seeking care) to comprehensive treatment, multicomponent and multidisciplinary service in a clinic specializing in the treatment of addiction to tobacco products.

According to international scientific evidence, about 70% of smokers want to quit, 30% have made a previous cessation attempt and 8% of them have used any medications for smoking cessation. A recent study reported estimations about individual cessation assistance in 15 middle and high income countries (five of them in Europe) participating in the International Tobacco Control (ITC) policy evaluation surveys. Results show that recent quitting activity varied considerably by country whereby reports of ever having tried to quit varied from around 60% in New Zealand, Mexico and China, to over 80% in most of the other countries. Prevalence of quit attempts in the last year varied from under 20% to over 50% across countries. The study also shows much higher use of quit smoking medications among those who made quit attempts in the previous year in western countries (over 40% in Australia, Canada, United Kingdom & USA) than in middle-income countries. Additionally, it is known that less than 3% of smokers quitting the habit have done this on their own (only with their own will power), while medication support may double or triple the probability of successful cessation long-term compared to unsupported attempts. Evidence shows that individual attempts to quit have low success rates: of those who try without the assistance of cessation programs, about 98% will have started again within a year. Offering support to smokers in the form of medication, facilitating access to those interventions through reimbursement and thereby increasing the probability of success seems desirable, so that every smoker who wants to quit smoking, has access to safe, effective and affordable medications to meet their needs.

The aim of this study is to review the current status of the tobacco epidemic globally and the different interventions to combat addiction with a particular focus on pharmacotherapeutic options. We also discuss whether there is a therapeutic gap in offering treatment for tobacco addiction currently and whether and where investment in research is desirable from a public health perspective.
1.1 What is the size and nature of the disease burden?

Smoking is considered the single most important cause of preventable morbidity and premature mortality worldwide due to the effects it has on numerous causes of illness and death. The regular consumption of tobacco is responsible for numerous diseases that cause premature death and/or disability in smokers and people exposed routinely to tobacco smoke in the environment. Since the 1950s when it was first documented that cigarette smoking was a major causal factor in the development of lung cancer, numerous studies described the health consequences resulting from the regular consumption of tobacco, both for smokers and for those who are affected due to passive smoking. For the last four decades the Surgeon General’s Reports in the United States have summarized and analyzed evidence about the negative health effects of the consumption of tobacco.

Addiction to tobacco caused about 100 million deaths during the 20th century, each year 5.4 million people die from this cause, and –if resolute and urgent action is not taken- by 2030 the epidemic will cause between 8 and 10 million deaths each year, of which over 80% will occur in low and middle income countries (LMIC). Additionally, in the 21st century it is estimated that, based on current patterns in the prevalence of smoking in the world, approximately between 500 million and one billion people will die as a result of the consumption of tobacco and of these, half will be between the ages of 35-69 years. The only way to reverse these estimates is to adopt effective strategies, efficient (with evidence of cost effectiveness) and affordable to the people in all the countries affected. Estimates from The World Bank show that 25% coverage with NRT would cost only US$ 276-US$ 297 per disability life year saved in low-income countries, values comparable to many health interventions financed by governments in these countries.

In the European Region in 2011, about 32% of the adult population were smoking on a regular basis. Data from the Global Adult Tobacco Survey 2009 (GATS 2009) show that the prevalence of smoking at country level is highly variable, with countries like the Russian Federation and other Eastern European countries with a higher prevalence (39.1% in the Russian Federation, 30.3% in Poland and 28.8% in Ukraine) than the rest of Europe (21% in Israel, 24% in United Kingdom, Republic of Moldova, Portugal, Kazakhstan and Iceland and 25% in Finland). Tobacco was the main risk factor associated with premature mortality in the region, causing about 1.6 million deaths. Currently, Europe, along with the Region of the Americas, shows the highest proportion of deaths attributable to tobacco (16%). Contrastingly, the proportion in Africa and the Eastern Mediterranean attributable to tobacco is 3% and 7%, respectively, with a global average of 12%. Overall, more men than women die from causes related to the consumption of tobacco. However, in the WHO European Region, at present, this difference is greater than the global average (5:1).

In 2010 in the WHO European region, 22% of women smoke which is high when comparing with Africa, Asia and the Middle East (3.5%). While the use of tobacco products was formerly largely a male phenomenon, the gap in use between male and female adults is now smaller in countries like Austria, Denmark, Ireland, Norway and the United Kingdom. In Sweden and Norway today, the prevalence of daily consumption of tobacco is higher in women. Also more girls than young boys use tobacco in Bulgaria, Croatia, Poland and Slovenia. A recently study in 1.3 million United Kingdom women shows that 20% were current smokers, 28% were ex-smokers, and 52% were never-smokers. Two-thirds of all...
deaths of smokers in their 50s, 60s and 70s are caused by tobacco use. Woman smokers lose at least 10 years of life.25

The WHO data base shows the age standardized prevalence rate use of any tobacco product in 2009 (Figure 6.17.1). Data suggests that tobacco use prevalence often differs across countries and by gender, indicating social inequity.5 The currently available evidence is very consistent in showing that smoking is a major cause of inequality in health between socioeconomic groups and (so far) between men and women. Mortality rates of smoking-related diseases (such as lung cancer and COPD), on average, are two to three times higher in low-income population groups compared to high income groups and, in addition, more men than women die from smoking-related diseases.2,3

Table 6.17.1: Deaths attributable to tobacco use by WHO Region

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>Proportion of all deaths attributable to tobacco (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>All adults</td>
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</tr>
<tr>
<td>Europe</td>
<td>25</td>
<td>7</td>
<td>16</td>
<td></td>
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<td>Americas</td>
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<tr>
<td>Global</td>
<td>16</td>
<td>7</td>
<td>12</td>
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</table>

Source: WHO Global Report 2012. Mortality attributable to tobacco.2

Tobacco addiction is a chronic medical condition and is treatable. The cessation of smoking produces immediate and substantial health benefits and reduces much of the risk from smoking within the first years after cessation.5,26,27 Smokers who manage to quit cigarette smoking before developing a smoking-related disease, avoid most of the risk of morbidity and mortality associated with the consumption of tobacco in a few years after overcoming their addiction, so that effective strategies to increase cessation rates (abandonment of addiction) may prevent millions of deaths associated with smoking in the next 50 years.10,28

Interventions for smoking cessation have been shown to be effective and cost-effective in a variety of settings compared with other interventions within the health system.4 Providing smoking cessation strategies within the benefit packages of all medical insurances or public health plans promotes access to these interventions to all smokers who seek help in their cessation attempt.
Figure 6.17.1: Current smoking of any tobacco product (age-standardized rate (%)). European Region 2009

Source: Own production based on World Health Organization data (http://apps.who.int/gho/data/#)\(^4\). Note: Data were not available for Cyprus, Ireland, Luxembourg, Monaco, Montenegro, San Marino, Sweden, Tajikistan, The former Yugoslav Republic of Macedonia and Turkmenistan.

1.2 What is the control strategy?

Reducing demand

The World Health Organization (WHO) in 2004 adopted the Framework Convention on Tobacco Control (FCTC), a global treaty to combat smoking, which took effect from February 2005. According to the WHO, until April 2012, 174 of the 194 WHO member countries have ratified the FCTC.\(^2\) To support countries to implement the FCTC, in 2008, the WHO introduced the initiative called "MPOWER" which brings together a series of cost-effectiveness measures and policies that act synergistically to combat smoking.\(^4,5\) These are:
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- Monitoring (Monitor the consumption of tobacco and prevention measures);
- Protecting (Protect the population from tobacco smoke exposure);
- Offering (Offer help to quit tobacco consumption);
- Warning (Warn about the dangers of tobacco);
- Enforcing (Enforce bans on tobacco advertising, promotion and sponsorship) and;
- Raising (Raise taxes on tobacco).

The MPOWER strategy - along with implementation guidelines of Article 14 of the FCTC have provided practical assistance to implement effectively policies to reduce demand for tobacco products at the country level. This MPOWER strategy has focused particularly on demand reduction, although the WHO has recognized the importance of implementing measures on the supply side that are contained in the FCTC.

Specific measures recommended to reduce the consumption of tobacco, and considered as one of the most powerful and cost-effective, are those related to fiscal and tax policy related to tobacco products. Other important measures to reduce the tobacco consumption are related to information (ban on advertising in certain places, including warnings about the health risks of smoking), prohibiting the consumption of tobacco in certain public places and some specific medical interventions. Those medical interventions include the medical advice provided by health care providers to patients on an individual basis, patient support groups which often involve psychologists, and medication for cessation support.

Recently the WHO has recommended a series of interventions as "best buy" for countries to control noncommunicable diseases (NCDs). The interventions can generate significant financial savings and improve health. They have low implementation costs as well as the feasibility of being scaled up, particularly in resource-constrained settings. Within this group of interventions are four key elements of the FCTC (increase the tax on tobacco products, comprehensive legal framework to ensure banning smoking from public places, information and warning about the harms of tobacco and the ban on advertising, promotion and sponsorship).

It has been estimated that these interventions alone could prevent more than five million deaths in 23 LMIC during the period 2006-2015. The evidence provided by these estimates indicate that the cost of implementing the four interventions could cost less than 0.40 US dollars per person per year in LMIC, while in high-income countries the cost would be between 0.5-1.0 US dollars per person per year.

Pharmacotherapeutic interventions

A recent systematic review published in 2012 shows that medication and behavioral therapies in the treatment of smoking cessation are cost-effective and even cost-saving for health systems in the long-term, generating substantial savings by avoiding costs associated with morbidity and mortality.

However, it is noteworthy that, although individualized interventions for smoking cessation such as medication have proven to be effective and, for many settings, to be cost-effective compared with other interventions within the health system, these individual interventions were not included in the group of "best buy" interventions recommended by WHO. The reason is concern about their currently low cost-effectiveness in LMIC. For example, a cost
effectiveness study conducted in 2011 in Viet Nam, a lower middle income country, compared a brief counseling intervention for smoking cessation and pharmacological therapies. The cost-effectiveness result of physician brief advice was 1,742,000 Vietnamese Dong (VND) per DALY averted (international dollars 543), which was considered as ‘very cost-effective’. Authors reported that varenicline dominated bupropion and nicotine-replacement therapies, although it did not fall within the range of being ‘cost-effective’ under different scenarios. The study concluded that the brief counseling intervention is cost-effective and should be included in the list of priorities within the tobacco control policies in the country, meanwhile, pharmacological treatments would not be recommended in this context, unless the same are locally produced at a significantly lower cost in the future.36

The currently available evidence is very consistent in showing that smoking cessation provides an important window of opportunity in combating the epidemic. Most smokers know the damage of tobacco products and want to stop smoking; however, quitting without help is hard because nicotine delivered in tobacco smoke is a highly addictive substance.4,5,26

Three types of treatments should be included in any individual smoking cessation effort: a) Medical counseling: brief advice offered by service providers in primary care units.26 b) Support lines on smoking cessation: cessation advice may also be offered from free helplines (internet or phone).26 c) Medication: Currently, there are several options to offer medication to those who try to quit smoking. (Annex 6.17.1).

The medication belongs mainly to two distinctive groups: (1) replacement therapy or nicotine replacement (NRT), mainly patches, gum and nicotine inhalers and (2) non-nicotinic compounds as bupropion hydrochloride, nortriptyline and more recently, varenicline tartrate and cytisine.8,37 Varenicline and cytisine are selective nicotinic receptor partial agonists, which block the action of nicotine, decreasing the urgency of smoking and withdrawal symptoms. In addition, it also decreases the rewarding effect of nicotine.8,36,39,40,41

The Public Health Service-sponsored Clinical Practice Guideline (a product of the Tobacco Use and Dependence Guideline Panel consortium representatives, consultants, and staff) had recommended NRT (nicotine gum, nicotine inhaler, nicotine lozenges, nicotine nasal spray and nicotine patches), bupropion and varenicline as first line drug therapy, while recommending the use of clonidine and nortriptyline as second-line treatments.42 The clinical selection among first-line treatments will depend on practical considerations such as patient preference, time and cost of treatments. For patients who do not show successful results with first-line treatments, administered individually or combined, or when there are contraindications to its use, the use of second line medication therapy for smoking cessation is recommended.42,43

Other medicines primarily used for a variety of indications other than smoking cessation have been evaluated as potential candidates for smoking cessation support demonstrating varying degrees of effectiveness (Annex 6.17.1). However side effects are common and this may reduce the widespread use of these products.

Similarly, there have been numerous studies documenting the utility of psychological interventions as a smoking cessation aid. This group of interventions includes besides the brief advice provided by health professionals, self-help materials and intensive individual or...
group counseling. Evidence suggests that these interventions increase the probability of success varying in their magnitude. Motivational therapy, for example, has shown a modest but significant increase in risk ratios (RR) of success compared with brief advice (RR 1.27, 95% CI 1.14-1.42), results improve when conducting motivational interventions of longer duration (more than 20 minutes per session), showing a RR of 1.31 (95% CI 1.16-1.49). Compared with short counseling and behavioral self-support the probability of individual and group therapy results was RR 1.39 (95% CI 1.24 to 1.57) and RR 1.98 (95% CI 1.60 to 2.46), respectively.

2. Why does the disease burden persist?

As argued by many organizations, smoking cessation is primarily a responsibility of the health systems of the countries. The available evidence suggests that smoking cessation services are more effective when they are part of a coordinated programme of tobacco control. The costs of these treatments change between countries and very few European nations offer reimbursement for providing these services. (Annex 6.17.2).

The offer of adequate insurance coverage for these treatments, including reimbursement for both patients and health providers; have been shown to be effective increasing quit rates. The available evidence shows that paying for tobacco use cessation treatments is the single most cost-effective health insurance benefit for adults that can be provided to employees. Coverage of tobacco-use cessation treatment increases both use of effective treatment and the number of successful quit attempts. However, the attempts of governments to provide broad coverage of these services to their populations are diverse and still insufficient. According to WHO estimates, between 2008 and 2010, only one additional country (Turkey) began offering comprehensive treatment for dependency to tobacco which includes phone support line, reimbursement for NRT and at least some of the additional individual cessation services. This brings the number of high income countries providing comprehensive treatment for smoking cessation services to 19, which have covered in 2011 up to 980 million people (about 14% of the world population), an increase from 76 million since 2008. In general, in the European Region only a few number of countries offer total or partial reimbursement of pharmacotherapy support of smoking cessation. (Annex 6.17.2)

Despite these successes in combating tobacco addiction only 30% of high-income countries are fully reimbursing smoking cessation services even though they are more likely to be able to fund cessation services than occurs in LMIC. Both high-and middle-income countries show progress in offering at least some coverage of costs for treatment of dependence to tobacco: 80% of high-income countries and about 40% of middle-income countries reimbursed some individual smoking cessation services in 2011. Only one of eight of the low-income countries provided reimbursement for currently available cessation services in 2011.

In relation to research funding in the area of tobacco control, many international and national organizations have funded projects. Also the European Union has funded a number of research projects related to it. One example is the project "Pricing Policies and Control of Tobacco in Europe (PPACTE)\", partly funded by the European Commission’s Seventh
Framework Programme (FP7). This project will provide a comprehensive analysis of the effectiveness of tobacco pricing policies products to date, available for each of the member countries of the European Union (http://www.p pacte.eu/). However, there is less financial support for research projects specifically related to medication for smoking cessation.  

3. What can be learnt from past/current research into pharmaceutical interventions for this condition?

3.1 Current pharmacotherapeutic interventions

More than half of all regular smokers have the desire to quit smoking. Motivation of the smoker to quit is crucial for successful cessation. However, at the same time it is known that the sheer force of will is often not enough to result in quitting smoking. Only 1 to 5% of smokers attempting to quit succeed with a high relapse rate of 93% after 10 months of follow up. Hence, it is particularly important to support smoking cessation with comprehensive and effective treatment options. A recent study analyzing individual cessation assistance in 15 high and middle income countries shows much higher use of quit smoking medications among those who made quit attempts in the previous year in high income countries (over 40%) than in middle-income countries, which the authors attributed to the increased coverage for smoking cessation treatments in high income countries compared to middle income countries. They recommend insurers and purchasers to ensure that all insurance plans include the counseling and medication.

3.1.1 Pharmacological intervention with nicotine

When a smoker starts smoking cessation treatment, they experience the so-called "withdrawal", due to the sudden removal of nicotine. Based on this principle, pharmacological treatment with replacement products or nicotine substitutes have been recommended. These replacement products have a lower addictive power because the plasma levels obtained are significantly lower than when inhaling cigarette smoke. In this way, smokers avoid the negative effects caused by smoke toxicity.

Among the compounds nicotinic or nicotine replacement therapy (NRT) are indicated as follows: (1) polacrilex gum (gum or nicotine gum), (2) nicotine patches, and (3) nicotine inhalers. Additionally, it identifies other nicotinic compounds as oral tablets and nasal spray. In general there is consensus that all forms of NRT are effective in the treatment of smoking cessation. (See Annex 6.17.1)

A systematic review reported a risk ratio (RR) of abstinence for any form of NRT of 1.60 (95% CI: 1.53-1.68) compared to no medication for smoking cessation. When gum was used the RR was 1.49 (95% CI 1.40-1.60). For patches, the RR was 1.64 (95% CI: 1.52-1.78) and for the inhalation device, the RR of achieving abstinence was 1.90 (95% CI: 1.36-2.67). Finally, a RR of 1.95 (95% CI 1.61-2.36) for oral tablets/lozenges, and 2.02 (95% CI: 1.49-2.73) for the nasal spray was also reported. One trial of oral spray had an RR of 2.48 (95% CI 1.24 to 4.94). These all reported RR are not absolute rate of success. These medications increase the long term successful rates by approximately 50% to 70% regardless of setting.
The most common side effects of these treatments are generally of mild intensity and are often related to effects on the site of action and/or application. For example, hiccups, gastrointestinal problems, jaw pain and orodentals problems were reported in the case of nicotine gum; increased sensitivity of the skin and mucous membrane irritation with light intensity that rarely lead to the suspension of treatment in the case of patches, burns for inhalers and nasal spray and smarting sensation in the mouth, throat pain, cough and sores dry mouth and lips in the case of oral nicotine tablets. 55

The basal rate of success in which smokers quit with their own willpower is estimated to be 3-5% after 6-12 months of follow-up, it is expected that with the use of NRT increases cessation rates by 2-3% with a number needed to treat between 33 and 50 (NNT). (NNT is used to express how many patients need to be treated to have one patient with the desired outcome; in this case it means that 33 to 50 would need to be treated to have one patient quitting smoking). However, if termination rates are estimated to be 15% because of receiving in addition intensive behavioral support, then one would expect an additional 8% probability of success with NRT resulting in a NNT of around 12 (meaning 12 people would need to receive NRT in addition to intensive behavioral support to quit smoking). 55 Another study reported that assuming a cessation rate of 7.5% with behavioral therapy, the NNT with any type of NRT would be of 23 (95% CI 20 to 27).8

The evidence suggests that all of the commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) can help people who make a quit attempt. The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the individual. 58

Pharmacological treatment without nicotine

Within the group of pharmacological treatment without nicotine are the antidepressants such as bupropion and nortriptyline, selective partial agonists of nicotinic receptors such as varenicline tartrate and others treatments including antihypertensives, opioid antagonists, silver acetate and anxiolytics.

3.1.2 Antidepressants

At least two arguments have been reported in the literature that justify the use of antidepressants in the treatment of smoking cessation:53,59 (1) nicotine withdrawal may produce depressive symptoms or trigger an episode of major depression and (2) nicotine may have some type of antidepressive effect that drive smokers to continue consuming it, so the use of antidepressant drugs can be a substitute for this kind of effect. Additionally, it is noted that some antidepressants may specifically act on neurotransmission pathways involved in the mechanisms of nicotine addiction, such as blocking nicotine receptors, independently of their antidepressive effects.53,59

Out of all antidepressants bupropion and nortriptyline have shown the best results in smoking cessation in clinical practice so far.

1. Bupropion: Originally, bupropion was marketed as an antidepressant; however, once it proved its utility as an adjunctive treatment for tobacco addiction it gained international acceptance as smoking cessation treatment. In North America, Australia and Europe, slow or
prolonged release bupropion, under the name Zyban, is licensed for smoking cessation.\(^{59}\) Compared to placebo it is twice as effective with a success rate of 35% at six months, and 30% at 12 months compared to 19 and 16% of placebo at the same intervals.\(^{53}\) Godfrey et al.\(^{60}\) reported that bupropion is the more cost-effective therapy for smoking cessation in USA and Europe. Additionally, Hughes et al.\(^{59}\) in a systematic review documented that the use of bupropion is associated with increased abstinence rates at one year (OR 1.94, 95% CI 1.72-2.19). Assuming a cessation rate of 7.5% for behavioral therapy, the NNT to obtain additional benefits with bupropion is 20 (95% CI 16 to 26).\(^{8}\)

However, the administration of bupropion has been associated with adverse events. (Annex 6.17.1) As an example: insomnia (30-40%), dry mouth (10%) and seizures (15%), among others, with a dropout rate between 7 and 12%.\(^{59}\)

2. Nortriptyline: The mechanism of action by which nortriptyline act as smoking cessation support is not yet clearly known.\(^{59}\) It seems that it achieves effects similar to those obtained with the use of bupropion. The recommended dose for smoking cessation is 25 mg every eight hours for 12 weeks, starting with 25 mg the first three days, continuing with 50 mg for four days and finally, for the remaining time with 75 mg per day. Nortriptyline has proved capable of doubling smoking abstinence rates, both in patients with and without depression.\(^{59, 61, 62}\) The use of nortriptyline is accompanied by an increase in abstinence rates a year with an OR of 2.34 (95% CI: 1.61-3.41).\(^{53}\) A recent systematic review documented a RR of 2.03 (95% CI: 1.48-2.78) versus placebo and a non-significant RR of 1.29 (95% CI: 0.97-1.72) for the association of nortriptyline and NRT versus NRT alone.\(^{59}\)

Dropout rates within the recommended dosing of nortriptyline range from 4 to 12%. The only serious adverse event in patients treated with nortriptyline was the association of collapse and palpitations. However, this treatment has not been officially approved for smoking cessation treatment in any country, so there are no post-marketing surveillance studies for this indication as this is in off-label use.\(^{59}\)

Other antidepressants as the selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, paroxetine and sertraline) have been tested for treatment of smoking cessation, however, the evidence available so far does not appear to support the use of other antidepressants than bupropion and nortriptyline. Other antidepressants such as fluoxetine have shown negative results.

### 3.1.3 Selective partial agonist of nicotinic receptors

Partial agonists of nicotinic receptors (cytisine, dianicline, varenicline) can help patients quit smoking through a combination of two effects: firstly, they help maintain moderate levels of dopamine related reducing withdrawal symptoms and nicotine reward (acting as agonists) and, moreover, reducing the feeling of satisfaction when smoking (acting as antagonists).\(^{8}\)

1. Cytisine: A systematic review found two trials reporting a RR in individuals treated with cytisine of 3.98 (95% CI: 2.01-7.87).\(^{8}\)

2. Dianicline: For the case of dianicline, the only reported clinical trial does not show enough evidence that this drug is effective in the treatment of smoking cessation (RR 1.20, 95% CI: 0.82-1.75).\(^{8}\)
3. Varenicline: The same systematic review of 50 clinical trials evaluating varenicline reported a RR of 2.27 compared to placebo for continuous abstinence at six months (95% CI: 2.02-2.55). A lower dose of varenicline was also be effective with a RR of 2.09 (95% CI: 1.56-2.78). The RR for varenicline versus bupropion at one year follow-up was 1.52 (95% CI: 1.22-1.88). The RR for varenicline versus NRT for 24 weeks of follow-up was 1.13 (95% CI: 0.94-1.35). Two trials documenting the use of varenicline beyond 12 weeks with a standard regimen found that varenicline was well tolerated during use over long periods of time. Based on the fact that a clinical trial typically assumes a rate of 7.5% efficacy of behavioral therapy, the NNT of varenicline is 10 (95% CI: 8-12).

The main side effect of varenicline is mild to moderate nausea that usually disappears with time of use. A meta-analysis of serious adverse events occurring during or after active treatment, and not necessarily considered as treatment related, suggests an increase by a third of severe adverse events among people using varenicline (RR 1.36, 95% CI 1.04-1.79) compared to placebo but these findings need more study. It should be noted that post-marketing safety studies have raised the question about the possible association between varenicline and depression, anxiety, suicidal intentions and suicidal thoughts and behavior. As a warning or alarm mechanism for these potential adverse events, labeling of varenicline was amended in 2008, and manufacturers produced a Medication Guide to guide health professionals in their prescription. However, while the monitoring reports and secondary analyzes are inconclusive, the possibility of a link between varenicline and serious psychiatric or cardiovascular events cannot be excluded.

3.1.4 Antihypertensives

Clonidine was originally used for the treatment of hypertension. Additionally, this drug acts on the central nervous system and can reduce withdrawal symptoms in various addictive behaviors, including consumption of tobacco. The RR of success with clonidine versus placebo was 1.63 (95% CI = 1.22-2.18). Others clinical controlled studies suggested that the success of the clonidine is higher (OR: 4.2) if it is associated with psychological and behavioral therapy, than without it (OR: 1.7). Likewise, the patches of clonidine seem to be more effective than the oral presentation (OR: 3.2 versus 2.2). Other studies demonstrate an OR of 1.89 (95% CI: 1.30-2.74). Nevertheless, there was a high incidence of dose-related adverse effects, including dry mouth, sedation, dizziness and symptomatic postural hypotension. The authors concluded, based on a small number of clinical trials, that clonidine is effective in promoting smoking cessation. However, significant adverse effects limit its consumption.

3.1.5 Additional pharmacological treatments for smoking cessation

Silver acetate

Silver acetate produces an unpleasant taste when combining with cigarettes. It has been suggested that it reduces the urge to smoke and to associate smoking with an unpleasant stimulus. Products containing silver acetate have been marketed in different presentation forms (gum, spray, etc). Its usefulness is questionable and it has only been tested in smokers with low nicotine dependence. A systematic review on pharmacological treatment for smoking cessation identified two long-term studies of patients randomized to either silver
acetate or placebo. The RR of ceasing after administration silver acetate versus placebo was 1.04 (95% CI: 0.69-1.57). The authors concluded that the existing clinical trials show little evidence of a specific effect of silver acetate in promoting smoking cessation. However, the absence of silver acetate effect may also be due to poor adherence to treatment.

Opioid antagonists
It has been documented that smokers experience a number of positive effects such as pleasure, increased alertness or relaxation, when consuming cigarettes. In this sense, the use of opioid antagonists or narcotics agents may be useful in smoking cessation because of the potential to mitigate the positive effects that smokers experience during tobacco consumption. However, the use of opioid antagonists such as naltrexone or naloxone which might create similar effects failed to demonstrate the utility of these drugs in the treatment of this addiction. All four clinical trials identified in a systematic review conclude that it is possible to detect a difference in cessation rates between naltrexone and placebo. However, no significant effect was found on long-term abstinence (OR 1.26, 95% CI 0.80-2.01). None of the trials of naloxone reported long-term monitoring. The authors concluded that, based on limited data from four clinical trials there is insufficient evidence on the effect size that naltrexone is effective as a smoking cessation support. Confidence intervals are compatible with both the ability to offer significant clinical benefits and the possibility of negative effects. Information from larger clinical trials would be needed to evaluate the potential role of naltrexone in smoking cessation.

Anxiolytics
There are two reasons to believe that anxiolytics may aid in smoking cessation. Anxiety can be a symptom of withdrawal and secondly, smoking itself can be seen as an attempt to self-medicate anxiety problems. However, there is no consistent evidence to support the conclusion that anxiolytics (diazepam, meprobamate, metoprolol, oxprenolol and buspirone) support smoking cessation, but the available evidence does not rule out or exclude a possible effect.

3.1.6 Combination pharmacotherapy for stopping smoking
Multiple combinations of medications have been shown to be effective. Some studies have shown therapeutic advantages of the combined use of different types of NRT and the use of combinations between NRT and other no nicotine smoking cessation treatments (buproprion, varenicline, nortriptyline, etc.). Combination therapy with different drugs provides the opportunity to gain therapeutic synergism by using medications with distinct mechanisms of action or therapeutic properties.

Table 6.17.2 shows examples of the two principal types of combination pharmacotherapy that have been used and evaluated. The first is the combination therapy with different forms of nicotine replacement therapy (NRT). Others examples are combinations between two medications that have different therapeutic targets.

A systematic review shows evidence that combining a nicotine patch with a rapid delivery form of NRT was more effective for long-term smoking cessation than a single type of NRT (RR 1.34, 95% CI 1.18 to 1.51). A combination of NRT and buproprion was more effective than buproprion alone (RR 1.24; 95% CI 1.06 to 1.45).
Table 6.17.2: Combination of pharmacotherapies for smoking cessation

<table>
<thead>
<tr>
<th>Combination Therapies</th>
<th>Estimated OR or RR</th>
<th>Estimated abstinence rate (%) at 3 or 6 months</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch + gum or spray</td>
<td>RR: 1.35 (95% CI: 1.11-1.63) 3.6 (2.5-5.2)</td>
<td>36.5 (95% CI: 28.6-45.3)</td>
<td>Stead et al. 2008&lt;sup&gt;55&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patch + gum</td>
<td>RR: 1.75 (95% IC: 1.04-2.94) versus patch alone RR: 1.38 (95% IC: 0.88-2.17) versus gum alone</td>
<td>Not available</td>
<td>Stead et al. 2012&lt;sup&gt;55&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nasal spray + patch</td>
<td>RR: 2.48 (95% IC: 1.37-4.49) versus patch alone RR: 1.23 (95% IC: 0.85-1.78) versus either patch or spray alone</td>
<td>Not available</td>
<td>Stead et al. 2012&lt;sup&gt;55&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patch + inhaler</td>
<td>RR: 1.39 (95% IC: 0.89-2.17) versus inhaler alone RR: 0.51 (95% IC: 0.17-1.52) versus either patch or inhaler alone</td>
<td>Not available</td>
<td>Stead et al. 2012&lt;sup&gt;55&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patch + lozenge</td>
<td>RR: 1.27 (95% IC: 1.09-1.48) versus either patch or lozenge alone</td>
<td>Not available</td>
<td>Stead et al. 2012&lt;sup&gt;55&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patch + inhaler</td>
<td>OR: 2.2 (95% CI: 1.3-4.2)</td>
<td>25.8 (95% CI: 17.4-36.5)</td>
<td>Fiore et al. 2008&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patch + Buproprion SR</td>
<td>OR: 2.5 (95% CI: 1.9-3.4) RR: 1.22 (95% IC: 0.86-1.73) versus buproprion alone RR: 3.99 (95% IC: 2.03-7.85) versus placebo</td>
<td>28.9 (95% CI: 23.5-35.1)</td>
<td>Fiore et al. 2008&lt;sup&gt;42&lt;/sup&gt; Stead et al. 2012&lt;sup&gt;55&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gum + bupropion</td>
<td>RR: 1.10 (95% IC: 0.76-1.60) versus bupropion alone</td>
<td>Not available</td>
<td>Stead et al. 2012&lt;sup&gt;55&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lozenge + bupropion</td>
<td>RR: 1.30 (95% IC: 1.07-1.58) versus bupropion alone RR: 1.54 (95% IC: 0.81-2.90) versus placebo</td>
<td>Not available</td>
<td>Stead et al. 2012&lt;sup&gt;55&lt;/sup&gt;</td>
</tr>
<tr>
<td>Buproprion + NRT</td>
<td>RR 2.61 (95% CI: 1.65-4.12) versus, placebo</td>
<td>Not available</td>
<td>Stead et al. 2012&lt;sup&gt;55&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nortriptyline + NRT (Patch)</td>
<td>OR: 1.29 (95% CI: 0.97-1.72) OR: 2.3 (95% IC: 1.3-4.2)</td>
<td>27.3 (95% CI: 17.2-40.4)</td>
<td>Hughes et al. 2007&lt;sup&gt;59&lt;/sup&gt; Fiore et al. 2008&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patch + second generation antidepressants (paroxetine, venlafaxine)</td>
<td>OR: 2.0 (95% CI: 1.2-3.4)</td>
<td>24.3 (95% CI: 16.1-35.0)</td>
<td>Fiore et al. 2008&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td>Varenicline + Buproprion SR</td>
<td>Not available</td>
<td>71 (95% CI: 54-85) at 3 months and 58 (95% CI: 41-74) at 6 months</td>
<td>Ebbert et al. 2009&lt;sup&gt;70&lt;/sup&gt;</td>
</tr>
<tr>
<td>Varenicline + NRT</td>
<td>Not available</td>
<td>54; 95% CI= 44-64 (Not significant difference with usual-care patients (59; 95% CI = 50-66))</td>
<td>Ebbert et al. 2009&lt;sup&gt;71&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
4. What is the current "pipeline" of products for smoking cessation? What is known, if anything, on the safety and efficacy of products in the pipeline?

At present much research is done in the area of gene therapy. With respect to smoking cessation gene therapy is aiming at immunomodulation via vaccination with nicotine molecules in the form of a conjugate with an antigen associated protein, which activates the patient's immune system and stimulates the formation of antibodies.\textsuperscript{5,61} The presence of antibodies in the blood limits the amount of nicotine that enters the brain without causing side effects, thereby reducing psychopharmacological response to this substance. This is possible because the molecules are too large to cross the blood brain barrier.\textsuperscript{72,73} Thus, a nicotinic vaccine could reduce the amount of nicotine that reaches the brain when a person smokes cigarettes which may help people to stop smoking or to prevent future relapses in recent quitters.\textsuperscript{74} Even though the compounds studied so far show good tolerance and efficacy it seems unlikely that they can be used as first line therapy or prevention.\textsuperscript{5,61,75}

Currently there are no licensed vaccines for public use, but some are in development. The authors of a recent systematic review\textsuperscript{74} found four trials that met the inclusion criteria, three of them comparing NicVAX (developed by Nabi Biopharmaceuticals/GlaxoSmithKline (GSK) with placebo and one comparing NIC002 (NicQbeta developed by Cytos Biotechnology/Novartis) with placebo. All four clinical trials were conducted by pharmaceutical companies as part of the development process of these products and the authors of the review concluded that there were high risks of bias. Overall, 2642 smokers participated in the four studies; none found significant differences in long-term cessation. The RR for 12 months of cessation between the active group and the placebo group was 1.35 (95% CI: 0.82-2.22) in the trial of NIC002 (NicQbeta) and 1.74 (95% CI: 0.73-4.18) for NicVAX. Two phase III clinical trials of NicVAX, for which the full results were not available, reported similar cessation rates of approximately 11% in both groups. In both studies, with all available results, further analysis found high rates of cessation in participants with high levels of nicotine antibodies, but these results are not generalizable. The trials demonstrated that NicVAX is tolerated with most adverse events classified as mild or moderate. In the NIC002 study, participants who received the vaccine were more likely to report adverse events such as mild to moderate flu-like symptoms, whereas in the study of NicVAX no significant differences were reported between the two arms. Information on adverse events was not available for the Phase III NicVAX study.\textsuperscript{74} A preliminary assessment of both trial data - first and second NicVAX(R) Phase III clinicals trials- showed that the primary end point was not met and there was no statistical difference between the NicVAX and Placebo groups.\textsuperscript{76,77}

The authors noted that further studies are required comparing vaccines with NRTs. Future studies also need to explore the potential of nicotinic vaccines in preventing relapses and adverse events and serious adverse events should continue need to be monitored and reported.\textsuperscript{74}

Additionally, another vaccine is currently in development which is called TA-NIC (Celtic Pharmaceuticals, Hamilton, Bermuda).\textsuperscript{78} Clinical research of this product includes clinical trials that have completed phase I/II and which have been found cessation rates at 12 months.
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of 19% and 38% in the groups treated with TA-NIC 250 mcg and 1000 mg, respectively, compared with those who received only placebo (8%).

Additionally, Independent Pharmaceutica AB (Sweden) is developing a new vaccine called Niccine. The multicenter clinical trial investigating the efficacy of this product is in phase II. The primary indication of the vaccine is the prevention of relapse in smokers who have recently quit smoking with the help of pharmacological treatment for smoking cessation.

The successful use of vaccines in the treatment of tobacco addiction could contribute to developing innovative ways to combat smoking. It has been noted that nicotinic vaccines may have the advantage of achieving a depot effect on the immune system, approximately six to 12 months after vaccination, which could reduce the relapse rate. Additionally, with the use of vaccines, it is not necessary to administer the full daily dose of smoking cessation medication. However, there are multiple challenges that still need to be overcome such as the need for multiple injections and the time to wait before they get an effective immune response. Finally, there are people who fail to reach antibody titers necessary for successful results which is a variation in efficacy which can still not be explained.

Other products are in development: they include new NRT (e.g. nicotine inhaled formulation ARD-1600, developed by Aradigm Corp.), cannabinoid 1 receptor antagonists (e.g. the inverse agonist CB1R taranabant Inc. of Merck & Co.), and antagonists of the dopamine D3 receptor (such as GSK598809 of GlaxoSmith Kline).

Finally, a new product is the battery-powered electronic delivery system (ENDS), with the appearance of a conventional cigarette, hence the colloquial names by which it is known such as "electronic cigarette", "e-cigarette ", "E-cigar "and" cigarette green", which is thought to allow aerosolized administration of nicotine in a more efficient way. However, these products have been brought onto the market against the principles of the WHO Framework Convention on Tobacco Control (FCTC). After reviewing the available evidence, the WHO recommended banning information suggesting that electronic nicotine vaporizers are an effective option in combating addiction to tobacco. This ban should be in effect until there is sufficient evidence to demonstrate health benefits. According to the WHO, the effectiveness of electronic cigarettes to quit smoking or health effects must be supported by reliable pharmacokinetic, safety and efficacy studies and appropriate certification by the regulating authorities.

5. What are the opportunities for research into new pharmaceutical interventions? What is the state-of-the-art science (basic and operational) for this disease and what does it offer? What is the current status of institutions and human resources available to address the disease?

The research currently available suggests that abstinence rates can be increased by combining different forms of nicotine replacement therapy or simultaneous administration of NRT and non-nicotinic compounds. However, more research is needed for a better
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definition of the criteria that need to be fulfilled in or to combine different therapeutic modalities.

There is some evidence about the efficacy of smoking cessation medications in smokers uninterested in quitting. Carpenter et al 2004\(^7\), reported results from a study in smokers unmotivated to quit showing that “a telephone intervention of smoking reduction plus nicotine replacement therapy and brief advice did not differ from motivational advice plus brief advice, but both were more effective than no treatment”.\(^7\)

Another study reported results from a meta-analysis (five studies) showing estimated odds ratio (95% C.I.) of 2.5 (1.7–3.7), and estimated abstinence rate (95% C.I.) of 8.4 (5.9–12.0) for Nicotine replacement therapy (gum, inhaler, or patch) versus placebo in patients who are not currently willing to make a quit attempt but who state that they are willing to reduce their smoking.\(^42\) However, because of the selective participant inclusion criteria among other aspects the authors concluded that it is unclear whether the results would be relevant to a broader population of smokers not wanting to quitting.\(^42\)

More evidence is need in relation to the use of NRT to help smokers who are currently NOT willing to quit to reduce their tobacco use, effectiveness of prequit NRT use to increasing abstinence rates, use of NRT in ‘practice quit attempts’ and extended use of NRT to maintain abstinence.

Additionally, evidence suggests that smokers who relapse sometime during their cessation attempt are at high risk of future relapses, so that rescue interventions for those smokers are necessary. Although there have been studies that suggest that continuing use of nicotine patches after a relapse can be a prevention for future relapses, more research is needed to define what treatments would work best after relapse.\(^88\) Similarly, more research is needed to document the possibility of a link between varenicline and psychiatric or serious cardiovascular events. Additionally, there is a need for testing the efficacy of varenicline beyond 12 weeks.\(^8\) So far the number of clinical trials evaluating the efficacy and safety of cytisine are limited. Future clinical trials of cytisine may improve its efficacy when combined with other individual interventions.\(^8\)

Most of the evidence of cost-effectiveness of drug treatments comes from industrialized countries or upper middle income; however, more research is needed on the cost-effectiveness of pharmacotherapy for smoking cessation in low and middle income countries. This evidence is needed to inform decision makers about the need for the development of medication at lower costs to their countries.

One area for future research is analyzing financing mechanisms of this type of intervention in different country settings. Currently, there is debate about whether these interventions should be totally covered by the public health systems or, on the contrary, it should take advantage of the ability and willingness to pay by some smokers to design innovative funding strategies. One possibility is the establishment of co-financing mechanisms for the latest technologies and high cost interventions, using international experiences.\(^89,90,91,92\)

Recent studies have explored the hypothesis that interventions to support the funding of cessation treatments on both the demand and supply increases success cessation rates. A recent systematic review\(^93\) demonstrates a beneficial effect (RR 2.45, 95% CI 1.17 to 5.12) in
financial support to smokers trying to quit smoking on success rates, however, more research is needed in this area.

6. 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?

Many pharmaceuticals which have been being tested for treatment of smoking cessation. In general, all seven first-line medications (five nicotine and two non-nicotine) are recommended and reliably increase long-term smoking abstinence rates. When combined with medical advice and psychological counseling for behavior change, most available treatments produce continuous abstinence rates around of 30%. However, these estimates come from randomized clinical trials involving smokers who are highly motivated and using rigorous monitoring methods, offering medical advice with high intensity, compared to what happens in real life scenarios.\(^94,95\) An issue has been raised about the effectiveness of NRT outside clinical trials. Many smokers in the “real world” may use the products sub-optimally leading to a lower level of effectiveness than the effectiveness reported in trials.\(^96\) However there is evidence that NRT use by smokers making self-initiated attempts to quit without formal behavioural support is associated with improved long-term abstinence rates [OR: 3.0 (95% CI 1.2 to 7.5)] comparing abstinence for six months in those smokers using and those not using NRT, adjusting for nicotine dependence.\(^96\)

Clinicians should encourage the use of cessation medications in patients attempting to quit smoking except when medical contraindication exists or with specific populations (i.e. pregnant women, smokeless tobacco users, light smokers, and adolescents) for which there is insufficient evidence of effectiveness. However some areas need more research [e.g. effectiveness of OTC nicotine patch, gum, and lozenge, extent to which individuals use medications appropriately, extent to which the effectiveness of OTC medication is enhanced by other treatments (e.g. pharmacist counseling, telephone counseling, computer self-help resources, clinician interventions)].\(^42\)

Annex 6.17.3 summarizes the objectives and future research areas. One solution is finding more effective medication for smoking cessation; other studies determine the most effective combination therapies and research on specific groups of smokers (teens, pregnant, cigar and pipe smokers, occasional smokers or light smokers, women, etc.) and its implications for the results of efficacy/effectiveness of pharmacotherapies. The effectiveness of smoking cessation therapies appears to be modulated by deep social inequities that need to be more clearly characterized and eliminated in order to reduce morbidity and mortality related to smoking in socially disadvantaged populations.\(^95,97\)

Considering the lack of research focused on a large number of smokers who are not currently willing to quit, further studies are required to identify mechanisms to increase motivation to quit smoking in this population as was analyzed above.\(^42,87\) Alternatively, highly effective new treatments regardless of the intrinsic motivation of the smoker would be desirable, but it is unlikely that these advances will be available in the near future.\(^95\)
Treatment costs can be an important barrier against effective uptake of smoking cessation treatment. Patients are more likely to use those treatment options that are free of costs to them or their costs may be reimbursed by their insurance company.\cite{96,99,100,101} Evidence on cost-effectiveness of these treatments, as well as findings from clinical studies show a significant increase in rates of abstinence followed by reimbursement of the cost of smoking cessation treatments. This supports the idea that during the development of those therapeutic options the reimbursement aspect needs to be included as one of the considerations of how the technology needs to be designed.\cite{95}

7. For which of these gaps are there opportunities for pharmaceutical research? Which issues can only realistically be addressed with increasing financial support or investment in human and institutional capacity? Which issues are best suited to the comparative advantage of the EU?

To date, pharmacological interventions for smoking cessation rates show moderate efficacy/effectiveness, so that more effective new treatment options are needed if one wants to substantially impact on morbidity and mortality associated with tobacco consumption. Regarding the cost-effectiveness evidence available today, many pharmacotherapeutic options for smoking cessation are cost-effective in high and upper middle income countries. However, in low and lower middle income countries, where the problem of consumption of tobacco and its impact on morbidity and mortality is very large and will continue to be very large, the limited evidence available indicates that smoking cessation treatments are not yet cost-effective, primarily due to the high cost of these products. It requires further research and development of low-cost products so that these countries have the opportunity to strengthen their programs to reduce tobacco consumption through interventions at individual level.

Additionally, future clinical research focused on medication already marketed or developed and which need to be tested in clinical trials should look for improvement in the quality of their design and analysis (e.g. analysis by group of smokers (age, gender, risk factors)) as well explicitly documenting the NNT, for each study. This would allow assessing more objectively the dimensions of health benefits that they report. Research on new low cost formulations of proven effective therapies would be worthy of support. This development might facilitate reimbursement or coverage by health insurance organizations.

To date, treatments for tobacco use (both medication and counseling) are not provided consistently as paid services for subscribers of health insurance packages.\cite{12,13,28,42} Without supportive systems, policies, insurance coverage, and environmental prompts, the individual clinician likely will not assess and treat tobacco use consistently.\cite{12}
References


31 WHO. First Global Ministerial Conference on Healthy lifestyles and Noncommunicable Disease Control. Moscow. 28-29 April 2011.


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Available at http://www.clinicaltrial.gov/ct2/show/NCT00728052%3Fterm=Gsk598809%26rank=4
Last accessed 9 April 2013


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# Annexes

## Annex 6.17.1: Pharmacological treatments for smoking cessation

<table>
<thead>
<tr>
<th>Pharmacological intervention</th>
<th>Presentation/Brand/Manufacturer</th>
<th>Dose/ treatment duration</th>
<th>Efficacy (Risk ratios, abstinence rate or odds ratios)</th>
<th>Number needed to treat (NNT)</th>
<th>Adverse effects</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine Products</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine Gum</td>
<td>2 mg, 4 mg (Nicorette, Pharmacia) (Nicotinell, Novartis Consumer Health) GUM, CHEWING; BUCCAL: EQ 2MG BASE ; EQ 4 MG BASE GLAXOSMITHKLINE (GSK)</td>
<td>2-4 mg during 2-3 months, fluctuating between 3 -12 weeks</td>
<td>RR: 1.49 (95% CI 1.40 to 1.60) (versus placebo)</td>
<td>23 (95% CI 20 to 27)</td>
<td>Hiccoughs, gastrointestinal disturbances, jaw pain, and orodental problems</td>
<td>Stead et al. 2012 (Cochrane Review) Cahill K, et al. 2012. (Cochrane Review) FDA</td>
</tr>
<tr>
<td>Nicotine patch</td>
<td>5 mg, 10 mg, 15 mg (Nicorette, Pharmacia) 7 mg, 14 mg, 21 mg per 24 hours (NICOTINELLE TTS 10, TTS 20 &amp;TTS 30 Novartis Consumer Health) 7 mg, 14 mg, 21 mg (NiQuitin CQ, GSK)</td>
<td>Daily maximum dose: 15 mg for 16 hours path 21 mg for 24 hours path During 2-3 months fluctuating between 3-12 weeks</td>
<td>RR: 1.64 (95% CI 1.52 to 1.78) (versus placebo)</td>
<td></td>
<td>Skin sensitivity and irritation</td>
<td>Stead et al. 2012 (Cochrane Review)</td>
</tr>
<tr>
<td>Nicotine Inhaler</td>
<td>10 mg (Nicorette, Pharmacia) INHALANT; ORAL: 4 MG/CARTRIDGE PHARMACIA AND UPJOHN</td>
<td>4 MG/CARTRIDGE</td>
<td>RR: 1.90 (95% CI 1.36 to 2.67) (versus placebo)</td>
<td></td>
<td>Local irritation at the site of administration (mouth)</td>
<td>Stead et al. 2012 (Cochrane Review) FDA</td>
</tr>
<tr>
<td>Nicotine lozenge and Nicotine Sublingual Tablet</td>
<td>1 mg (Nicotinell, Novartis Consumer Health) 2 mg and 4 mg (NiQuitin CQ, GSK)</td>
<td>Daily maximum dose: 1 mg, 2 mg or 4 mg (depending of</td>
<td>RR: 1.95 (95% CI 1.61 to 2.36) (versus placebo)</td>
<td></td>
<td>Hiccoughs, burning and smarting sensation in the</td>
<td>Stead et al. 2012 (Cochrane Review)</td>
</tr>
</tbody>
</table>
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#### Nicotine Nasal Spray

| Nicotine Nasal Spray | 0.5 mg per puff metered nasal spray (Nicorette and Pharmacia) | 0.5 mg | RR: 2.02 (95% CI 1.49 to 2.73) (versus placebo) | Local irritation at the site of administration (nose) | Stead et al. 2012 (Cochrane Review) | FDA |

#### Antidepressants (there is an indication for smoking cessation for buproprion, whereas for the other anti-depressants, there is no indication for smoking cessation)

| Bupropion (sustained release) | Zyban, tab 100 mg | 150 mg once a day for three days increasing to 150 mg twice a day continued for at least seven weeks. There should be an interval of at least eight hours between successive doses. The maximum single dose should not exceed 150 mg and the total daily dose should not exceed 300 mg. | RR: 1.69 (95% CI: 1.53-1.85) (versus placebo) | 20 (95% CI 16 to 26) | Insomnia, nausea, anorexia, seizures, changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide | Hughes JR, et al. 2011 (Cochrane Review) | Cahill K, et al. 2012 (Cochrane Review) | FDA | EMEA |

| Nortriptyline | CAPSULE; ORAL: EQ 10 MG BASE | 75 to 100 mg/day | RR: 2.03 (95% CI: 1.48-2.78) | Not available | Dry mouth, | Hughes JR, et al. |
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Dosage Details</th>
<th>RR and CI (versus placebo)</th>
<th>Side Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moclobemide</td>
<td>Not available</td>
<td>400 mg/day began one week before quit day and continued for two months, reducing to 200 mg/day for a further month.</td>
<td>RR 1.57 (95% CI 0.67 to 3.68)</td>
<td>Not available</td>
<td>Hughes JR, et al 2011. (Cochrane Review) FDA</td>
</tr>
<tr>
<td>Selegiline</td>
<td>SELEGILINE HYDROCHLORIDE CAPSULE; ORAL: 5 MG TABLET; ORAL: 5 MG</td>
<td>10 mg/day for 9-26 weeks</td>
<td>RR 1.45 (95% CI 0.81 to 2.61) (versus placebo)</td>
<td>Not available</td>
<td>Hughes JR, et al 2011. (Cochrane Review) EMEA</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Not available</td>
<td>225 mg/day</td>
<td>RR 1.22 (95% CI 0.64 to 2.32). (versus placebo)</td>
<td>Increase suicidal thoughts and behavior, and attempted suicide</td>
<td>Hughes JR, et al 2011. (Cochrane Review) FDA</td>
</tr>
<tr>
<td>Nicotine receptor partial agonists</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cytisine</td>
<td>Tabex, tab 1.5 mg, Sopharma Pharmaceuticals</td>
<td>1.5 mg over 20 days or 25 days</td>
<td>RR of 3.98 (95% CI: 2.01 to 7.87) (versus placebo)</td>
<td>Nausea, restlessness, insomnia, irritability, Dyspepsia, headache, gastrointestinal</td>
<td>Cahill K, et al 2012. (Cochrane Review)</td>
</tr>
</tbody>
</table>

### Notes
- Nortriptyline + NRT versus NRT: drowsiness, light-headedness and constipation
- Collapse/palpitations
- Nortriptyline + NRT versus NRT: 2011. (Cochrane Review) FDA
- Not available
- FDA
- EMEA
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<table>
<thead>
<tr>
<th>Dianicline (Averted by Sanofi-Aventis)</th>
<th>Tab 40 mg, Sanofi-Aventis</th>
<th>40 mg tablet twice a day for seven weeks</th>
<th>RR 1.20, 95% CI 0.82 to 1.75 (versus placebo)</th>
<th>Not available</th>
<th>Not available</th>
<th>Cahill K, et al 2012. (Cochrane Review)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline</td>
<td>Chantix, tab, 0.5 mg, 1 mg, Pfizer Inc (FDA) Champix, tab, 0.5 mg, 1 mg, Pfizer Inc (EMEA)</td>
<td>1.0 mg twice a day for 9-12 weeks</td>
<td>RR: 2.27 (95% CI 2.02 to 2.55) (versus placebo, six months)</td>
<td>RR 2.23, 95% CI 1.93 to 2.58 (versus placebo, 12 months)</td>
<td>RR: 2.32, 95% CI 2.08 to 2.58 (versus placebo, 24 weeks)</td>
<td>RR: 2.53 (95% CI 2.32 to 2.76) (versus placebo, 9-12 weeks)</td>
</tr>
</tbody>
</table>
### Antihypertensives agents

<table>
<thead>
<tr>
<th><strong>Clonidine</strong></th>
<th><strong>Oral or transdermal clonidine</strong></th>
<th><strong>Treatment with oral or transdermal clonidine with a maximum daily dosage of ( \geq 0.2 \text{ mg} ).</strong></th>
<th><strong>RR: 1.63 (95% CI: 1.22 to 2.18) (versus placebo)</strong></th>
<th><strong>Not available</strong></th>
<th><strong>Dry mouth and sedation dizziness</strong></th>
<th><strong>Gourlay SG, et al 2008 (Cochrane Review)</strong></th>
</tr>
</thead>
</table>

**DAVA PHARMS INC/ VINTAGE/ IMPAX LABS/ UNICHEM/LUITPOLD/ALEMBIC PHARMS LTD/HIKMA FARMACEUTICA/APP PHARMS**

**Tablet; Oral: 0.1 MG ; 0.2 MG ; 0.3 MG**

**Oral dosage varied from a maximum allowed of 0.15 mg per day to 0.45 mg per day. Transdermal dosages were 0.1 to 0.3 mg per day.**

### Nicotine antagonists

| **Mecamylamine** | **Capsule 2.5 mg** | **2.5-20 mg/day 2.5 mg twice daily two weeks before the quit date, and increased to 5mg twice daily, continued for three weeks after quitting** | **A combination of mecamylamine plus nicotine patch was more effective than nicotine patch alone (abstinence rate at one year 37.5% versus 4.2%).** | **Drowsiness, postural hypotension and constipation** | **Lancaster T, et al. 2011 (Cochrane Review)** |

### Opioid antagonists

| **Naltrexone** | **NarpanTM, ReviaTM; half-life 240 min** | **50 mg per day during 8-12 weeks** | **OR: 1.34, 95% CI: 0.49 to 3.69 (versus placebo) OR: 1.24, 95% CI: 0.74 to 2.09 (Naltrexone +NRT versus placebo +NRT)** | **Not available** | **Not reported** | **David SP, et al. 2009 (Cochrane Review) FDA** |

**Tablet; Oral: 100 MG ; 25 MG ; 50 MG**
## Selective type 1 cannabinoid (CB1) receptor antagonist (limited evidence available)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose and Duration</th>
<th>Relative Risk</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rimonabant</strong>&lt;br&gt;Acomplia, 20 mg&lt;br&gt;Sanofi-Aventis&lt;br&gt;Zimulti, 20 mg</td>
<td>5 mg or 20 mg during 10 weeks</td>
<td>RR 1.50 (95% CI 1.10 to 2.05) (20 mg dose) (versus placebo)</td>
<td>Nausea (feeling sick), infections of the upper respiratory tract and serious harm</td>
<td>Cahill K, et al 2009. (Cochrane Review) EMEA</td>
</tr>
</tbody>
</table>

## Other treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Relative Risk</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Silver acetate</strong>&lt;br&gt;6 mg silver acetate chewing gum&lt;br&gt;2.5 mg silver acetate lozenges sprays</td>
<td>Total dose of silver no greater than 756 mg</td>
<td>OR: 1.05 (95% CI: 0.63-1.73)</td>
<td>Not available</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Vaccines</strong>&lt;br&gt;NicQbeta, Cytos Biotechnology in Switzerland and Novartis&lt;br&gt;Niccine, Independent Pharmaceutica AB (Sweden)&lt;br&gt;NicVAX, Nabi Biopharmaceuticals (USA)*&lt;br&gt;TA-NIC, Xenova and Celtic Pharma (United Kingdom)</td>
<td>200 or 400 µg</td>
<td>RR: 1.35 (95% CI: 0.82 to 2.22) (NicQbeta vs placebo)&lt;br&gt;RR: 1.74 (95% CI: 0.73 to 4.18) NicVAX vs placebo</td>
<td>Not available</td>
<td>Flu-like symptoms, fever, myalgia, general discomfort/malaise, and headache</td>
</tr>
</tbody>
</table>

* Recently Nabi Biopharmaceuticals had reported that the two phase III clinical trials of NicVAX failed to meet primary endpoint.

**Annex 6.17.2: Public coverage and three months complete treatments cost in some European countries**

<table>
<thead>
<tr>
<th>European Country</th>
<th>Reimbursement of pharmacotherapies by public insurance</th>
<th>NRT</th>
<th>Bupropion</th>
<th>Varenicline</th>
<th>Currency/Year</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>213.15</td>
<td>285.02</td>
<td>290.62</td>
<td>Euros, 2006</td>
<td>Vemer et al. 2010 98</td>
</tr>
<tr>
<td>Spain</td>
<td>Not covered by public insurance*</td>
<td>155</td>
<td>154</td>
<td>N/A</td>
<td>153</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>155.28</td>
<td>154.62</td>
<td>360.68</td>
<td>Euros, 2006</td>
<td>Fernández de Bobadilla et al. 2008 99</td>
</tr>
<tr>
<td>France</td>
<td>Only NRT are covered. The rest of treatments are not covered by public insurance**</td>
<td>214</td>
<td>259</td>
<td>N/A</td>
<td>242</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>387.03</td>
<td>327.15</td>
<td>390.6</td>
<td>Euros, 2006</td>
<td>Vemer et al. 2010 Error! Bookmark not defined.</td>
</tr>
<tr>
<td>Sweden</td>
<td>Not reported*</td>
<td>153</td>
<td>157</td>
<td>364</td>
<td>189</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>365.76</td>
<td>350.92</td>
<td>401.9</td>
<td>Euros, 2006</td>
<td>Vemer et al. 2010 Error! Bookmark not defined.</td>
</tr>
</tbody>
</table>
**Update on 2004 Background Paper, BP 6.17 Smoking Cessation**

<table>
<thead>
<tr>
<th>Country</th>
<th>Information</th>
<th>Cost 2006</th>
<th>Cost 2007</th>
<th>Cost 2008</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Netherlands</td>
<td>Not reported*</td>
<td>323.35</td>
<td>327.81</td>
<td>391.79</td>
<td>Euros, 2006</td>
</tr>
<tr>
<td>Belgium</td>
<td>NRT and Bupropion are reimbursed under specific conditions**</td>
<td>311.05</td>
<td>277.42</td>
<td>391.78</td>
<td>Euros 2006</td>
</tr>
<tr>
<td>Germany</td>
<td>Not reported*</td>
<td>317.13</td>
<td>292.22</td>
<td>337.28</td>
<td>Euros 2006</td>
</tr>
</tbody>
</table>

*Data available in Cornuz et al. 2006 or Králíková et al. 2008.

**PPRI Network Query: Smoking cessation (February 2009). Specific reimbursement conditions in Belgium: chronic obstructive pulmonary disease (GOLD classification stage II, III or IV); 35 years or older; test treatment of 18 days; maximum one package of 100 tablets (150 mg)/attempt to quit smoking; maximum three attempts/five years (at the least six months between two attempts); Co-payment of 8.90 euros (preferentially insured patients) or 13.50 euros (patients with “standard” insurance).
## Annex 6.17.3: Future research areas for smoking cessation

### Pharmacological intervention

#### Nicotinic products

<table>
<thead>
<tr>
<th>Future research areas</th>
<th>Products under development</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Direct comparisons between the various forms of NRT and between different doses and durations of treatment.</td>
<td>1. ARD-1600 (Aradigm Corporation) an inhaled aerosolized nicotine developed using AERx inhalation technology. (Phase I)</td>
<td>Stead et al 2008 (Cochrane Review)</td>
</tr>
<tr>
<td>3. Direct comparisons between NRT and newer pharmacotherapies including varenicline</td>
<td>3. NAL2771 (NAL Pharmaceuticals) a New nicotine 24 hour matrix patch (Phase I)</td>
<td></td>
</tr>
<tr>
<td>4. The effect of starting NRT use before the quit date.</td>
<td>4. NAL2762 (NAL Pharmaceuticals) developed as a nicotine orally dissolving film (ODF) for smoke cessation (Phase II)</td>
<td></td>
</tr>
<tr>
<td>5. How best to overcome safety and efficacy misperceptions among smokers?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Efficacy of extended use of NRT to maintain abstinence and determining which smokers are most likely to benefit from such a regimen.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Antidepressants

<table>
<thead>
<tr>
<th>Future research areas</th>
<th>Products under development</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Determine which antidepressants or classes of antidepressant are effective in smoking cessation.</td>
<td>1. EVT 302 (Evotec, MAO-B inhibitor) (Phase II)</td>
<td>Hughes JR, et al 2011.</td>
</tr>
<tr>
<td>2. Determine the action mechanism of antidepressant efficacy and the biological factors controlling nicotine dependence and smoking.</td>
<td>2. Selegiline (National Institute on Drug Abuse) (Phase II)</td>
<td>(Cochrane Review)</td>
</tr>
<tr>
<td>4. Research on the use of antidepressants in combination with nicotine replacement therapy, in smokers who have failed with NRT, and smokers with baseline dysphoria.</td>
<td>4. Bupropion HCl RPCI (Roswell Park Cancer Institute) (Phase II)</td>
<td></td>
</tr>
<tr>
<td>5. Continued monitoring, given the numbers of</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Update on 2004 Background Paper, BP 6.17 Smoking Cessation

Deaths and psychiatric disorders from antidepressants used for smoking cessation reported.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Monitoring the incidence of serious adverse events</td>
<td></td>
<td>Polosa et al 2011</td>
</tr>
<tr>
<td></td>
<td>3. Further exploration of safety issues, including psychiatric and cardiovascular adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Additional trials of cytisine to explore variations in the drug regimen and in the level of behavioural support</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Antihypertensives agents** | 1. Determine whether the efficacy of drugs acting via these mechanisms can be dissociated from adverse effects. | Not reported | Gourlay SG, et al. 2008 (Cochrane Review) |

<table>
<thead>
<tr>
<th><strong>Nicotine antagonists</strong></th>
<th>1. Determine whether mecamylamine, combined with nicotine replacement, is more effective than nicotine alone.</th>
<th>Not reported</th>
<th>Lancaster T, et al. 2011 (Cochrane Review)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Determine the best dose and timing if this therapy is used.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Whether mecamylamine is more effective when given prior to, or following, cessation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. How it is best combined with nicotine replacement.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Opioid antagonists</strong></th>
<th>1. Determine whether naltrexone is efficacious for smoking cessation.</th>
<th>1. Nalmefene (Somaxon Pharmaceuticals) (Phase II)</th>
<th>David SP, et al. 2009 (Cochrane Review)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Investigate the efficacy of combining naltrexone with other smoking cessation medications (e.g., bupropion, nortriptyline, clonidine).</td>
<td>2. Naltrexone (University of Chicago) (Phase II)</td>
<td>Polosa et al 2011</td>
</tr>
</tbody>
</table>
**Update on 2004 Background Paper, BP 6.17 Smoking Cessation**

<table>
<thead>
<tr>
<th><strong>Selective type 1 cannabinoid (CB1) receptor antagonist</strong></th>
<th>1. Compare Rimonabant with other pharmacotherapies, such as nicotine replacement therapy, bupropion and varenicline.</th>
<th>1. MK0364 (Taranabant, Merck &amp; Co) acts by reducing the food intake and increasing energy expenditure and fat oxidation (Phase II)</th>
<th>Cahill K, et al 2009. (Cochrane Review) Polosa et al. 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Consider the benefits of rimonabant for sub-groups of smokers (e.g. obese versus overweight versus healthy weight).</td>
<td>3. Rimonabant direct comparisons and interactions with nicotine replacement therapy, bupropion, exercise, etc.</td>
<td>2. MK0364 (Taranabant, Merck &amp; Co) acts by reducing the food intake and increasing energy expenditure and fat oxidation (Phase II)</td>
<td></td>
</tr>
<tr>
<td><strong>Silver acetate</strong></td>
<td>1. Further research on silver acetate for smoking cessation is unlikely to be helpful.</td>
<td>Not reported</td>
<td>Lancaster T, et al. 2009 (Cochrane Review)</td>
</tr>
<tr>
<td>2. Explore the potential of nicotine vaccines as an aid to relapse prevention.</td>
<td>2. NIC002 (Cytos Biotechnology/Novartis) (Phase II)</td>
<td>2. NIC002 (Cytos Biotechnology/Novartis) (Phase II)</td>
<td></td>
</tr>
<tr>
<td>3. Adverse events and serious adverse events should continue to be carefully monitored and reported.</td>
<td>3. Niccine (Independent Pharmaceutica) (Phase II)</td>
<td>3. Niccine (Independent Pharmaceutica) (Phase II)</td>
<td></td>
</tr>
<tr>
<td>4. Report and categorize nicotine-specific antibody levels.</td>
<td>4. NicVAX (GlaxoSmithKline/Nabi Biopharmaceuticals) (Phase III)</td>
<td>4. NicVAX (GlaxoSmithKline/Nabi Biopharmaceuticals) (Phase III)</td>
<td></td>
</tr>
<tr>
<td>5. Specified the method used for antibody calculations.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Update on 2004 Background Paper

Background Paper 6.18
Obesity

By Veronika J. Wirtz
Update on 2004 Background Paper, BP 6.18 Obesity

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   1.3 Morbidity and mortality related to overweight and obesity ............................................................... 8
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Executive summary

Obesity is a chronic and multi-factorial disease and one of the most important causes of morbidity and premature mortality worldwide.

Currently, over a billion people are overweight and half a billion are obese. In more than half of the EU countries one in two individuals are overweight or obese. The epidemic is still increasing in many European countries, whereas in some it seems to have slowed down. In the United States, obesity has been declared the number one health threat.

Non-surgical and non-pharmacotherapeutical treatment options include diet, exercise, behaviour modification and psychological support. The effect size has been reported with a single digit weight loss in kilograms which can be maintained. In contrast to experimental settings, implementing life-style interventions in routine primary care that reduce morbidity at population level have proven to be difficult.

There are only very limited pharmacotherapeutic treatment options. Overall, pharmacotherapy has played a minor role in the treatment of obesity. Only one medicine is currently available in most European countries (orlistat). No current pharmacotherapy possesses the efficacy needed to produce clinically significant weight loss (at least 5 to 10% weight loss) in a large proportion of morbidly obese patients in the long-term. More research is needed on whom to treat, adherence factors and the regain of body weight after discontinuation of pharmacotherapy to more adequately evaluate the cost-effectiveness of pharmaceutical therapy. It has been challenging to develop pharmacotherapy that has gained acceptance by medicines regulatory authorities or remained available for a long time due to their adverse benefit/risk profiles that have emerged with use.

Bariatric surgery is currently the only intervention providing significant and long-term weight loss for the morbidly obese (approximately 20% weight loss after ten years) which improves diabetes, hypertension and quality-of-life. However, it is associated with surgical risks (mortality less than 1%), long-term digestive problems and nutritional deficiencies. Savings might be achieved six years after the surgery for the health care systems but whether there are savings after ten years is unclear.
1. **What is the size and nature of the disease burden?**

Obesity is a chronic and multi-factorial disease which is characterized by an excess of body fat. The Body Mass Index (BMI) is most commonly used to define what is regarded as an “excess” (see Table 6.18.1).

### Table 6.18.1: Classification of body weight according to the Body Mass Index (BMI)

<table>
<thead>
<tr>
<th>BMI</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5–24.9</td>
<td>Normal weight</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>Overweight</td>
</tr>
<tr>
<td>30.0–34.9</td>
<td>Class I obesity</td>
</tr>
<tr>
<td>35.0–39.9</td>
<td>Class II obesity</td>
</tr>
<tr>
<td>40 and above</td>
<td>Class III obesity</td>
</tr>
</tbody>
</table>


Note: the BMI is calculated as the weight in kilograms of a person divided by the square of his/her height in meters (kg/m²). The BMI is highly correlated with body fat.

The World Health Organization (WHO) classifies adults as overweight when the BMI is equal or greater than 25 and obese when the BMI is equal or greater than 30.¹

In 1980, fewer than one in ten people were classified as obese. Since then, the global numbers on obesity have doubled, and in some countries it has tripled. In 2008, worldwide more than half a billion adults were obese (205 million men and 297 million women).² In 2008, the highest mean BMI for adults over 20 years of ages both sexes were found in the Oceania region (33.9 BMI for males and 35.0 BMI for females in Nauru) and the lowest in sub-Saharan Africa (21.5 BMI) and some countries in East, South and South-East Asia.² The USA is the high income country with the highest mean BMI for adults over 20 years old, where 35% of the population within this group is obese. Japan is the high income country with the lowest mean BMI.² Even though there is a positive relationship between BMI and GDP, wealth and its related changes in behaviours namely in diet and physical activity can only partly explain the variation in prevalence of overweight and obesity among countries.³ Prevalence rises with age and in certain ethnic populations, such as American Indians, Hispanic Americans and Pacific Islanders.⁴

The new Global Burden of Disease 2010 data presented in 2012 shows that risk factors, such as underweight children, dropped from first place to eighth position on the ranking of attributable risk factors for the burden of disease and high body mass index jumped to sixth rank from tenth globally between 1990 and 2010.⁵ High body mass index is ranked third in Western Europe and fourth in Central and Eastern Europe as an attributable risk factor for the burden of disease.
In more than half of the member states of the EU one in two people are overweight or obese (Figure 6.18.1). Countries most affected by obesity are the United Kingdom and Malta and least affected are Italy and Bulgaria.

**Figure 6.18.1: Percentage of population with Body Mass Index (BMI) above 30 (defined as obese), age-standardized estimate, based on available data for Member States of the European Union in 2008/2009**

Source: Author’s own elaboration based on Eurostat data Nov 2011 (Eurostat Press Office, 2011)
Note: According to Eurostat there was not recent data available for Denmark, Ireland, Lithuania, Luxembourg, Netherlands, Portugal, Finland, and Sweden.

In some countries such as Italy the obesity epidemic has come to a halt over the last decade. In some countries, such as France and Spain, only a modest increase in the magnitude of obesity was recorded (2 to 3% increase).

### 1.1 Adult obesity

More women than men are obese, and the obesity rate has increased faster in men than women. There is not only a difference in the prevalence of obesity between men and women but also a large disparity which has been remarkably stable over the last decade in high income countries: less educated and lower-income individuals are more likely to be overweight and obese. Women with little education are two to three times more likely to be overweight than more educated women, but smaller or no disparities exist for men. For low- and middle-income countries (LMIC) a reverse relationship has been found: more wealthy middle-aged adults in urban areas are obese than are those from lower socio-economic backgrounds. For some middle income countries it has been documented that
these patterns change with increasing gross domestic product, where more individuals living in rural areas and belonging to lower socio-economic households are increasingly affected.\textsuperscript{13}

Urbanisation might also play a major role in the development of obesity. In China, the overall rate of obesity is less than 5%, but in some cities it is more than 20%.\textsuperscript{11} It is expected that obesity will further increase globally. Rates are rising faster in low- and middle-income than in high-income countries.

According to global projected trends it is expected that in 2030, one billion people will suffer from obesity.\textsuperscript{12} Projected trends of obesity in the EU27 countries between 2005 and 2020 indicate an increase of an average of 3.8% in prevalence (Figure 6.18.2).\textsuperscript{13} For the United Kingdom, a 10% increase in obesity is expected between 2010 and 2020.\textsuperscript{7} There are some exceptions in which no increase in obesity is expected based on current data: Estonia, Hungary, Latvia, Lithuania, Poland and Romania.\textsuperscript{13} Updated figures on projected trends in obesity are expected to be published later in 2013 by the WHO.\textsuperscript{1}

\textbf{Figure 6.18.2: Future projection of obesity range in Europe}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6_18_2.png}
\caption{Future projection of obesity range in Europe}
\end{figure}

Source: Author’s own elaboration from the White paper “Impact Assessment Report - A Strategy for Europe on Nutrition, Overweight and Obesity related health issues” European Commission.\textsuperscript{13}

\subsection{1.2 Child obesity}

Since the bodies of children and adolescents undergo a number of physiological changes as they grow, developing a simple body mass index is difficult. Hence, the WHO has developed growth charts to measure for overweight and obesity in infants and young children up to age
five and for individuals between five and 19 years. Globally, the rate of childhood obesity has increased dramatically over the past two decades and is still rising in some countries (e.g. Canada, Mexico, China and India). The proportion of obese children in Canada has increased from 10% in the 1980s to 30% in 1990s, and in Brazil from 4% to 14% during the same period. Also in India and China, childhood obesity continues to rise. It has been estimated that nearly every other child in North America (40%) and Eastern Mediterranean WHO regions is overweight or obese; in Europe 38%, in the western Pacific 27%, and in South-East Asia 22%. Recent data published in 2013 from the Childhood Obesity Surveillance Initiative 2008 shows a high variation of the prevalence of obesity (6.0 to 26.0% for boys and 4.6 to 17.3% for girls) between 12 European countries with the highest level of overweight in southern European countries and the lowest in northern European countries.

There are some indications that the epidemic of child obesity is slowing down in some countries; for instance, in the last 20 years child obesity in France has been relatively stable at around 6 to 8%. A series of biological and environmental factors have been identified that contribute to higher food intake in children such as longer working hours of parents, lack of cooking skills, limited money to buy healthier food and very successful marketing campaigns for unhealthy food targeting not only children but also adults. There is an increased risk for overweight children and adolescents to become obese adults. Adulthood obesity seems to be more severe if it has developed since childhood. Childhood obesity has been associated with higher mortality in adulthood and with a higher risk of nutritional deficiencies such as Vitamin D and iron deficiency.

1.3 Morbidity and mortality related to overweight and obesity

Obesity is an important risk factor for hypertension, dyslipidaemia, diabetes, cardiovascular diseases, obstructive sleep apnoea, fatty liver disease, osteoarthritis and asthma; It has been estimated that the global burden attributable to increased BMI were 12% for colon cancer, 8% for postmenopausal breast cancer and 32% for endometrial cancer in women. In terms of diabetes, it has been estimated that 64% of cases of diabetes in men and 77% of cases in women can be attributed to excess weight gain. The same is true for 33% of ischaemic heart disease and ischaemic strokes, 50% of hypertensive disease and 25% of osteoarthritis.

Overweight and obesity are also associated with a higher mortality risk, see Figure 6.18.3. Severely obese people die 8-10 years sooner than those with normal weight; for every additional 15 kilogram of excess weight the risk of an early death increases by 30%. In 2004, the estimated disability due to obesity and its effects was estimated with more than 36 million disability-adjusted life-years (DALYs). In the USA alone, obesity kills more than 100 000 adults per year. In the European Region, obesity is responsible for about 10 to 13% of deaths according to the WHO regional office in Europe.

Many of the health consequences (among them cardiovascular diseases) that are observed in adult-onset obesity are often preceded by abnormalities manifested during childhood. Health consequences of childhood obesity are similar to adults; cardiovascular diseases, diabetes, breathing problems such as sleeping apnoea and asthma, joint problems, fatty liver disease, gallstone, gastro-oesophageal reflux. A systematic review found that blood pressure, cholesterol and triglycerides, fasting insulin and insulin resistance were higher in overweight and obese than in normal weight children.
Overweight and obesity also have psychological and social effects which are often difficult to quantify; many obese individuals suffer from depression and eating disorders.2 It has been found that elevated BMI adversely effects quality of life in adult.24 In children, obesity has been linked to sadness, loneliness and nervousness.5

Figure 6.18.3: Mortality risk as estimated hazard ratio associated with being under- and overweight

Source: Constructed by author using data provided by Berrington de Gonzalez.19
Note: Hazard ratio calculated with age as the underlying time scale, stratified by study and adjusted for alcohol (g/day), education, marital status and overall physical activity.

A project funded by DG SANCO - Dynamo-HIA (Dynamic Modelling for Health Impact Assessment) has modelled the health impact of obesity (see also http://www.dynamo-hia.eu/) in Europe with respect to a series of diseases. For instance, it calculated an increased risk in ischaemic heart disease of 1.35 for men and women who are classed as being overweight and 2.0 for obese individuals. Overweight men and women have an estimated relative risk of 2.30 for diabetes which increases to 5.50 for obese men and 7.0 for obese women.25 Overall, over a million deaths in the EU region annually are due to diseases related to excess body weight.26

1.4 The costs associated with overweight and obesity

Together with the associated diabetes and cardiovascular diseases, obesity is becoming the greatest health care burden affecting European society. An obese person incurs 25% more health expenditure than a person of normal weight. Obesity alone is consuming 1 to 3% of the total health expenditure in most OECD countries (estimates of direct costs of obesity alone in the EU in the 1990’s ranged from 1% of health care expenditure in the Netherlands,
Update on 2004 Background Paper, BP 6.18 Obesity

up to 3.1-4.2% in Germany and 6% in Belgium.)\textsuperscript{8-13} In the United States, 5 to 10% of the total health expenditure is estimated to be spent on prevention and treatment of overweight and obesity and their related health consequences.\textsuperscript{8}

It is important to consider that much of the cost of obesity falls outside the health sector. For instance, it has been estimated that obesity costs the United Kingdom two billion GBP, out of which only 24% (479.3 million GBP) are related to the health sector; the rest is attributed to the loss of productivity and costs that individuals, households and carers incur.\textsuperscript{26} In 2007, the Wanless Report from the King’s Fund in the United Kingdom\textsuperscript{27} argued that obesity could cripple the NHS if no further action was taken. In the USA, the annual economic costs (comprising medical costs, loss in productivity and additional economic impacts) associated with obesity has been estimated to be US$ 215 billion.\textsuperscript{28} In 2012 the OECD reported that obesity accounts for an estimated 1% of the GDP.\textsuperscript{8}

2. What are the control strategies?

There are control strategies at individual and population levels, some aimed at preventing further overweight and obesity, and others at treating those already affected. In the following sections we will first briefly describe preventative strategies at population level and individual non-pharmacotherapeutic treatment. The main focus of the background paper will be on pharmacotherapeutic interventions that are currently available.

2.1 Population measures for the prevention of overweight and obesity

There is widespread agreement that the obesity epidemic is a “normal response of normal people to an abnormal environment”.\textsuperscript{29} Control strategies require the leadership of governments and international organizations. The World Health Organization with the member states in the EU agreed in 2006 on the European Charter on Counteracting Obesity\textsuperscript{30} and the European Action Plan for Food and Nutrition Policy 2007–2012.\textsuperscript{31} The Charter stresses the need to align health goal with those in other areas such as economy, society and culture and defines nine principles which should guide the action of member states; the first three include the call for political will and leadership, the action against obesity should be linked to wider strategies to prevent non-communicable diseases, and governments need to take responsibility, as well as individuals.\textsuperscript{30}

The European Action Plan for Food and Nutrition Policy 2007 to 2012\textsuperscript{31} identified six fields of action: supporting a healthy start; ensuring a safe, healthy and sustainable food supply; providing comprehensive information and education to consumers; carrying out integrated actions to address related determinants; strengthening nutrition and food safety in the health sector; monitoring and evaluation. As a key indicator for progress, the Member States chose prevalence of obesity, particularly in children and adolescents. Along with the Action Plan, a structure for its implementation was created which includes (1) the High Level Group on Nutrition and Physical Activity, (2) promotion of concrete stakeholder-driven action, and (3) ensuring reliable, comparable and regularly updated data.\textsuperscript{32} The Action plan 2012 to 2016 for the implementation of the European Strategy for the Prevention and Control of Non-
Communicable Diseases (NCD),\textsuperscript{33} highlights that obesity requires special attention as it is a result of common risk factors and a cause of many NCDs.

There are a variety of policy measures (voluntary or statutory) that governments can use to promote the consumption of healthier food.\textsuperscript{33} For instance, in Denmark a tax on food rich in saturated fats was introduced in 2011; as a result, consumer prices of those products have increased. For instance, butter prices were higher by an average of 0.29 euros per 250 g (this tax was abolished in 2013;\textsuperscript{34} see Section 6.0 “What are the opportunities for research into new pharmaceutical interventions?”).\textsuperscript{35} Other examples include Hungary, where a tax on pre-packed products with high salt and sugar content was introduced and Finland, that has a tax on sugary products such as soft drinks, ice cream, and chocolate.\textsuperscript{36} The literature on the effects of fiscal measures to promote healthier food choices indicates that taxes are likely to shift consumption in the desired direction and that the tax would need to be at least 20\% to have a significant effect on population health.\textsuperscript{33}

There is also an increasing interest in combining soft (voluntary) measures with hard (statutory) policy measures such as fiscal measures to influence consumer choices. Apart from fiscal measures, governments have been encouraged to consider putting a ban on the sales of certain products: The City of New York put a sales ban on sweetened beverages in containers of more than 480 ml (16 OZ).\textsuperscript{37} Three recently published studies show an association between the consumption of sugar sweetened beverages and the development of overweight and obesity.\textsuperscript{38} The intake of sweetened beverages was found to determine body weight indicating that the excess in calorie intake from beverages results in higher body weight rather than consumption of specific foods.\textsuperscript{39}

Analysis of the cost-effectiveness of a series of interventions to prevent and treat obesity in Australia showed a series of measures that are cost-savings and are currently recommended (see also Appendix 1) including tax on sugar sweetened beverages, traffic light labeling of food and reducing junk food and beverage advertisement to children.\textsuperscript{40}

\subsection{Prevention of adult and childhood obesity}

Population interventions to prevent adult obesity include promoting lifestyle changes, healthier diets and increased physical activity. However, changes in diet habits and increased physical activity are very challenging for most people, although achievable through either community support or strong motivation; for instance, it has been estimated that with dietary and lifestyle modification around 80\% of highly motivated patients are unable to achieve weight loss long-term.\textsuperscript{41} Around 60\% of the world’s population are getting insufficient exercise. This is primarily due to mechanized transportation and labour-saving technology at home. For instance, in both children and adults there is an association between hours of viewing television and the risk of obesity.\textsuperscript{42}

Many population interventions to prevent childhood obesity have targeted schools. One common strategy is to ban vending machines that dispense snacks and sugary beverages, while reducing calories in school meals and increasing the children’s physical activity.\textsuperscript{16} Public policies in the United Kingdom have introduced mandatory screening in schools of children and reporting results to parents about their children’s body weight.
Ensemble, prévenons l’obésité des enfants (Together, let’s prevent obesity in children, or EPODE) has been developed in France and implemented in many cities across various countries in Europe to prevent childhood obesity.\textsuperscript{43} It aims at modifying behaviour and the environment which includes the development of public transport, the promotion of physical activity, strengthening food and non-alcoholic beverage labelling, restricting food and non-alcoholic beverage promotion and removing vending machines from schools. It has shown encouraging results for small cities in lowering childhood obesity and more studies are underway to test whether it also worked in larger urban or very rural areas.\textsuperscript{43}

2.2 Non-pharmacotherapeutic treatment options

The goal of obesity treatment is to achieve an individual negative energy balance. As in prevention, dietary changes in combination with increased physical activity are defined as first-line therapy in adults and children. Due to the benefit-risk balance, pharmacological and surgical treatments are considered second- and third-line treatments.

2.2.1 Dietary changes and increased physical activity in adults

Diet changes and increased exercise are the first-line treatments combined with behaviour modification and psychological support. Weight loss in overweight and obese participants of about 5% to 10% of initial body weight is associated with an improvement in cardiovascular risk factors\textsuperscript{4} and a reduction in the incidence of type 2 diabetes in high-risk individuals.\textsuperscript{44} However, the effect size is very modest with a long-term weight loss of less than 10kg over time.\textsuperscript{45} Regaining weight over time is very common.\textsuperscript{43}

A health technology appraisal found that a fall in systolic blood pressure of 6.1 mmHg was associated with weight loss of 10% and a 10 kg weight loss with an average fall in total cholesterol of 0.25 mmol/l and a fall in diastolic blood pressure of 3.6 mmHg.\textsuperscript{46} Even though some studies report clinically meaningful reduction in cardiovascular risk, maintenance of weight loss over time remains a major challenge.\textsuperscript{43}

A meta-analysis of studies analysing the long-term effect of low calorie diets (which included 600 kcal/day deficit diets) demonstrated weight reduction of \(-5.31\) kg (95% CI \(-5.86\) to \(-4.77\) kg) after one year and weight loss continuing for three years.\textsuperscript{47} Low-fat diets were associated with the prevention of type 2 diabetes, and improved control of hypertension. Effect size increased with adding an exercise programme and behaviour therapy programmes to the low calorie diet. A Cochrane Review published in 2009 on psychological interventions for overweight and obesity concluded that with increasing intensity of behavioural interventions more weight loss was achieved. Combining cognitive-behaviour therapy with a diet / exercise intervention increased weight loss by \(-4.9\) kg (mean differences weight loss from baseline; 95% CI \(-7.3\) to \(-2.4\)) compared with diet/exercise alone (see also Table 6.18.2).\textsuperscript{45} However, no data on mortality, morbidity or quality of life were found in this review.
Table 6.18.2: Summary of results from a Cochrane Review of behavioural intervention for overweight and obesity in adults

<table>
<thead>
<tr>
<th>Interventions studied</th>
<th>Intervention (No. of participants)</th>
<th>Control (No. of participants)</th>
<th>Effect size (mean change in weight loss in kg)</th>
<th>Upper 95% CI</th>
<th>Lower 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behaviour therapy versus control, Outcome: Mean change in weight – studies 12 months or less duration.</td>
<td>686</td>
<td>619</td>
<td>-4.46</td>
<td>-4.57</td>
<td>-4.34</td>
</tr>
<tr>
<td>Behaviour therapy versus control, Outcome: Mean change in weight - studies &gt;12 months duration.</td>
<td>673</td>
<td>581</td>
<td>-2.00</td>
<td>-2.03</td>
<td>-1.97</td>
</tr>
<tr>
<td>Behaviour therapy plus diet / exercise versus diet / exercise, Outcome: Mean change in weight - studies 12 months or less duration.</td>
<td>235</td>
<td>232</td>
<td>-4.71</td>
<td>-4.97</td>
<td>-4.45</td>
</tr>
<tr>
<td>More intensive versus less intensive behaviour therapy, Outcome: Mean change in weight - studies with a duration of 12 months or less</td>
<td>155</td>
<td>151</td>
<td>-2.34</td>
<td>-3.27</td>
<td>-1.41</td>
</tr>
</tbody>
</table>

Source: Author’s own elaboration from Shaw et al

In a review of the evidence on cost-effectiveness of non-pharmacological interventions in obese adults the National Institute for Clinical Excellence concluded in 2007 that these interventions are cost-effective but points out that there are several limitations in the quality of evidence. Preventive programmes are cost-effective in the long run but not necessarily in the short run. A study published in 2011 on the cost-effectiveness of diet and exercise on overweight and obesity in Australia concluded that these interventions could be considered cost-effective if time and travel of the participants are ignored.

2.2.2 Non-pharmacological treatment of childhood obesity

As in adults, non-pharmacological and non-surgical interventions are the first-line treatment for childhood obesity. Currently the step care approach is the recommended model to treat overweight and obesity in children and adolescents in the United States. With this approach, intensity (and associated treatment risks) is increased according to the degree of excess weight, age/maturation, health risks and motivation: starting with simple preventive messages to those who are not overweight, to weight-management interventions with increasing intensity for those who have become overweight and have weight-related health problems.

Treatment is recommended in children with a BMI of equal or above 95th percentile of their age and gender or equal or above the 85th percentile with co-existing co-morbidities. The goal of treatment of childhood obesity is to reduce childhood morbidity, increase childhood functioning and reduce risk of morbidity and mortality in adulthood.

Non-pharmacological interventions include dietary changes and increasing activity levels and often involve the family or the care takers of children or adolescents. Changing behaviour such as diet can be extremely difficult. To support behaviour changes several techniques have been proposed which are based on the assumption that successful

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1 NICE has not published newer evidence on the cost-effectiveness of non-pharmacological treatment.
behaviour change can be achieved through self-monitoring, problem-solving, goal setting, rewarding of successful change and minimizing exposure to unhealthy food.\textsuperscript{14}

In childhood obesity, evidence suggests that increasing physical activity alone is effective to achieve changes in adiposity.\textsuperscript{47,49} There is no general agreement between professional associations and institutions about the exact recommended energy intake relative to body weight to achieve medium/long-term weight loss.\textsuperscript{16} One of the challenges in children and adolescents is the potential harm of a diet that is too restrictive in energy intake as it can affect growth and social and biological development.\textsuperscript{16} Some authors have calculated that the reduction in energy intake needs to be significant (around 250kcal per day) to achieve a least no weight gain in children with more than 90\% of overweight children;\textsuperscript{50} 250 kcal represent nearly one fifth of the total daily energy intake and children would need to walk one to two hours at a speed of 2 km/hour to burn this amount of energy.

A meta-analysis of interventions to treat overweight or obesity in children or adolescence showed larger effects for moderate- to high-intensity behavioural interventions (standardized mean difference in weight loss (SMD): -1.01 [95\% confidence interval (CI): -1.24 to -0.78]) compared to very low-intensity interventions (SMD: -0.39 [95\% CI: -0.66 to -0.11]).\textsuperscript{14} Only half of the studies report on secondary outcomes and those that do report only minimal impact with respect to lipid levels, blood pressure, diet, physical activity level, and psychosocial measures.\textsuperscript{14} Another meta-analysis done by a Cochrane Review concluded similarly that combined behaviour lifestyle interventions are recommended over self-help or standard clinical care, and they have proven to result in clinically meaningful reduction in overweight children.\textsuperscript{49}

### 2.3 Pharmacotherapeutic options

The development of current pharmacotherapeutic options for the treatment of obesity is derived from the knowledge of the biological pathway of the anabolic and catabolic effects (for more detailed information see also Appendix 6.18.2). It has been found that both insulin and leptin are secreted in proportion to body fat and serve as adiposity signals.\textsuperscript{16} Ghrelin, which is secreted by the stomach and duodenum, serves as a hunger signal at the hypothalamus and brainstem, whereas other peptides secreted by the gastrointestinal tract, including peptide YY and GLP-1, act as satiation signals.\textsuperscript{16}

The main mechanism of action of existing pharmacotherapeutic agents are to: (1) block the absorption of macronutrients; (2) decrease energy intake; (3) increase energy expenditure.

The FDA\textsuperscript{51} and EMA\textsuperscript{52} coincide that a key requirement of a medicine to be granted market authorization is weight reduction plus clinically meaningful improvements in cardiovascular risk factors. Weight reduction alone is insufficient. Table 6.18.3 shows the different criteria that the FDA and EMA have defined in order to consider market authorization of an anti-obesity product.
Since obesity has been described as a chronic condition which requires treatment over a long period of time, short-term trials of these interventions are of limited value to assess the effects of pharmacotherapy among other interventions. Short term trials (less than one year) are indeed overly optimistic for long term prognosis as patients often regain weight after treatment is discontinued. With respect to the duration of the clinical trials, Han et al\textsuperscript{16} writes that with reference to child obesity: “long-term clinical trials are needed to show safety and efficacy of treatments, not only for a few months, but also during the crucial period of active growth and maturation.”

2.3.1 Orlistat in adults

The only marketed pharmaceutical product licensed for the long-treatment of obesity in the Europe is orlistat.\textsuperscript{53} Orlistat blocks a fat digesting gastric and pancreatic enzyme lipase. It has to be taken three times per day and patients have to supplement diet with vitamins to avoid nutritional deficits.4 In its reduced strength it is available over the counter in Europe, the USA and some other countries.

A Cochrane Review found 16 clinical studies with a length of at least 12 months on orlistat. Average weight loss compared to placebo was 2.9 kg (95% confidence interval (CI) 2.5 to 3.2 kg) (see also Appendix 6.18.3). Since the weight loss is moderate, the majority of patients remain significantly obese. Regarding secondary outcomes, orlistat has been shown to reduce the incidence of diabetes. It also improves total cholesterol, LDL-cholesterol and blood pressure (systolic and diastolic) and slightly lowers HDL levels. In diabetic patients it improved glycaemic control. No RCT has mortality as a primary outcome.

In contrast to some other systemic acting anti-obesity agents orlistat has minimal systemic side-effect but a series of undesired effects, most importantly some very unpleasant gastrointestinal side effects including the production and occasionally leaking of a fatty
Even though the discontinuation rate was relatively low with about 5% of patients, data from clinical practices have reported that only 10% of patients continue treatment after one year.

Cost-effectiveness varies by health care setting. A recently published systematic review of cost-effectiveness of orlistat in primary care in the United Kingdom, including 10 trials comparing orlistat with some kind of lifestyle invention, found that the mean incremental cost-effectiveness ratio was £1 665. The authors concluded that using a threshold of 20 000 GBP per QALY “In clinical practice orlistat should be considered [in the United Kingdom] to aid weight reduction with lifestyle interventions in those individuals who have not been successful in reducing their weight with lifestyle alone”. For the Australian health care setting, it was found not to be cost-effective when defining an Incremental Cost-Effectiveness Ratio (ICERs) below 50 000 Australian dollars per disability adjusted life year (DALY) averted as good value for money. The authors argued that in contrast to previous studies that found orlistat cost-effective, their model was more pessimistic in assuming weight regain to baseline within two years; in addition, only a (substantial) ‘utility’ gain to reductions in disease-related quality and length of life and not only weight gain itself attributable to the treatment was taken into account. Adherence can be relevant to consider: in a study published in 2011 using data from 1.8 million HMO members in Israel found that only 25% of patients continue therapy for four months and less than 2% of patients completed 12 months of therapy. In general, there are not many studies analysing adherence to orlistat in routine clinical practice.

Clinical guidelines recommend the criteria that patients should fulfil before considering to start orlistat. NICE in the United Kingdom recommends pharmacotherapy for patients with a BMI of 28.0 kg/m² or more with associated risk factors (such as diabetes or hypertension) or a BMI of 30.0 kg/m² or more. In terms of continuation beyond three months this should only be done if the person has lost at least 5% of their initial body weight since starting drug treatment (unless the patient has diabetes which might slow down loss of body weight). The decision to use drug treatment for longer than 12 months (usually for weight maintenance) should be made on an individual basis.

### 2.3.2 Orlistat in children and adolescents

Orlistat has also been used in adolescents (12 years and above) resulting in small BMI reduction (0.85 kg/m² for orlistat). In combination with lifestyle changes the additional BMI loss found between placebo and orlistat at six months after initiation was –0.76 kg/m² (95% CI –1.07 to –0.44). No effect on secondary outcomes was found. Only one randomized controlled trial was for over 12 months, which showed a statistically significant change between the intervention group (orlistat) and placebo, –0.55 kg/m² versus 0.31 kg/m² respectively. With respect to secondary outcomes, there was a small reduction in the diastolic but not in the systolic blood pressure when compared to the control group (–0.51 mmHg in the intervention group compared to an increase the patients on placebo (1.30 mmHg) (p=0.04). In comparison with life-style interventions orlistat has shown side-effects similar to those in adults: oily stool (42%), abdominal pain (11%), faecal incontinence (9%), and new cholelithiasis (2%). The placebo controlled trial reported 11 adverse events with the intervention group of 352 adolescents which included seizure, depression, asthma attack,
appendicitis, gallbladder disorder followed by cholecystectomy, pilonidal abscess, adenoidal hypertrophy, cholelithiasis and aseptic meningitis.59

Due to a lack of data on long-term effects of drug treatment and poor effectiveness, pharmacological treatment is only recommended in children with a BMI higher than the 95th percentile who have substantial medical complications of obesity.14,16

In 2006, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom reported that there was not sufficient evidence to conclude that the use of orlistat in children and adolescents is cost-effective.26

2.3.3 Metformin

Metformin is a first-line drug for type II diabetes, particularly in overweight and obese patients as it has shown a favourable effect on body weight.60 It is usually well tolerated, with gastrointestinal side effects being the most common. There is increasing body of evidence demonstrating benefits of metformin in non-diabetic patients both as diabetes prevention and also for weight loss: in a long-term follow-up study with adults who had impaired glucose tolerance or elevated fasting glucose, the mean weight loss was ~2.7 kg in the metformin group and ~0.4 kg in the placebo group at the one year follow-up.63 Only about 4% of participants were unable to continue metformin due to adverse effects.61

Metformin might also be beneficial in overweight adolescents with impaired fasting glucose or impaired glucose tolerance when combined with life-style modifications.62 Interestingly, even in the absence of weight loss, metformin was reported to have the ability to improve insulin sensitivity in obese adolescents.63

2.3.4 Lorcaserin and phentermine plus topiramate

Two new pharmaceutical products have been granted market authorization in the USA in 2012: lorcaserin, a centrally acting selective agonist of the serotonin (5-hydroxytryptamine) 2C (5-HT2c) receptor, and phentermine plus extended-release topiramate. Phentermine is a non-selective releaser of noradrenaline, dopamine and 5-HT, acting as an anorectic agent and topiramate an antiepileptic drug.64,65

They are indicated in adults who are obese (defined as having a BMI of ≥30) or overweight (BMI ≥27) at least with one weight-related co-existing condition and only recommended in combination with a reduced-calorie diet and increased physical activity.

Both medicines have been studied in placebo-controlled trials in combination with life-style modifications indicating meaningful weight loss (over 5% of body weight) in more than half of the study participants in the intervention group. For lorcaserin, the placebo subtracted mean percentage body weight loss from baseline was 3.0 to 3.3%.64 The placebo subtracted mean percentage body weight loss from baseline was substantially higher for phentermine plus topiramate (from 3.5 to 6.6% weight loss with the lower dose of the combination and 8.6 to 9.4% with the full dose of it weight).65 Even though the higher weight loss with phentermine plus topiramate is regarded as sufficient to achieve market authorization in Europe,66 it received a negative opinion by EMA in October 2012 due to cardiovascular and psychiatric side effects, but also because of a high probability of extensive off-label use.67
In addition to weight loss, lorcaserin and phentermine plus topiramate demonstrated favourable effects in cardio-metabolic and anthropometric parameters (e.g., blood pressure, high-density lipoprotein cholesterol levels and waist circumference). Both medicines also improved glycated hemoglobin levels in overweight and obese participants with type 2 diabetes. However, both products have potentially serious side-effects and the FDA is concerned about off-label use particularly in patients who would like to lose some pounds for cosmetic reasons but could do so using interventions which do not pose such potentially serious side-effects.

In 2010, the FDA denied market authorization to lorcaserin arguing that –according to the study information– it achieved only marginal weight loss (a placebo adjusted average weight loss of only 3.6%). Preclinical studies indicated a potential increase in the risk of breast cancer and astrocytoma at relatively low doses. Also in 2012, the FDA pointed out two potentially life-threatening side-effects of lorcaserin; multiple tumours and valvulopathy. With respect to the latter, the FDA later concluded that it is unlikely that lorcaserin increases the risk of valvulopathy in humans. Other side-effects reported with lorcaserin are increased incidences of blurred vision, dizziness, somnolence, headache, gastrointestinal disturbance and nausea.

For phentermine plus topiramate teratogenicity and elevations in resting heart rate are safety concerns. For women taking topiramate during their pregnancy there is an elevated risk for infants born with an orofacial cleft. The FDA decided that this product requires a Risk Evaluation and Mitigation Strategy (REMS) consisting among other measures of a medication guide, a patient brochure and prescriber training; the prescriber has to inform the patient about the teratogenic risk and the need for contraception for women of the reproductive age. The FDA has requested that both manufacturers monitor the long-term cardiovascular risks in patients taking the products.

2.4 Surgical interventions
2.4.1 Surgical interventions in adults

Bariatric surgery is an intervention in which the stomach size is reduced and/or the absorption of nutrients decreased and has proven to provide consistent and long-term weight loss for the morbidly obese. Procedures include gastric banding (a band is put around the stomach to reduce it size) and gastric bypass (the surgeon creates a bypass which reroutes food to a small stomach pouch). Other procedures include removing a portion of the stomach (sleeve gastrectomy) and bilo-pancreatic diversion (see also more detailed explanation in Appendix 4). Laparoscopic interventions instead of open surgeries are most commonly done. The mechanism by which bariatric surgery works is not fully understood yet.

As invasive interventions, they are associated with surgical risks but also with long-term digestive problems and nutritional deficiencies. Hence, life-long care is needed for patients undergoing this type of intervention. Financial savings are achieved three to four years after the surgery for the health care systems but whether these savings are maintained after ten years is unclear.
The rate of surgery varies between countries and within countries: in the USA around 220,000 individuals underwent bariatric surgery in 2008, making this the second most frequent elective surgery.\textsuperscript{70} In comparison to the USA, the number of people undergoing bariatric surgery in the United Kingdom is much smaller but has risen ten-fold between 2000 and 2010.\textsuperscript{71} Reports indicate that in 2008 most bariatric surgeries were carried out in France (over 13,000) followed by Belgium (8,700), Spain (6,000), Italy (4,842), the Netherlands (3,500), Greece (2,875), Germany (2,117), Denmark (2,004) and Austria (1,741).\textsuperscript{69} Considering the millions of patients in Europe for whom the need for surgery would be indicated, these numbers can be considered low.

There is evidence that more women and girls undergo surgical treatment than men.\textsuperscript{72} Barriers to accessing surgery for those in need have been identified in a number of settings.\textsuperscript{73}

A Cochrane Review on the efficacy of bariatric surgery did a meta-analysis using a total of 26 studies out of which six studies compared surgery with non-surgical treatments and the rest compared different bariatric surgery procedures.\textsuperscript{73} From the six studies comparing surgical with non-surgical intervention it is clear that surgical interventions resulted in larger weight-losses over time; but comparison in the effect size was difficult as the studies used different measures (excessive weight loss, percentage weight loss from baseline, difference in BMI between intervention and control group).\textsuperscript{73} Secondary outcomes such as diabetes and hypertension also improved; one important secondary outcome measure was quality of life, which improved after the first two years after surgery. However, there was conflicting evidence with respect to long-term quality of life (more than 10 years after surgery).\textsuperscript{73} Even though there was a difference in the percentage of patients dying between different surgical interventions (2.1% died who underwent open Roux-en-Y gastric bypass, but no death occurred in patients undergoing laparoscopic adjustable gastric banding) this difference was not found when adjusting for risk factors (patients undergoing open Roux-en-Y were more ill than patients receiving other types of surgeries).\textsuperscript{73}

A long-term study (20 years of follow-up) found that patients with surgery had on average a 17% weight loss at 10 years and 18% at 20 years compared to a weight gain of 1% at 10 years and a loss of 1% at 20 years among those in the control group.\textsuperscript{74} Another long-term cohort study and two RCT\textsuperscript{76,77} were consistent in reporting improvement in diabetes: those enrolling individuals with no diabetes found a reduced incidence of diabetes at ten years.\textsuperscript{75} The number of individuals with diabetes before surgery recovering from diabetes was higher in the intervention than the control group.\textsuperscript{77} Therefore, some proposed diabetes as an independent indication for patients whose BMI is less than 35 kg/m\textsuperscript{2} (metabolic surgery).\textsuperscript{69}

Long-term studies found a reduced mortality of 29% when compared to standard weight loss measurements.\textsuperscript{79} A study enrolling 4,776 patients undergoing bariatric surgery in the USA found that 4.1 per cent of the patients had at least one major adverse outcome (death, development of blood clots, repeat surgeries, or failure to be discharged from the hospital within 30 days of surgery).\textsuperscript{70} Another systematic review reported a two-year mortality which ranged from 0% after sleeve gastrectomy to 1.7% after bilo-pancreatic diversion.\textsuperscript{79} An estimated mortality of 1 in 200 for bariatric surgery has been described.\textsuperscript{79} For surgical compared with non-surgical interventions, an increased incidence of cholelithiasis and cholecystectomies was reported for men but not for women. Comparing different surgical interventions showed that there is only limited evidence to recommend one surgical procedure over the other.\textsuperscript{73} However, there is limited evidence that biliopancreatic
diversion/duodenal switch surgery had the greatest weight loss and diabetes resolution compared with other types of surgery. One out of ten patients required further surgery at some point due to inadequate weight loss, regained weight, or early or late complications.

In terms of costs, a recent 20-year observational study showed that compared to patients without a surgical intervention, patients who underwent bariatric surgery had a higher utilization of in-hospital and specialists’ care in the first six years after surgery; after that period no difference was found. However, a reduction in medication costs, particularly antihypertensive and antidiabetic medicines was found seven years after surgery.

What seems clear is that the benefit of bariatric surgery outweighs the risk for those with a BMI of 30 and over. However, patients need to be committed to change their life-style profoundly and to receive long-term follow-up care. The reduction of 30 to 35% of overweight has often been much lower than the expected or desired weight loss by patients undergoing surgery. Many patients wish for a weight loss of around 70% of excessive weight as their target but only very few are able to achieve this target.

Which patients will benefit most from surgical interventions?

Clinical recommendations vary from country to country in Europe. As an example the National Institute of Health and Clinical Excellence in the United Kingdom recommends in their guidelines for the prevention and management of obesity in adults and children which was published 2006 the following criteria that patients should fulfil:
- a BMI of 40 kg/m² or more, or between 35 kg/m² and 40 kg/m² and other significant disease (for example, type 2 diabetes or high blood pressure) that could be improved if they lost weight;
- all appropriate non-surgical measures have been tried but have failed to achieve or maintain adequate, clinically beneficial weight loss for at least six months;
- the person has been receiving or will receive intensive management in a specialist obesity service;
- the person is generally fit for anaesthesia and surgery and is committed to the need for long-term follow-up.

Also, surgery is recommended as a first-line option (instead of lifestyle interventions or drug treatment) for adults with a BMI of more than 50 kg/m² in whom surgical intervention is considered appropriate.

2.4.2 Surgical interventions in children and adolescents

A systematic review on surgical interventions in children and adolescents from 19 observational studies reported for gastric banding a 95% CI of –13.7 to –10.6 kg/m² for change in BMI from baseline, and for gastric bypass, at one to three years a 95% CI of –17.8 to –22.3 kg/m². Life-threatening adverse outcome was pulmonary embolism; other adverse outcomes reported were shock, intestinal obstruction, postoperative bleeding, staple-line leak and severe malnutrition. Currently, surgical interventions in children and adolescents are only recommended to patients with a BMI ≥50 kg/m², or ≥40 kg/m² with important comorbidities. Without evidence from long-term follow-up studies it is difficult to say whether the potentially life-threatening risks of the surgical interventions and life-long nutritional deficiencies outweigh the benefit of a reduction in morbidity and mortality.
2.4.3 Other interventions

Other invasive interventions such as a more recent endoscopically delivered duodeno-jejunal bypass device (EndoBarrier) has been developed that reduces the absorption of food from the small intestine; as it has been insufficiently evaluated yet, it will not be further discussed.83

3. Why does the disease burden persist?

It has been argued that a series of measures are necessary to halt the obesity epidemic and that it will be much more complicated to succeed than for instance, in tobacco control.40 As with many other medical conditions, obesity is caused by genetic and environmental factors. Whereas genetic factors can explain in part the development of overweight and obesity it has been argued that environmental factors should be given priority in addressing obesity globally.9 A major factor in the rise of the obesity epidemic has been the increased energy intake which has to do with a change in the food supply which provides affordable, well marketed and energy dense food; another has been reduced physical activity.9

As it is so difficult to reverse obesity through interventions. many argue that prevention is the only way to tackle it. Reversing obesogenic environments seems one of the most important objectives.40 Even though international institutions have recommended a series of population measures over the last 10 years, national governments have made only very slow progress in implementing these.9 The disease burden persists due to at least two other factors: (1) current individual treatment options are not effective while there is still an increase of the epidemic in many countries and (2) very few examples exists in which interventions at population level have had an effect on the disease burden.43 Another important aspect determining interventions is patient adherence, especially to achieve long-term weight loss maintenance.72

Evidence of how to most effectively prevent childhood obesity is lacking.16 A Cochrane Review on interventions to prevent or treat childhood and adolescent obesity undertook a meta-analysis by age-subgroups.15 A meta-analysis of eight interventions (non-pharmacological) of less than 12 months in young largely non-overweight children (0-5 years old) have only shown moderate effect size (-0.26 loss in BMI in the intervention group when compared to the control group) which was not statistically significant, although it indicated a tendency towards a positive impact of the interventions. These studies only measured the effect on the adiposity and not on other related risk factors such as cardiovascular disease risk factors, e.g. blood pressure, heart rate, blood lipids, or cardiovascular fitness. Except for a single study, none of the eight studies targeting 0-5 year olds explicitly reported unintended outcomes or measures of harm.15

Another meta-analysis of interventions targeting mostly non-overweight 6 to 12 year old children taking place in educational institutions (32 out of 39 studies) report a mean effect size of -0.15 BMI (on average the BMI of the intervention group decreased statistically significant by 0.15 more than the control group). While these effect sizes may appear small, they represent important reductions at a population level if sustained over several years.15 As most of the studies in children and young people are of less than 12 month duration, long-
term follow-up of study participants is most likely to provide valuable insight into the effect size over time.

4. What can be learnt from past/current research into pharmaceutical interventions for this condition?

So far it has been very challenging to develop a treatment that has an acceptable benefit/risk profile but with a clinically meaningful reduction in the risks of development of diabetes and cardiovascular diseases. Most pharmacotherapies achieve a weight loss of 2 to 7.9 kg more than that usually achieved with placebo treatment. (Whether this is sufficient to result in a clinically meaningful reduction of cardiovascular diseases or diabetes; a reduction of 5 to 10% body weight has found to be sufficient to result in changes in glycemic control, blood pressure, HDL cholesterol, and triglycerides at one year in adults with type II diabetes, depends on the individual goal of weight loss). The overall picture of available treatment for overweight and obesity has changed significantly over the last few years as requirements for tolerability and safety have become more stringent. In the past, many pharmacotherapeutic options were anorectics only for short-term use of less than 12 weeks. There is widespread fear of abuse due to the addictive potential of amphetamine and its derivates which have been withdrawn in many countries. When proven to be effective it is expected that those medicinal products would be used in a very large and diverse population group, often off-label, which makes assessment of benefit-risk balance and subsequent market authorization very complex.

A series of pharmaceutical products have been taken off the market in recent years (see Table 6.18.4) due to an unfavourable benefit-risk balance.

Table 6.18.4: Pharmaceutical products that have been taken from the market in recent years

<table>
<thead>
<tr>
<th>Product names</th>
<th>Active substance</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menocil®</td>
<td>Aminorex</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Redux® Pondimin®</td>
<td>Fenfluramine and dexfenfluramine</td>
<td>Valvulopathy</td>
</tr>
<tr>
<td>Acomplia®</td>
<td>Rimonabant</td>
<td>Suicidal ideation and behavior</td>
</tr>
<tr>
<td>Reductil®</td>
<td>Sibutramine</td>
<td>Myocardial infarction and stroke</td>
</tr>
</tbody>
</table>


FDA and EMA have taken the position that pharmacotherapies are not acceptable if there are severe side-effects. However, it has been argued that expecting that a pharmacotherapy has a safety and efficacy profile similar to a change in diet and exercise is unrealistic, and that different risk benefit profiles should be recognised within the population with obesity. Managing risks after market approval have shown to be very important but also very
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challenging. Even though the requirements in terms of safety and efficacy are very high, there is a window of opportunity in which new agents in the development pipeline could offer important clinical advantages over existing therapies.

5. What is the current "pipeline" of products?

There is a wide variety of targets and pharmacotherapeutic options being tested at present, out of which only the most advanced in their development will be described in the following sections.

5.1 Fixed-dose combinations of central nervous system (CNS) agents

Some of the options for weight loss are fixed-dose combinations of CNS agents which have previously been used for weight loss but were taken from the market due to safety concerns and products which are currently used off-label for weight loss. Fixed-dose combinations offer the advantage of multi-target therapy with sometimes higher efficacy, but may also reduce side effects and risks.

Two of the fixed dose combinations include bupropion, a norepinephrine and dopamine reuptake inhibitor which is combined with the opioid receptor antagonist naltrexone or with the sulfonamide anticonvulsant, zonisamide. For the combination of bupropion and naltrexone; four pivotal, 56-week, multicentre, randomized, double-blind placebo controlled studies have been conducted which show that 23 to 37% of patients achieved a weight reduction from baseline of over 5% of their body weight and 13 to 22% achieved a reduction of at least 10%. Lipid profile and glycaemic control also improved: an increase in high-density lipoprotein cholesterol and triglycerides were reported as well as a reduction in fasting plasma insulin and glucose concentrations. The most frequent side-effects were gastrointestinal but also headache, dizziness, insomnia and dry mouth. Due to concerns over increasing blood pressure in patients taking the combination, in 2011 the FDA denied market authorization and requested data from long-term cardiovascular outcome trials. However, the manufacturer is planning to resubmit its market authorization application in early 2013.

Quite substantial weight losses have been reported in phase II studies for the combination of bupropion with zonisamide: a reduction of body weight of 15% in obese people with no other co-morbidity in the absence of diet and exercise. Since the clinical studies involved zonisamide are short-term evaluations it needs to be seen if the clinical studies of more than three months duration and more subjects will not result in the identification of serious adverse side effects which would change the risk-benefit profile of the medicine. Studies for up to three months reported headache, insomnia, nausea and urticaria.

5.2 Antidiabetic agents (GLP-1 and amylin analogs)

Some authors believe that since metabolic syndrome is not a discrete disease entity that is accepted by the FDA and EMA, diabetes is viewed as the most appropriate alternative indication. Emerging type II anti-diabetic agents have been discussed as potential
candidates for effective weight loss. Table 6.18.5 presents a series of new anti-diabetic agents with weight loss properties.⁹⁰

### Table 6.18.5: New antidiabetic agents with weight loss properties

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type</th>
<th>Reported serious adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>Glucagon-like peptide-1(GLP-1) analogs</td>
<td>Pancreatitis, thyroid cancer*</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Glucagon-like peptide-1 agonist</td>
<td>Hemorrhagic and necrotizing pancreatitis, renal impairment and failure, thyroid cancer*</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>Amylinomimetic (amylin analog)</td>
<td>No serious adverse effects reported so far but needs to be injected three times daily it has not been tested in large clinical trials</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>SGLT-2 inhibitor</td>
<td>So far no serious side effects reported as not tested in large clinical trials</td>
</tr>
</tbody>
</table>

Source: Author’s own elaboration from Ioannides-Demos⁹⁰ and Thomson Reuters⁹⁰; thyroid cancer has only been reported in rodents not in humans.

Liraglutide, a glucagon-like peptide-1 (GLP1) analogue, and exenatide, a GLP-1 receptor agonist (GLPs), were developed and are approved for the treatment of type 2 diabetes. Both increase the secretion of leptin which suppresses appetite, energy intake and delays gastric emptying and they have both demonstrated a reduction in blood pressure and HbA1c levels.⁹⁰ In a trial comparing liraglutide with orlistat for nondiabetic patients, greater weight losses were found in patients taking liraglutide which was dose-dependent from 4.8 kg and 7.2 kg for liraglutide compared with 2·8 kg with placebo and 4·1 kg with orlistat (P < .0001). The most common adverse events with liraglutide were nausea and vomiting.

Pramlintide, a synthetic analog of the pancreatic hormone amylin, has been associated with reduced appetite and food intake.⁹⁰ In a RCT with subcutaneous administration of pramlintide over 16 weeks, an average of 3.7% weight loss was achieved with 31% of patients achieving a ≥5% weight loss (P < .001). Pramlintide has also been tested in a variety of fixed-dose combinations such as metraleptin.⁸⁴

For canagliflozin the information available is very limited. One published trial published in 2012 reports that canagliflozin reduced HbA1C levels more than placebo and for higher dosing (200 and 300 mg) the reduction was larger than for sitagliptin.⁹²

Other agents that regulate appetite include gut hormones such as ghrelin, cholecystokinin, peptide YY and oxyntomodulin.⁵³ However, when given as infusion PYY3–36 to lean and obese individuals it was associated with nausea and increased postprandial glucose⁸⁴ although there might be advantages when used in combination with oxyntomodulin, which has a glucose level-reducing effect.⁹³

Ghrelin, an amino acid peptide which stimulates food intake and inhibits insulin secretion, has been tested in studies but they were inconclusive.⁹³ It is not clear whether it can be used
in the future for weight reduction. Similarly, cholecystokinin (CCK), a gastrointestinal hormone secreted from the I-cells, has been studied but has not shown success.

A recently developed co-agonist comprising of a single molecule with the combined property of activating both glucagon and GLP-1 receptors such as glucagon analogues with additional GLP-1 receptor agonistic activity has been tested in animals. When they were PEGylated and administered over a month long period in mice they showed body weight reduction and improved glucose tolerance.\(^9^3\)

Several analogues of oxyntomodulin, a peptide and an agonist both for GLP-1 and glucagon receptors, are in preclinical development.\(^9^3\) Overall, apart from the agents mentioned above, peptide agents mimicking satiety hormones have not demonstrated efficacy. It is hoped that better delivery formulations will provide more promising candidates for the treatment of obesity.

Another avenue to develop new therapies for obesity is the combination of gut hormones analogues in an attempt to mimic the physiological fed state using combination of gut hormone analogues. It has been found that after gastric bypass surgery the gut hormones including PYY and GLP-1, are elevated.\(^9^4\) A study administrating analogues of PYY and GLP-1 after infusion reported that the individuals had a 27% reduction in energy intake which was not observed with administration of these agents individually.\(^9^4\)

### 5.3 Other agents currently tested

Most ahead in the development is cetilistat which has a very similar acting mechanism to orlistat. Table 6.18.6 provides an overview of newer agents currently being tested in addition to cetilistat. Not much is known about them as some of them are still in the pre-clinical development phase.\(^8^6\)

<table>
<thead>
<tr>
<th>Candidates</th>
<th>Type of class</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetilistat</td>
<td>Non-systemic lipase inhibitor</td>
<td>Potentially improved tolerability</td>
<td>Dry mouth, GI disturbances and insomnia, potential for heart rate and blood pressure increases</td>
</tr>
<tr>
<td>Tesofensine</td>
<td>NeuroSearch’s monoamine reuptake inhibitor, modulates appetite and increases metabolic energy expenditure and fat metabolism</td>
<td>Potentially least twice the level of weight loss of currently available drugs</td>
<td></td>
</tr>
<tr>
<td>Velneperit</td>
<td>Oral neuropeptide y5 antagonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obinepitide</td>
<td>7TM Pharma’s synthetic analog of Pyy3-36 and pancreatic polypeptide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6. What are the opportunities for research into new pharmaceutical interventions?

6.1 Non-pharmacological interventions

With respect to non-pharmacological intervention, comprehensive prevention strategies are needed to improve diet and increase physical activity. Many country-wide programmes have been launched, including programmes in schools.9 There is an increasing sense that changing behaviour needs to be integrated with strategies to modify the environment.40

There is continuing discussion on whether price policies including taxation and subsidies are an effective mechanism to promote healthier food choices. Some argue that consumers, instead of choosing healthier foods, would prefer to buy other unhealthier food as a result of pricing policies.33 Another argument is that taxes on food are regressive in that they have a greater effect on the poor. However, it has been pointed out that the revenue generated will disproportionately benefit the poor. Some believe that a better way to change consumer behaviour is to make unhealthy food less easily available (for instance, not offering them right next to the check-out in a supermarket). More social marketing of healthier food choices by linking them to fictional characters or making them more attractive might be more effective at reaching children and parents than prohibitive measures.95 Using the example of Denmark, the tax on food rich in fat, was abolished in 2013 for a variety of reasons including that some consumers bypassed the intended reduction in butter consumption by crossing the country border to neighbouring countries to do their shopping.35 There were also commentaries that it was to appease business in an already weak economy.95 The evidence base seems not yet sufficient to evaluate the chances of success of a well-designed, well-marketed food tax.96

There are a series of aspects which are unresolved. With respect to life-style interventions, very little is known about who is most likely to respond to them. In the USA, around 40% of adults state that they want to lose weight but only very few are successful in losing significant weight on a long-term basis.21 In general, addressing inequality related to obesity remains difficult. Inequality does not only play a role in non-pharmaceutical inventions but also in accessing pharmaceutical and surgical interventions.

With regard to child obesity, raising public awareness through the media and more informative labelling of food might have a positive effect on energy balance.16 There is likely to be more leverage that can be used to promote healthier food choices in the media.

6.2 Pharmacological interventions

At present there are very large unmet medical needs for safe and effective pharmacotherapeutic interventions for the treatment of overweight and obese patients.87 Despite the fact that the centrally acting agents have a much higher risk of side effects, several of these are still considered good candidates, as they are expected to show larger effect size (e.g. the combination of zonisamide plus bupropion).
In 2012, the FDA deliberated on the assessment of cardiovascular safety of anti-obesity medication, since this has shown to be of major concern in many medicines marketed or applying for market authorization over the last decade. This will potentially result in an updating of the current guidance on the appraisal of weight-loss products and subsequently to different criteria for the benefit-risk assessment of those products.

6.3 Surgical interventions

So far, it has been argued that it is not feasible to treat all patients requiring surgery due to costs and risks of complications. For instance, in 2010 out of one million severely and morbidly obese people in the United Kingdom there were an estimated 230,000 people eligible for surgery; however, fewer than 2% of these patients actually received this treatment, one reason being the current limited capacity to perform the surgery. In the USA, 15% of the adult population would be eligible for bariatric surgery given current guidelines. However, it is important to develop robust pricings for bariatric surgery procedures to more accurately estimate the direct and indirect costs of the interventions including pre-operative and post-operative management.

Finally, biomarkers and genetic profiling might be useful to identify those who will be most successful in benefitting from life-style interventions, even in the short-term. More research is needed in this field.

In summary, while about 33% of individuals with BMI of 30 or more obtain some benefit from lifestyle interventions, the challenge remains to identify the profile of those who will be successful, even in the short-term. The development of biomarkers may prove useful in this regard. It is not clear who will benefit from what type of surgery; better tailoring is needed and this requires more intervention research. At the same time there is need for health care management, which is more integrated between primary and tertiary care, surgical and medical care where obese patients can be managed by a multidisciplinary care team including rehabilitation, nutrition and mental health.

7. Feasibility of closing the gap in the next 5 to 10 years worldwide and in Europe?

Given the current level of the epidemic, there are many millions of patients that are eligible for treatment resulting in an enormous level of unmet clinical need.

Dealing with the causes at the same time as the consequences is relevant. The key will be to make our environment less obesogenic. As mentioned before, at a population level there is no exemplar which leads the way to reverse the epidemic of obesity at country level. There are political and ethical questions around the governmental mandate to steer individual choices.

There are many avenues that are currently being explored in developing new pharmacotherapy for the treatment of obesity. It seems that it is not only the research and
development part that needs to be taken into account when promoting investment into developing new pharmacotherapeutic options but also the way in which regulatory decisions are made. Some authors have argued that regulatory decision-makers are perhaps too restrictive when it comes to evaluating medicinal products for obesity given the large unmet need for treatment.98

With respect to pharmacotherapy in children and adolescents it has been argued that as long as there is a lack of efficacious medicines for clinically substantial weight loss, priority should be given to a model that is targeting those with the greatest metabolic risk. Long-term studies of pharmacotherapeutic interventions are needed to determine their benefit-risk profile; at present there is a lack of high quality evidence from long-term studies, both in terms of efficacy and of safety of pharmacological agents.82 There are safety concerns in terms of severe liver disease related to orlistat.99 Currently there is a lack of options with proven efficacy in practice for child obesity.100

Key problems with bariatric surgery are the low number of procedures done in comparison to the scale of the problem and the perception of the public (reluctance to finance the intervention and labelling obesity as an individual problem and choice).68

8. Conclusions

As a chronic and multi-factorial condition, obesity will be near the top of the public health agenda globally for many years to come as quick solutions are not within sight. The complexities of factors that are at play influence the epidemic (national wealth, government policy, cultural norms, the built environment, genetic and epigenetic mechanisms, and biological bases for food preferences and biological mechanisms that regulate motivation for physical activity) and require a very comprehensive package of strategies, a large stakeholder involvement and a long-term perspective. Scaling up effective interventions at national level and evaluation of their effects on sustainability and equity will be a priority. There is a need to develop and better target intervention strategies.

Pharmacotherapy has not yet played a large part in reducing the burden of the disease, as effect size is small or benefit-risk profiles of different products have not been regarded as acceptable assuming that the products will be used by a large and diverse group of the population. Even though surgery for obese adults has been regarded as cost-effective in a variety of settings, only a small proportion of those in need have received surgery, one major factor being the capacity of health services to carry out the intervention as well as to provide pre- and post-operative care.

Since existing non-invasive therapeutic options have only a moderate effect on reducing obesity-related illness and deaths, there may be an opportunity to develop effective and affordable treatment for those affected by obesity in Europe and worldwide.

More research is needed on adherence and the regaining of body weight after discontinuation of pharmacotherapy in order to better evaluate its cost-effectiveness.8 Research is also needed into the long-term savings of surgical interventions.
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Even though the current emphasis on prevention at population level should be the focus to combat the epidemic, there is a large unmet need for effective treatment for those affected when lifestyle changes are insufficient.

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### Appendix 6.18.1: Cost-effectiveness for selected interventions evaluated in Australia

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Target population</th>
<th>Strength of evidence</th>
<th>DALYs saved</th>
<th>Gross cost (A$ million)</th>
<th>Net cost per DALY saved (A$ million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unhealthy food and beverage tax (10%)</td>
<td>Adults</td>
<td>4</td>
<td>$590,000</td>
<td>18.00</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>Front-of-pack traffic light nutrition labelling</td>
<td>Adults</td>
<td>5</td>
<td>$3,100</td>
<td>8.00</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>Reduction of advertising of junk food and beverages to children</td>
<td>Children (6-14 years)</td>
<td>2</td>
<td>$7,000</td>
<td>0.13</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>School-based education programme to reduce television viewing</td>
<td>Primary schoolchildren (5-10 years)</td>
<td>3</td>
<td>$590</td>
<td>27.70</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>Multi-faceted school-based programme including nutrition and physical activity</td>
<td>Primary schoolchildren (5-8 years)</td>
<td>3</td>
<td>$8,000</td>
<td>40.00</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>School-based education programme to reduce sugar-sweetened drink consumption</td>
<td>Primary schoolchildren (7-11 years)</td>
<td>3</td>
<td>$3,000</td>
<td>3.30</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>Family-based targeted programme for obese children</td>
<td>Obese children (10-11 years)</td>
<td>1</td>
<td>$2,000</td>
<td>11.00</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>Multi-faceted targeted school-based programme</td>
<td>Overweight/obese primary schoolchildren (7-10 years)</td>
<td>3</td>
<td>$2,000</td>
<td>0.56</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>Gastric banding—adolescents</td>
<td>Severely obese adolescents (14-19 years)</td>
<td>1</td>
<td>$12,000</td>
<td>130.00</td>
<td>440.00</td>
</tr>
<tr>
<td>Family-based GP-mediated programme</td>
<td>Overweight/moderately obese children (6-9 years)</td>
<td>3</td>
<td>$5,100</td>
<td>6.30</td>
<td>470.00</td>
</tr>
<tr>
<td>Gastric banding—adults</td>
<td>Adults BMI &gt;35 kg/m²</td>
<td>1</td>
<td>$14,000</td>
<td>120.00</td>
<td>580.00</td>
</tr>
<tr>
<td>Multi-faceted school-based programme without an active-physical activity component</td>
<td>Primary schoolchildren (6 years)</td>
<td>3</td>
<td>$1,000</td>
<td>51.20</td>
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<tr>
<td>Diet and exercise</td>
<td>Adults BMI &gt;25 kg/m²</td>
<td>1</td>
<td>$3,000</td>
<td>140.00</td>
<td>28.00</td>
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<tr>
<td>Low-fat diets</td>
<td>Adults BMI &gt;25 kg/m²</td>
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<td>$1,000</td>
<td>94.00</td>
<td>37.00</td>
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<td>Active After Schools Communities Program</td>
<td>Primary schoolchildren (5-11 years)</td>
<td>5</td>
<td>$450</td>
<td>40.3</td>
<td>82,000</td>
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<tr>
<td>Weight Watchers</td>
<td>Adults</td>
<td>1</td>
<td>$54</td>
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<td>Lighten up to a healthy lifestyle weight loss programme</td>
<td>Adults</td>
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<td>$38</td>
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<td>TravelSMART school</td>
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**Source:** Gortmaker et al, Lancet 2011
Appendix 6.18.2: Simplified model of the leptin signaling pathway

Source: Han et al, 2010
### Appendix 6.18.3: Comparison 1 Orlistat: Anthropometric Outcomes, Outcome 1 Orlistat: Change in Weight (%)

Review: Long-term pharmacotherapy for obesity and overweight

Comparisons: 1 Orlistat: Anthropometric Outcomes

Outcomes: 1 Orlistat: Change in Weight (%)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Control</th>
<th>N</th>
<th>Mean(SD)</th>
<th>N/R</th>
<th>Random 95% CI</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>N/R</th>
<th>Random 95% CI</th>
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<tr>
<td>Davidson 1999</td>
<td>657</td>
<td>-8.8 (10.25)</td>
<td>223</td>
<td>-5.8 (10.45)</td>
<td>5.5 %</td>
<td>-3.00 [-4.56, -1.44]</td>
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<td></td>
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<tr>
<td>Hollander 1998</td>
<td>163</td>
<td>-6.2 (6.39)</td>
<td>159</td>
<td>-4.3 (6.3)</td>
<td>6.7 %</td>
<td>-1.50 [-3.28, -0.52]</td>
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<tr>
<td>Hauptman 2000</td>
<td>210</td>
<td>-7.9 (11.48)</td>
<td>212</td>
<td>-4.2 (8.74)</td>
<td>4.0 %</td>
<td>-2.70 [-5.64, -1.76]</td>
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<td>Beirne 2004</td>
<td>111</td>
<td>-5.5 (5.97)</td>
<td>109</td>
<td>-1.8 (5.97)</td>
<td>5.5 %</td>
<td>-1.40 [-3.47, -0.12]</td>
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<td>Broom 2002</td>
<td>259</td>
<td>-5.8 (7.8)</td>
<td>263</td>
<td>-2.3 (6.2)</td>
<td>8.0 %</td>
<td>-4.00 [-4.71, -2.29]</td>
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<tr>
<td>Fixer 2000</td>
<td>110</td>
<td>-8.5 (10.5)</td>
<td>108</td>
<td>-5.4 (9.35)</td>
<td>2.3 %</td>
<td>-3.10 [-5.74, -0.46]</td>
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</tr>
<tr>
<td>Kelley 2002</td>
<td>266</td>
<td>-3.76 (4.24)</td>
<td>269</td>
<td>-1.22 (4.92)</td>
<td>12.9 %</td>
<td>-2.54 [-3.32, -1.76]</td>
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<td>Krempf 2003</td>
<td>346</td>
<td>-5.4 (11.16)</td>
<td>250</td>
<td>-2.6 (9.35)</td>
<td>5.8 %</td>
<td>-1.60 [-3.93, -0.01]</td>
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<td>Lindgarde 2000</td>
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<td>-5.9 (5.5)</td>
<td>186</td>
<td>-4.6 (5.4)</td>
<td>9.0 %</td>
<td>-1.10 [-2.40, -0.20]</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Miles 2002</td>
<td>250</td>
<td>-4.6 (4.74)</td>
<td>254</td>
<td>-1.7 (3.19)</td>
<td>13.9 %</td>
<td>-2.90 [-3.91, -1.90]</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rossner 2000</td>
<td>242</td>
<td>-9.7 (6.3)</td>
<td>237</td>
<td>-6.6 (6.8)</td>
<td>8.3 %</td>
<td>-3.00 [-4.27, -1.39]</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sjostrom 1998</td>
<td>343</td>
<td>-10.2 (7.4)</td>
<td>340</td>
<td>-6.1 (6.45)</td>
<td>9.6 %</td>
<td>-4.10 [-5.14, -0.06]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swinburn 2005</td>
<td>170</td>
<td>-4.4 (6.6)</td>
<td>169</td>
<td>-0.9 (3.9)</td>
<td>8.5 %</td>
<td>-3.50 [-4.86, -2.13]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>3317</td>
<td>2879</td>
<td>*</td>
<td>100.0 %</td>
<td>-2.93 [-3.35, -2.50]</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.21, Chi² = 189.7, df = 12 (P = 0.00), I² = 37%

Test for overall effect: Z = 13.45 (P < 0.00000)

Source: Padwal et al, 2009

6.18-37
Appendix 6.18.4: Different forms of bariatric surgery

**Figure 1**
Gastric banding: An adjustable gastric band is used to divide the stomach into a small proximal compartment (pouch) and a larger distal compartment (residual stomach).

**Figure 2**
Roux-en-Y gastric bypass: The stomach is taken down a few centimeters distal to the gastric inlet. The jejunum is divided 50 cm beyond the ligament of Treitz, and its aboral end is connected to the small gastric pouch. Some 150 cm distal to this point, ...

**Figure 3**
Sleeve gastrectomy: More than 80% of the stomach is resected, and the gastric remnant is tubularized, with an initial filling volume of less than 100 ml. Mechanism of effect: restriction and hormonal mechanisms.

**Figure 4**
Biliopancreatic diversion (BPD) with duodenal switch (DS): First, the stomach is reduced in size as in sleeve gastrectomy. Next, the duodenum is divided distal to the pylorus, and the jejunum is divided 250 cm proximal to the ileocecal valve and anastomosed ...

Source: Runkel et al, 2011
Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper
Written by S. van Weely, Ph.D. and Prof. H.G.M. Leufkens

Background Paper 6.19
Rare Diseases

By R. de Vrueh, Ph.D., E.R.F.Baekelandt, and J.M.H. de Haan
12 March 2013
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Abbreviations

COMP, Committee on Orphan Medicinal Products
DALY, Disability Adjusted Life Years
EMA, European Medicines Agency
EPPOSI, European Platform for Patients’ Organisations, Science and Industry
EU, European Union
EuroBioBank, European Network of DNA, Cell and tissue banks for rare diseases
EUROCAT, European network of population-based registries for the epidemiologic surveillance of congenital anomalies
EURODIS, European Organisation for Rare diseases
EUROSTAT, Statistical Office of the European Communities
FDA, Food and Drug Administration
ICD, International Classification of Diseases
ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
NIH, National Institutes of Health
NORD, National Organization of Rare disorders
ODA, Orphan Drug Act
OOPD, Office of Orphan Products Development
ORD, Office of Rare Diseases
ORPHANET, database dedicated to information on rare diseases and orphan drugs
PKU, PhenylKetonUr ia
QALY, quality adjusted life years
SME, Small and Medium-sized Enterprise
USA, United States of America
WFH, World Federation of Haemophilia
WHO, World Health Organisation
Executive Summary

A disease is considered rare when it affects one person out of 2,000 or less. They are between 5,000 and 8,000 rare diseases, most of them genetic. A very rough estimate would be that in the world, one person out of 15 could be affected by a rare disease, this represents 400 million people worldwide of which 30 million Europeans and 25 million Americans. Rare diseases are serious chronic diseases, and are often life-threatening. While most genetic diseases are rare diseases, around 20% of rare diseases are not caused by genetic defects. There are very rare infectious diseases for instance, as well as auto-immune diseases and very rare poisonings. To date, the cause remains unknown for most rare diseases. This makes rare diseases truly a global health issue. In recent decades, considerable attention has been paid worldwide to stimulate the research, development and marketing of medicinal products for rare diseases. In the United States over 400 products have been approved as therapy in more than 200 rare diseases indications and in EU over 70 products for around 45 indications. Many orphan medicinal products are innovative, biotechnological products. Apart from treatments coming available, the introduction of various (research) programmes and networks has advanced understanding and diagnosis of rare diseases as well.

Despite this positive development overall the rare disease burden continues to persist. This persistence is due to lack of knowledge/training, lack of or delayed diagnosis, limited disease understanding, lack of treatment, and lack or limited access to therapy or medical care. Being a complex and heterogeneous mosaic of an estimated 5,000-8,000 conditions, it has become clear that the research need can differ considerably between groups of rare diseases:

Lack of disease understanding: need for fundamental research into disease process

For many rare diseases basic knowledge, like cause of the disease, pathophysiology, semiology, natural course of the disease and epidemiological data is limited or worse, missing. This significantly hampers the ability to both diagnose and treat these diseases. To address this challenge public funding of fundamental biomedical research into the disease process is necessary both at national and at international/European level. While only a small number of pharmaceutical companies are engaged in investing in fundamental research for rare diseases, public-private partnerships are key in view of new therapy development.

Patients with rare diseases are scattered across countries with the consequence that medical expertise on each of these diseases is a scarce resource. Most physicians will never heard of most rare diseases and even less have a chance to diagnose an affected patient. Fragmented knowledge about such diseases, and often limited access to research material (biological samples, mice models, etc) means it is critical that investments in fundamental research go hand-in-hand with investments in dedicated infrastructure and international networks (biobanks, registries, networks of expertise etc). Where needed, these networks can also provide effective medical education and opportunities to train health professionals on rare diseases.

Equally important is the availability of an an appropriate and internationally recognised rare disease classification system which will help generate reliable epidemiological data. Such a system would provide a useful basis for further research into the natural history and causes of rare diseases, allows monitoring of safety and clinical effectiveness of therapies and
measuring quality of care. Several systems are currently considered suitable for coding rare diseases diagnosis: International Classification of Diseases-11 (ICD11; currently in Beta phase), the Orphanet classification, OMIM (Online Mendelian Inheritance in Man) and SNOMED CT (Systematised NOmencature of Medicine – Clinical Trials). Each system has its advantages and disadvantages, and important questions remain unanswered with regard to funding and maintenance of such a system.

Translation of disease understanding into product development or healthcare innovation is hampered

Ongoing fundamental research into the disease process (etiology, genetics, pathophysiology, natural history, etc) will result in more targets for pharmaceutical intervention or healthcare innovation for rare diseases. It can enable the development of new molecules, it also allows researchers to revisit existing drug libraries with fresh knowledge, or to repurpose well known molecules for a specific rare disease. An analysis of designated and approved orphan medicines in the USA and EU revealed that treatment of rare diseases were mainly developed in the field of oncology followed by metabolism. The translation of research into product development or healthcare innovation is not happening equally across all disease categories. It is important to understand the factors that are responsible for this imbalance and the role of a persisting limited interest from industry in certain disease areas. Public funding of translational research, including proof of concept studies, might act as a catalyst to translate rare disease research into the development of new medicines. Making a disease easy to diagnose at an early stage will allow the development of prevention strategies that even in the absence of a underlying treatment can have a significant positive impact on a patient’s life. Diagnosis and prevention strategies represent important tools in reducing the burden of rare disease. Phenylketonuria (PKU) is a classical example where newborn screening allows successful therapeutic intervention through a strict diet or through sapropterin dihydrochloride (Kuvan® ) in conjunction with diet that dramatically modify the patients prognosis.

For some rare diseases, translation of research into product development or healthcare innovation has taken place, but further development is hampered.

A key issue with rare diseases is that they present with fundamentally different challenges than more common diseases, like asthma or diabetes. This is most apparent during the clinical development stage where rarity significantly complicate the task. Problems include the small number of patients, the logistics involved in reaching widely dispersed patients, ethics (e.g. use of placebo), lack of validated biomarkers and surrogate end-points, poor diagnostics, limited clinical expertise and expert centres.

Clinical trial-funding programmes (e.g. FDA Orphan Products Grant Program, EU Seventh Framework Programme (FP7)) remain essential for orphan drug development. Such programmes are especially important for rare diseases that appear less attractive for the pharmaceutical industry. Critical for marketing authorization and reimbursement is the acceptance of the evidence generated during the drug development. Due to the high medical need, a treatment can become available at an early stage where evidence is robust but limited. This represents a significant hurdle for some methodological assessments and developing alternative methods in small and very small populations is desirable. Similar to fundamental research, large multidisciplinary networks should be funded to stimulate
collaboration between all interested parties and bring together medical experts, reference centers, and patients’ groups for rare diseases. This infrastructure is necessary for performance of clinical trials for rare diseases and subsequent monitoring of the newly authorized products.

A whole new generation of more targeted therapies, like stem cell therapies, gene therapies or therapeutic gene modulations (exon skipping, antisense drugs, RNA interference) is in development and new products are becoming available. To allow these targeted therapies for smaller patient groups to become more common practice in the future, it is critical to continue funding the research and development of these highly innovative therapies through specific budgets or public-private partnership (PPP) programs. The first clinical proof of concept study of alipogene tiparvovec (Glybera®), the first gene therapy product approved in the EU, was partially funded through a translational research programme of the Netherlands Organisation for Health Research and Development (ZonMw).

The use of optimized delivery methods (such as controlled or site-specific delivery) for existing orphan drugs could be of significant benefit for patients with rare diseases. These methods entail an improved pharmacokinetic profile of existing orphan drugs, and consequently an improved efficacy, safety profile or convenience for the patient. Despite these apparent advantages, innovative drug delivery systems remain underused in the area of orphan drugs. The ability to measure the added value these innovative drug delivery methods bring to patients and/or the health care system are critical to justify the additional developments costs for industry and the willingness for payers to fund the treatment. Examples of innovative drug delivery systems are: alternatives for intravenous administration, controlled delivery systems, and site-specific drug delivery.

Another opportunity for research in pharmacological intervention for rare diseases is to pursue the development of molecules that are running out of patent protection, but have demonstrated potential with a favorable benefit/risk ratio for treating a rare disorder. This is known as drug repurposing. The advantage is that more is known about these molecules and that knowledge can be leveraged in a new development programme.

Although the main focus of this chapter is on developments in Europe and the USA, the aforementioned research initiatives to improve treatment and care of rare diseases have the potential to make a difference in the lives of rare disease patients around the world.

Ultimately the continuous support of human society to allocate resources to more vulnerable patient population is critical for research efforts to bear fruits and for new treatments to benefit patients.

CONCLUSION

In the area of rare diseases, there are many opportunities for the EU to build on the successful programmes, projects and networks that have been supported so far. The most important ones that should continue to be supported are:

- Networks of excellence that focus on research infrastructure (e.g. registries) as well as provision of disease-related information at EU level and beyond (guidelines, diagnosis, patient experience)
Update on 2004 Background Paper, BP 6.19 Rare Diseases

- Initiatives that focus on rare disease classification
- Fundamental research into the disease process to increase rare disease understanding
- Incentives for development of therapeutics (e.g. clinical trial-funding programmes)
- Assessment methods adapted to small and very small patient populations (e.g. marketing authorisation and reimbursement).

In addition, more support is needed for:

- Translational research to increase translation of disease understanding into drug development or healthcare innovation (e.g. NIH bench-to-bedside grants)
- Innovative diagnostic methods of rare diseases to enable early intervention
- Research, infrastructure as well as implementing guidelines for medical and psychosocial care for rare diseases. This would be especially beneficial for those patients for whom underlying treatment is not yet available.
- Incentives for development of preventive strategies and validated diagnostic techniques
- Incentives to leverage existing knowledge and optimize the use of existing drugs (innovative drug delivery systems and drug repurposing).
- Giving easy access to available healthcare (diagnostic, medical, pharmacological or other types of care) to patients regardless of where they live.
1. Introduction

In 2004, Warren Kaplan and Richard Laing authored a report called Priority Medicines for Europe and the World. Within the report there is a section on Orphan Diseases and in addition there is an extensive background paper written by Sonja van Weeley and Bert Leufkens. ([http://archives.who.int/prioritymeds/report/background/rare_diseases.doc](http://archives.who.int/prioritymeds/report/background/rare_diseases.doc)) This 2013 background paper builds on this previous work.

Terminology concerning, orphan, rare and neglected diseases has evolved when the previous background report was published. In the 1980s and 1990s particularly in the USA, the term “orphan diseases” was commonly used to designate diseases that because they were only affecting a small population, saw no investments to find a diagnosis and a cure. Recognizing these facts led to ground breaking legislation. In the late 1990s the term “neglected diseases” was promoted which referred to tropical infectious diseases that existed in substantial numbers in remote poor areas of low income countries and hence suffered from the same lack of investments. These diseases are the subject of another background paper (Chapter 6.9) and are not addressed in this background paper. Rarity is the key concept on which the orphan diseases definition rests, rarity either in terms of absolute numbers of patients in the USA or in rates of prevalence in Europe and other countries. This mean that all types of diseases below a certain frequency threshold regardless of their etiology, symptoms or age of onset are covered by the definition. The definition clusters a mosaic of diseases like genetic disorders, rare cancers, autoimmunological disorders or infectious diseases. Today the term “rare diseases” is preferred and used in existing legislation. The term incorporates orphan diseases. This background paper on rare diseases should be considered as the successor to the 2004 background paper on orphan diseases. For medicines, the term orphan drugs is used in the USA and in Europe the regulation is talking about orphan medicinal products.

Rare diseases are a complex and heterogeneous mosaic of an estimated 5 000-8 000 conditions.1 For many of these diseases we do not know what the appropriate medical interventions are. A rare disease is, according to the European definition, a life-threatening or chronically debilitating condition from which not more than five persons per ten thousand citizens in the European Community suffer.8 In other regions, a somewhat different definition is used, e.g. in the USA a disease is called rare when less than 200 000 inhabitants suffer from this disease. It is estimated that about 30 million Europeans in 27 EU-countries and 25 million Americans suffer from a rare disease.1

While medicine was making striking progress in understanding pathology and in developing evidence based treatments for more common diseases, patients suffering from rare diseases were left behind underrecognized, non diagnosed or with limited treatment options. Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients with more frequently occurring disorders (Regulation EC 141/2000; preamble 7, article 3.1b).9 Therefore, more attention has been paid worldwide over the last few decades to stimulate the research, development and bringing to the market of orphan medicinal products. "Orphan" drugs are medicinal products intended for the diagnosis, prevention or treatment of rare disorders.
Examples of rare diseases

Some rare diseases are actually known to the general public. Examples of the best known rare diseases may be cystic fibrosis, sarcoidosis, haemophilia, phenylketonuria (PKU) and severe acute respiratory syndrome (SARS). But in general, most names of rare diseases are totally unknown to the general public like primary ciliary dyskinesia, Darier disease, erythropoietic protoporphyria, Smith-Lemli-Opitz syndrome, Usher syndrome, alkaptonuria and many others.

Sometimes, rare diseases are especially frequent within a region or a specific ethnic group. For example thalassaemia is rare in Northern Europe but more frequent in the Mediterranean area and Gaucher type 1 disease is most prevalent within the Ashkenazi Jewish population.

Diseases may be rare in a specific area (e.g. Western Europe) whereas it is not rare in another. A typical example of this are infectious diseases like certain types of tuberculosis and malaria. Populations migrations will also influence the incidence and prevalence of diseases. For example nowadays a haemoglobinopathy typical for African-like sickle cell anaemia, is becoming more frequent throughout Europe.

Rare diseases can be grouped by affected organ systems or other pathological characteristics e.g. neuromuscular diseases, inborn errors of metabolism (like lysosomal storage disorders, peroxisomal disorders and mitochondrial disorders), chromosomal disorders, rare forms of cancer, etc.

Specific legislation has been set up in various jurisdictions across the globe to provide incentives to attract investment in Research & Development and marketing for orphan medicinal products.\(^6\)\(^10\)

In the United States over 400 orphan medicinal products for more than 200 indications and the EU over 70 orphan medicinal products for more or less 45 indications have been approved as therapy for a rare disease.\(^3\)\(^4\)\(^11\) These numbers demonstrate that introduction of specific orphan drug legislation has been successful in stimulating orphan drug development and making therapies for patients with rare diseases available. Apart from pharmacological treatments coming available, the introduction of various (research) programmes and networks has advanced understanding, diagnosis and quality of care of several rare diseases.\(^12\)\(^13\)\(^14\)\(^15\)

A recent special Eurobarometer focussed on European awareness of rare diseases revealed that “Europeans have a relatively accurate understanding of what rare diseases are but detailed knowledge and awareness remain low”. Moreover, in the same survey strong support for policy initiatives linked to rare diseases at both national and European level was expressed.\(^16\)

However, despite the growing number of approved orphan drugs, enhanced rare disease understanding and improved public awareness of rare diseases in the last the decade, many gaps remain. In this background paper, we will present the need for additional initiatives to develop pharmacological interventions for the unmet medical needs and to make them
equally accessible to the biggest number of patients with a rare disease. We will also touch upon the need for health care innovations and their implementation in clinical practice. Both ways may progress at different speed but are complementary and critical to steadily improve the quality of life of rare disease patients.

Although the main focus is on developments in Europe and the USA, rare diseases are not confined to Europe and the USA. Rare diseases affect people all over the world, and are a true global health issue. Additional initiatives to improve treatment and care of rare diseases have the potential to make a difference in the lives of rare disease patients around the world.

2. What Is the Size and Nature of Disease Burden?

According to the European definition rare diseases are not only rare but also life-threatening or chronically debilitating conditions. An estimated 80% of rare diseases have a genetic origin, being either monogenic or polygenic. The other rare diseases may for instance be rare infectious diseases, rare cancers or rare auto-immune diseases. The 30 million Europeans and 25 million Americans suffering from a rare disease coincide with six to eight per cent of the total population.1

The reliability of epidemiological data has improved, but remain inadequate for most of the rare diseases to give firm details on the number of patients with a specific rare disease. In 2013 the impact and burden of disease is beginning to receive more attention from investigators in public health and are better funded at national and European level.

However today we still miss reliable quantitative data for the burden of disease even if it is generally known that people with a rare disease can suffer significantly.19,20,21 Most rare diseases manifest during childhood; about 30% of affected children die during infancy, and the health and economic burden on survivors can be tremendous.21 In 2002, a retrospective survey by Dionisi-Vici et al. showed that the incidence of inborn errors of metabolism was 1:6 200 in newborn babies in Italy20 and that only 11% reached adulthood. The authors concluded that inborn errors of metabolism constitute a highly heterogeneous category of rare diseases, representing a relevant cause of morbidity and mortality in childhood.

For some monogenetic rare diseases not only the burden for the patients themselves but also in some regions the burden for the society is significant, like for thalassemia and sickle cell anaemia.19

Also childhood cancers are rare diseases with potentially dramatic outcome. One estimate that in European countries, one out of 500 children are diagnosed with cancer before the age of 15.21 As epidemiologic information on rare cancers was scarce, the project Surveillance of Rare Cancers in Europe (RARECARE) was funded by the EU and ran between 2007 and 2010.22,23 The aim of the project was to provide estimates of the incidence, prevalence and survival of rare cancers in Europe. First estimate of the rare cancer burden is that 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.
In particular for rare cancers, but also inborn errors of metabolism a considerable number of Orphan Medicinal Products (OMPs) are in development or have been approved. Although perhaps coincidentally, the availability of epidemiological data for these groups of diseases may have contributed to this development.

The research focus is not only on groups of rare diseases, but also on the burden of specific rare diseases, like scleroderma and immune thrombocytopenic purpura. Attention is also paid to the impact of diagnosis on the caregivers well being and on the family economic income. In April 2010 BURQOL-RD, a three year project under the Second Programme of Community Action in the Field of Public Health, commenced. The main aim of BURQOL-RD is to generate an integrated and harmonized set of instruments to quantify the socioeconomic costs and Health Related Quality of Life (HRQOL), of both patients and caregivers. Ten rare diseases were selected with a Delphi approach to run a representative pilot survey in eight European countries. Also included is “a detailed analysis of the services (health and social care) received by people with specific rare diseases in different EU countries, including the identification of formal and informal care”. Results and deliverables will be shared with relevant stakeholders, like patient associations, policy makers and medical community and is anticipated to stimulate the future comparability and monitoring of rare diseases care in Europe.

An appropriate and internationally recognised rare disease classification system is critical in making rare diseases more visible in health information systems and consequently provide reliable epidemiological data from existing and future databases. Potentially, such a system will not only generate reliable prevalence/incidence data, but also constitute a useful basis for further research into the natural history and aetiology of rare diseases. It will also allow the evaluation of the economic burden of the disease, and monitoring of clinical effectiveness of therapies and measuring the quality of care. Moreover, as reliable prevalence data has to be provided to regulatory authorities in order to obtain an orphan designation, increased availability of such data for all rare diseases could represent an important preparatory step in facilitating orphan drug development.

A recent European Union Committee of Experts on Rare Diseases (EUCERD)/Eurogentest workshop identified several classification systems that are currently considered suitable for coding rare diseases diagnosis: International Classification of Diseases-11 (ICD11; currently in Beta phase), the Orphanet classification (Orphacode), OMIM and SNOMED CT. Each system has its advantages and disadvantages. ICD is a widely used clinical tool to register a patient diagnosis using a defined nomenclature. However, specific ICD codes are present for not more than 240 rare diseases (e.g. thalassaemia, cystic fibrosis, haemophilia etc.). Other rare disorders are often summed up as ‘other endocrine and metabolic disorders’. In practice, the existing ICD system cannot be used for specific rare diseases. It is expected that ICD-11 will improve the breadth of coverage, but it will not fully overcome this problem. The SNOMED CT is the most comprehensive disease terminology system. It is intended to be used in electronic health records to code the health status of patients; but as system designed to be comprehensive for common occurrences it has some shortcomings when it comes to rare diseases. In contrast to SNOMED CT, the Orphanet classification system is entirely dedicated to rare diseases and requires acceptance in national health record systems. Finally, OMIM is the standard coding system for genetic phenotypes widely used for that purpose.
Recommendations by the experts present at the workshop were to continue to focus on ICD11 meeting the needs of the RD community as much as possible. Second recommendation was to set up an active collaboration with SNOMED CT to ensure that missing codes are considered for incorporation. Third recommendation was to raise the acceptance of Orphanet and OMIM codes as the standards of the rare disease community. Final recommendation was to “continue cross-referencing OMIM and Orphanet codes with the standard terminologies (ICD and SNOMED CT), as it is a quality-control exercise for all of these terminologies and as it is necessary for navigation from one classification to another.” To provide the rare disease community with tools to navigate from one database to another, the four classification systems have recently been cross-referenced by Orphanet. Further work will be required to improve these different systems of classification.

3. What Is the Control Strategy?

Representing a group of 5 000-8 000 complex and heterogeneous conditions makes the description of a specific control strategy for rare diseases extremely difficult if not impossible. The control strategy for a specific rare disease depends on the nature of the disease (genetic or non-genetic), the knowledge obtained for a specific disease, translation of this knowledge into an effective treatment, diagnostic or preventive tool or some other kind of healthcare innovation. Moreover, various socio-economic and demographic factors also play an important role.

In general, a large group of rare diseases have to be managed through care alone, because no therapy is available. Another group of rare diseases are managed through existing medical treatment combined with care. Finally, with new therapies becoming available a growing group of rare diseases are managed through some form of intervention.

For several (mono)genetic rare diseases prenatal and/or newborn screening is possible. In case a high risk for genetic disorders is known prenatal screening is in many cases possible and performed in clinical genetic centres or in other referral centres. In case of the general population, many countries screen newborns for certain metabolic defects. In this way early diagnosis of the defect can lead to early intervention and preventive care. Despite important technological progress that could facilitate newborn population screening a high variability exist between countries/regions in the type and number of diseases screened. This is mainly due to the lack of data on the cost effectiveness and the ethical implications of the screening strategies.

An effective control strategy for a single disease will depend on a combination of three strategies: an effective early diagnosis, the development of optimal care including preventive care and the availability of a drug or another therapeutic interventions. As explained in the examples below, the importance gained by each strategy will vary per disease.

The impact of early diagnosis is best exemplified by classical phenylketonuria (PKU). This inherited metabolic disease is characterized by an inability of the body to utilize the essential amino acid, phenylalanine, due to a deficiency of the enzyme phenylalanine hydroxylase. Without this enzyme, phenylalanine and other biochemical products accumulate in the
blood and body tissues. The excess phenylalanine is toxic to the central nervous system, and results in mental retardation and other neurological problems when left untreated. When a very strict diet is begun within the first few weeks of life and is well-maintained, affected children can expect normal development and a normal life span. Recently a pharmacological treatment (sapropterin dihydrochloride, Kuvan®) stimulating the residual enzyme activity and lowering the phenylalanine blood levels became available to use in conjunction with a restricted diet. Because of the very positive outcome when children are treated early and well, newborn screening for PKU is carried out in most developed countries.

Haemophilia remains a prime example of a rare disease for which the control strategy in developed countries has had enormous effects on reduction of morbidity, burden of disease and prevention of mortality. Haemophilia is an X-linked inherited coagulation disorder due to a partial or total lack of an essential coagulation factor. Haemophilia A is the most common form, referred to as classical haemophilia, and is the result of a partially or complete deficiency of coagulation factor VIII; haemophilia B is caused by a deficiency in activity of Factor IX. It is a chronic disorder affecting mostly males, characterised by internal bleedings in joints (ankle, knee, elbow, shoulder and hip), in muscles and soft tissue. Without treatment the bleedings causes malformation of the joints and chronic disability. The patients have a low quality of life and usually die in childhood or early adult life.

Diagnosis is carried out via blood tests in which the coagulation factor can be measured and mutation analyses can be performed. Carrier detection and prenatal diagnosis is possible, but not in all cases. Preimplantation diagnostics (PIGD) gives the possibility to implant unaffected female embryos in the uterus of women who are a carrier for haemophilia, circumventing the possibility of giving birth to an affected child. However, the ethical issues concerning prenatal diagnosis and PIGD have to be taken into account.

Effective treatment for haemophilia has become available in the last forty years and consists of supplementation of the deficient coagulation factor via intravenous administration. In the first decades the coagulation factors were purified from human plasma. From the 1990’s recombinant (genetically engineered) factor VIII or IX have become available and increased safety of administration by eliminating the risk of viral contamination. When patients suffer severely from haemophilia current standard therapy includes treatment with prophylactic intravenous infusions several times a week, and additional infusions for any bleeding which may occur, or for surgery or other invasive procedures. The patients most often treat themselves at home or with help of a family member to prevent bleedings and joint disease. Monitoring of treatment usually takes place in centres of expertise with a multidisciplinary approach. Advisory guidelines have been developed for prevention and appropriate treatment. Currently under development are a number of modified versions of native clotting factors, most of which are longer acting and directed at providing an opportunity for prophylactic infusions to be administered less frequently.

Healthcare innovations and their implementation in clinical practice have proven to be an important way to improve the quality of life of rare disease patients. Cystic Fibrosis (CF) is one example of a rare diseases that has benefited from improved care and symptomatic treatment.
The disease is complex and can lead to many different complications (see Figure 6.19.1 for details). In the 1930s, life expectancy of a patient with CF was less than a year but through increased understanding and improved diagnosis and care, nowadays patients with CF can expect to live into their 30s, 40s and beyond. Medicinal products have been approved for symptomatic care e.g. treatment of bacterial infections or to help clearance of the airways. However, they are part of the overall care of patients that also include diet, exercise, infection control. This total “care” package has contributed considerably in increasing the life expectancy of a CF patient as well as improving the quality of his/her life. Patient organisations, like the CF Foundation (www.cff.org), play a key role in continuously providing patients with relevant information on the current state of care, research as well as which products are in development. The inherited chronic disease affects 70,000 people worldwide. Much is known about the disease manifestations and the natural history of the disease has been modified through optimal and preventive care. The defective gene was discovered in 1989 and more than 900 mutations have been identified. However the first medicine (ivacaftor; Kalydeco™) targeted at the underlying cause of the disease was only approved recently in 2012 for a subset of CF patients presenting the G551D mutation.37

As stated in the introduction, specific orphan drug legislation in various jurisdictions has given a significant stimulus to the development of therapies for rare diseases (see next
Update on 2004 Background Paper, BP 6.19 Rare Diseases

paragraph for an overview). The American Orphan Drug Act (ODA) was the first orphan drug regulation and came into force in 1983. An important incentive of the ODA for the pharmaceutical industry is the market exclusivity of seven years for products with an orphan designation that have got marketing authorisation. The status of orphan designation qualifies the sponsor of the product for a credit against tax, up to 50 per cent, of certain clinical testing expenses related to the use of a drug for a rare disease or condition and for protocol assistance.

Other regions have followed this policy for rare diseases and developed orphan drug regulations themselves: Singapore in 1991, Japan in 1993, Australia in 1998, and the EU and Taiwan in 2000. Each Orphan Drug Regulation has its own characteristics, both in criteria of a rare disease and in the incentives to stimulate orphan drug development (see Annex A for an overview of various regulations). In EU Regulation No 141/2000 a 10-year market exclusivity period is provided after granting of a marketing authorisation. In addition, protocol assistance, fee reductions, use of the EU centralised procedure for marketing authorisation and incentives for research into orphan medicinal products are included. To benefit from these incentives in the two largest jurisdictions, a sponsor has to apply and obtain an orphan designation for its product from the Food and Drug Administration (FDA) or European Medicines Agency (EMA)/European Commission in the USA and the EU, respectively. Products intended for treatment, diagnosis or prevention of rare diseases that fulfil a set of predefined criteria are eligible for an orphan designation.

Both EU and United States orphan legislation include a definition of the rarity of the indicated disease. In the EU, the first criterion to be fulfilled for designation as OMP requires either that the targeted rare disease does not affect more than five people per 10 000 (= prevalence criterion), or that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment (= return on investment criterion). The EU has two additional important criteria that have to be fulfilled. In the EU, an orphan designation will only be provided if the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition (= seriousness criterion). Moreover, the sponsor should establish that there exists no satisfactory method for the diagnosis, treatment or prevention of this condition, or if such a method exists, that the new product will be of significant benefit for those affected by that condition (= significance criterion). What this means is that if an approved product for the indicated disease already exists, the market exclusivity for that product (with OMP status) will end if a so-called follow-on orphan drug has a clinically relevant advantage or a major contribution to patient care. In the USA, a rare disease is defined as a disease with a maximum of 200 000 patients (equivalent to seven patients per 10 000 residents).

4. What Is the Current "Pipeline" of Products that Are to Be Used for these Particular Conditions?

The lists of designated orphan medicinal products in the various regions with specific legislation in place can be considered as the pipeline of pharmacological interventions for rare diseases. These products are investigated further in clinical trials, but have already been
recognised as potential products for rare diseases. Table 6.19.1 provides an overview of designated and approved orphan medicinal products in USA, Japan, Australia and EU (Status: June 2012)

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>OMP Status</th>
<th>OMP Market Authorisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>2609</td>
<td>403</td>
</tr>
<tr>
<td>Japan</td>
<td>269</td>
<td>173</td>
</tr>
<tr>
<td>EU</td>
<td>1000</td>
<td>70</td>
</tr>
<tr>
<td>Australia</td>
<td>231</td>
<td>62</td>
</tr>
</tbody>
</table>


The overview shows that the introduction of specific Orphan Drug legislation has facilitated the development of therapies for several rare diseases. As reported by Haffner et al. in the decade prior to 1983 fewer than ten such products came to market. The regulations have proven to be an effective strategy to attract the pharmaceutical industry, especially the small biotech industry, to find their niche in rare diseases. According to Haffner, the orphan drug act in the USA allowed the start of a number of USA-based biotechnology companies, like Genentech, Amgen and Genzyme, and the translation of rare disease knowledge into numerous highly innovative rare disorder therapies.

In the last three years we have witnessed a growing interest from larger pharmaceutical companies in orphan drugs and rare disorders. This is best exemplified by the introduction of specific rare disease units, for example at Pfizer, GSK and Sanofi who bought Genzyme in 2011, or by giving them a more prominent position in their business model, such as at Novartis. This growing interest should not be interpreted as a lack of activity by large pharmaceutical companies at all in the field of orphan drugs previously. Most companies have been involved from the start of the legislation and some drugs are indicated for rare diseases without enjoying an OMP status. They might however not have had a visible focus on rare diseases and hence their role has been slightly less prominent than SMEs.

### 4.1 USA

Since 1983 the Orphan Drug Act more than 2 600 products have been designated as orphan, and more than 400 products have been approved. Braun et al. showed that in the first 25 years of the Orphan Drug Act, 326 products have been approved that target more than 200 rare diseases and really make a difference in the lives of millions of rare disease patients. These products do not target only the more prevalent rare diseases, but also quite a number
of very rare diseases.\textsuperscript{3} In contrast, in the decade prior to 1983 fewer than ten such products came to market.\textsuperscript{6}

Although in the last decade the annual number of orphan designations has continued to grow, the annual number of orphan drugs that has been approved in the same period remains more or less constant.\textsuperscript{3} Nevertheless, the number of non-orphan drugs approved has declined in the last decade, and consequently the proportion of all drug approvals that are orphan drugs has almost doubled in the last twenty years.\textsuperscript{47} According to Cote\textsuperscript{47}, orphan medicines roughly represent one third of all newly approved drugs and biologics in the USA.

4.2 EU

In the first twelve years (2000-2012) of the EU Orphan Medicinal Product Regulation around 1 000 products were designated as OMP of which 70 have received marketing authorisation.\textsuperscript{11,4} As with the US Orphan Drug Act,\textsuperscript{6,43} the EU Orphan Medicinal Product Regulation is highly appreciated for its role in creating a favourable orphan drug development environment.\textsuperscript{4} Unlike the US, annual approval of orphan drugs in the EU in the last decade has been variable.\textsuperscript{48}

4.3 Japan

In Japan, 269 drugs were designated as orphan drugs for more than 100 diseases and 173 were approved between 1993 and 2012.\textsuperscript{11} In the first six years after the orphan legislation came into force, thirty eight percent of the designated orphan entities were biological in origin. In Japan 32\% of the orphan medicinal products were already approved in other countries when they were designated as orphan drugs in Japan. Ten drugs were developed for the first time in Japan.\textsuperscript{49}

4.4 Australia

In Australia 231 products were designated as orphan drug and 62 of them received a market authorisation in the period between 1998 and 2012.\textsuperscript{11}

5. Why Does the Disease Burden Persist?

Although therapies are becoming available, it is important to understand that the burden of rare diseases continues to persist. Of course, an obvious reason is that the number of therapies coming available is still very low compared with the total number of diseases. Another reason is that many rare diseases are chronic debilitating diseases, that are diagnosed or presented at an early age. Growing older will in general coincide with the same or even a lower quality of life. Furthermore, many of these diseases are genetic and will therefore exist for generations. There are a number of key factors that continue to have an impact on the burden of disease.\textsuperscript{50}
5.1 Lack of knowledge and training

Basic knowledge about diseases, list of available drugs, lists of specialists or consultants specialised in a given disease, are still not widely available in the world.\textsuperscript{51,52,53,54} In general, medical doctors and general practitioners are not trained in rare diseases and lack experience. The latter was confirmed in a recent report by the UK think-tank; ‘2020health’.\textsuperscript{55} Because of the sheer number of diseases (5 000-8 000) and the multiplicity of disease presentations doctors cannot be expected to know the symptoms of the many rare disorders. Most diseases names are unknown to physicians However, they can develop a sense of urgency that a specific patient with unfamiliar cluster of symptoms and complaints should be referred to a specialist. We can also expect that bioinformatics and computer assisted diagnosis will be tools to help physicians in better recognizing rare ailments.

5.2 Lack of information

Dissemination of information is a key issue in the field of rare diseases. Without information, diagnosis and treatment cannot be improved, research will not continue, the patients are not empowered and there is ineffective use of clinical resources. In 2004 a lack of infrastructure and exchange of information was reported as a considerable hurdle. However, in the last decade, American organisations like NIH, NORD and FDA, and European organizations like EURORDIS, ORPHANET and EPPOSI and various EU programmes (the EU Framework Programmes for Research and Technological Development; the EU Health Programmes) have considerably improved the infrastructure and exchange of information on specific rare diseases or general issues on rare diseases. The organizations and programmes mentioned are examples of good intra- and intercollaboration between the different stakeholders (patients, science, industry, government) and are considered successes of American and European funding.

Orphanet has contributed to the broad worldwide exchange of information on rare diseases. Currently around 5 954 rare diseases are registered on the site.\textsuperscript{56} Similarly, OMIM provides a comprehensive overview of human genes and genetic phenotypes. EURORDIS, a patient alliance, represents more than 510 rare disease organizations in 48 different countries and covers a total of more than 4 000 rare diseases (www.eurordis.org).\textsuperscript{57} Many national alliances and rare disease-specific patients organizations have evolved. These organizations are playing a key role in both providing support to rare disease patients, facilitating access to updated information on rare diseases, exchanging information and networking and stimulating scientific research.\textsuperscript{58} Moreover, they provide patients with a common voice and seriously impact national policies on rare diseases. An example of a national patient organization is VSN (Vereniging Spierziekten Nederland), a patient organization for neuromuscular diseases in the Netherlands which collaborates closely with national and international (such as Treat-NMD) partner organizations.\textsuperscript{59} These networks will require ongoing support as an organisational basis for research and the provision of information.

5.3 Lack or delay of diagnosis

Important factors that contribute to the burden of disease of rare disorders are a lack or delay of diagnosis due to a lack of awareness within the community but also because easy and reliable tests are missing. For several genetic diseases the diagnosis can be suspected by detecting biochemical changes in biological samples (enzyme activity, high or low level of
specific substances in blood or urine), the genetic defect can then be confirmed by molecular biology techniques. Some diagnosis methods are more invasive and will require organ biopsies. However, for many diseases specific diagnostic tools are still missing partly due to a lack of research and understanding on the pathophysiology of these diseases. In some cases the diagnosis is based only on clinical symptoms or made by excluding other diseases.

Over the last years, major progress in gene identification has been translated into diagnostic testing. These tests are now available internationally, through both the public and private sector genetic testing service. In 1997, Orphanet set up a database of medical laboratories. In 2011, data was collected from 36 countries and funded by the European Commission. Over the past five years, in collaboration with EuroGentest Network of Excellence (financed by the European Commission) information on quality management has been added. In 2011, 1056 laboratories offering tests for 1 811 genes were registered in Orphanet. Tests offered differ greatly between countries, highlighting the need to provide access to services in all EU countries.

These developments are promising, but it is important to understand whether they result in early and confirmatory diagnosis of rare diseases and ultimately improve patient outcome or quality of life. In a survey by EURORDIS in collaboration with 70 European rare disease organisations (EurordisCare2) several aspects concerning diagnosis were compared for eight rare diseases in 16 European countries (5 980 patients). Important findings were that “25% of patients had to wait between five and 30 years from early symptoms to confirmatory diagnosis of their disease”. Moreover, before receiving a confirmatory diagnosis, 40% of patients first received an erroneous diagnosis that subsequently led to medical interventions (surgery, medicinal treatment or psychological care). Finally, “the genetic nature of the disease was not communicated to the patient or family in 25% of cases”. This is paradoxical, given the genetic origin of 80% of rare diseases. Most importantly, “the results of the survey highlight the dilemma of rare diseases: lack of information, lack of appropriate medical training, difficulties in accessing care, and as a result, loss of confidence of patients in the health care system and the medical profession”. The aforementioned 2020 health report provides corroborative evidence that “the quality of life of those suffering with rare diseases is severely impeded”. Moreover, the report reveals that wrong or late diagnosis costs considerably more than early diagnosis and consequently requires expensive and invasive medical treatment. This again stresses the already mentioned importance of raising awareness, education, training and the right tools to help physicians in better recognizing rare ailments.

The availability of an effective intervention is a strong incentive to diagnose patients earlier in their disease course. The impact of early diagnosis has been described above for classical phenylketonuria (PKU). Like PKU many rare (metabolic) disorders are expressed early in infancy or childhood. Some of these diseases (e.g. lysosomal storage disorders like Gaucher, Fabry, several type of mucopolysaccharidosis and Pompe) are treatable and as such could benefit from early diagnosis. The introduction of multiplex technologies, in particular tandem mass spectrometry, has the potential of simultaneous multi-disease screening using a single analytical technique. It has already resulted in the inclusion of other genetic metabolic disorders in a number of national newborn screening programmes or pilot programmes. However, as stated in a recent report by the EU Network of Experts on

1 Crohn’s disease, Cystic fibrosis, Duchenne muscular dystrophy, Ehlers-Danlos syndrome, Marfan syndrome, Prader Willi syndrome, Tuberous sclerosis and Fragile X syndrome
Newborn Screening and confirmed by others it also “raises concerns about privacy and autonomy, highlighting the importance of the evaluation of ethical, legal and societal aspects.”62,66,67 Other aspects that have been reported and need to be taken into account are clinical effectiveness as well as cost-effectiveness of newborn screening.68

5.4 Natural history of the disease

For many rare diseases the etiology of the disease and physiopathology remain unknown and/or there is not much insight into the natural history of these diseases.69 There are no animal models available or in vitro and in vivo studies possible. In all those diseases, it is not possible to identify possible pharmacological/therapeutic targets. Very few diseases are well enough understood to start research for an effective treatment.

The absence of knowledge on the natural course, including cause, of a disease makes it difficult for diagnosis, especially when no diagnostic tools are available and diagnosis has to be made clinically. Furthermore, knowledge of the natural course of the disease is critical to develop clinical guidelines by the scientific societies and design valuable endpoints in clinical trials. Disease registries can play an important role in recording the natural history of the disease, for instance for research, epidemiological and post-market studies purposes. In Europe, more and more registries are now available through various initiatives by hospitals, patient organisations, pharmaceutical companies or even a combined effort.70 Orphanet nowadays provides an extensive overview of disease registries in Europe.71 The coverage of the registries reveals that registries exist at regional, national and/or international level. It also appears that registries are mostly located in Western European countries and less in Eastern European countries. Unfortunately, registries are not always compatible with each other and may not use the same coding system. Consequently, this hampers the collection of reliable epidemiological data on rare diseases across registries. Current efforts are undertaken to combine various (national) databases into larger overarching international disease registries.72 An example in this respect is Treat-NMD (Translational Research in Europe – Assessment and Treatment of Neuromuscular Disease), which not only combines many national Duchenne muscular dystrophy registries into one international database but also oversees the sharing of data with relevant stakeholders.73 Treat-NMD was initially established as a EU funded ‘network of excellence’.

5.5 Lack of treatment

As mentioned above specific orphan drug legislation in various jurisdictions has given a major stimulus to the development of therapies for rare diseases. However, recent overviews and studies also indicate that certain rare diseases are favoured. The majority of designated and approved orphan drugs in the first ten years (2000 - 2010) of the EU Orphan Drug Regulation were intended for treatment of rare diseases in the field of oncology followed by metabolism.41 Similar results have been reported for the USA.63 The latter indicates that translation of rare disease research into an orphan drug development is not equally shared between disease classes, which was confirmed by Heemstra et al.74

Designated and approved orphan medicinal products do not only target the more prevalent rare diseases, but also quite a number of less prevalent rare diseases.34 Products are on the market for less prevalent rare diseases, such as tyrosinemia type I (Orfadin®) and N-acetylglutamate synthetase (NAGS) deficiency (Carbaglu®). For other less prevalent rare
diseases, products are in development. Apparently, given the right circumstances orphan drug development for less prevalent rare disorders is feasible. The question is what drives the rare disease research process towards product development.

Heemstra et al. showed that translation of rare disease research into an orphan drug discovery and development programme is more likely for a more prevalent rare disease than a less prevalent rare disease. The latter was confirmed by Yin who reported that “the United States Orphan Drug Act has led to a significant and sustained increase in new trials among more prevalent rare diseases, but not for less prevalent rare diseases”.

A key issue with rare diseases is that they present with fundamentally different challenges than more common diseases, such as asthma or diabetes. This is most apparent during the clinical development stage where rarity significantly complicate the developers task: too small a number of patients, clinical trial logistics, ethics (e.g. use of placebo), lack of validated biomarkers and surrogate end-points, poor diagnostics, limited clinical expertise and expert centres.

Studies have shown that experience in orphan drug development is needed for a pharmaceutical company to perform a multinational clinical development programme for an orphan drug that supports a successful marketing authorization application. The same studies also indicated the importance of interaction with the regulatory authorities during development. Regulatory authorities have gained more experience with clinical trials in which a small population have been studied.

Moreover, specific legislation has been implemented in the USA and the EU to allow earlier and faster approval of medicines that treat serious diseases with a high medical need. Approaches implemented in the USA are fast track, accelerated approval and priority review. The EU has implemented similar approaches: exceptional circumstances, conditional approval and accelerated assessment. Although these approaches are not specific for orphan drugs, OMP easily qualify for these approaches as they treat chronically debilitating or life-threatening diseases that also happen to be rare. It is however really important to realize that orphan drugs do not automatically qualify for the aforementioned approaches.

There is criticism whether these approaches have been effective or optimally used in providing early access of rare disease patients to innovative therapies. In the EU several orphan drugs have been granted approval under exceptional circumstances. However, most approvals were granted in the first years of the EU orphan legislation, which suggests that granting approval of orphan drugs under exceptional circumstances has become more or less exceptional. Moreover, Boon et al. showed that neither exceptional circumstances nor conditional approval accelerated the approval process for innovative medicines in the EU. In the USA accelerated approval of therapies for rare diseases has been limited. Only one drug (agalsidase beta; Fabrazyme®) among 73 new chemical entities (NCE) has successfully followed the accelerated approval route. In their study, Miyamoto and Kakkis build a convincing case that more appropriate use of the accelerated approval route could also have a profound impact on driving therapeutic innovation for rare diseases, in particular ultra-rare ones. As the authors demonstrate “better accelerated approval access could reduce development costs by approximately 60%, increase investment value, and foster development of three times as many rare disease drugs for the same investment”. Through extensive lobbying by numerous stakeholders, including patient organizations, new legislation to allow early
access of orphan drugs in the USA may soon become a reality in the USA (FAST Act, TREAT Act, ULTRA Act). How effective these new legislations will work remains to be determined.78

5.6 Inequity in terms of accessibility of the treatments

A growing hurdle for the successful delivery of new orphan drugs to patients is the uncertain access and reimbursement of orphan drugs after marketing approval. Without access to the approved orphan drugs for the patient, the product has little utility. For various reasons, including pressure on national healthcare budgets and public health policies, access and reimbursement of orphan drugs vary between the individual member countries within the EU.

5.6.1 Public health priorities

A 2007 survey by Eurordis, the European organisation for patients with a rare disease, showed that access to orphan drugs in Europe was highly variable between countries.74 Only in four out of 28 countries did patients have access to at least 20 out of 22 orphan drugs a year after approval. The variability in access to orphan drugs may also be the result of other factors: in its 2007 survey report, Eurordis revealed a longer delay for countries with a smaller population. European lower- and middle-income countries are still having problems in terms of access to orphan drugs which would assist in the care for rare disease patients.79 A number of orphan drugs are in development by (small) companies that do not have a sales force in all European countries and may consequently need more time to be able to reach smaller markets. Moreover, companies (including large ones) might also voluntarily decide not to market (or to delay the marketing) in various countries (including larger countries).

5.6.2 Pricing and reimbursement

There has been growing debate of the orphan drug field which centre around three key perceptions of the field: the high price of orphan drugs, their inability to meet the standard cost effectiveness threshold and the construct of the system itself which allows companies major benefits from labelling a product as an orphan drug.80,81,82,83

Recently, Roos et al. claimed that the highly praised market exclusivity incentive basically creates a market monopoly that in their view has allowed manufacturers to charge ‘exorbitant’ prices for orphan drugs.84 Tambuyzer, in contrast, argued that “if an approved Orphan Medicinal Product (OMP) is currently the only product on the market, it is either because a company was the first to develop a treatment for this disease and competitors have yet to enter the market or because the market is too small to attract competition, rather than because the incentives have created a monopoly”.85 Brabers et al. provided evidence that absence of follow-on OMP development is more a matter of time or market size, rather than the creation of a market monopoly.86

A significant challenge may persist in generating evidence in small to very small heterogeneous population. Due to the high medical need, a treatment can become available at an early stage where evidence is robust but limited. In rare diseases it is also not unusual due to the small heterogeneous sample size that clinical significance is greater than statistical significance. This represent a significant hurdle for some methodological assessments that will consider. More research for alternative methods in small and very small populations is
desirable to increase acceptance of the data that can be generated from a limited patient pool in a rather short period of time.

Whatever the reason, a delay in market access of orphan drugs to the European market will be a disincentive for sponsors of potential orphan drugs and hence may reduce the number of new orphan drugs that will be developed in the long term. Consequently, obtaining access and reimbursement for an authorised orphan medicinal product is of great importance for the sponsor and for the patient.

One of the ways forward is to reduce the knowledge and data gap between the regulatory process that evaluate the risk benefit profile and grant marketing authorisation for an orphan drug and the reimbursement process that focus on clinical effectiveness and cost-effectiveness in a local health care system. Steps are undertaken to identify and assess the possible options for the creation of a mechanism for the exchange of knowledge between European authorities and Member States and facilitate the flow of information to support the scientific assessment of the Clinical Added Value of Orphan Medicinal Products (CAVOMP). Finally, a new assessment tool is needed for Member State governments to evaluate a new orphan drug at the time of pricing and reimbursement. Such a system should be adapted and able to consider the peculiarities of the clinical evidence available, the sample size, and the burden of the disease. From a public health perspective, it should be able to give to these rare patient populations equal access to treatment when it comes to life-threatening diseases and where no other alternative exists for these patients.

5.7 Access to medical care
Focus should not be just on cure but also, or perhaps even more, on (access to) high-level medical care. As mentioned above, for many rare diseases currently no treatment exists. For some rare diseases, a treatment based on the current state of scientific knowledge may not be realistic. Even if a therapy is feasible, drug development still takes around 10-15 years. Compared to drug development, healthcare innovations and their implementation in clinical practice represent a real short term opportunity to improve the quality of life of rare disease patients.

Bottlenecks in care for rare disease patients have been mentioned as an important burden in daily life. A study in 2003 by the Dutch research institute; Nivel, showed that the quality of life of patients with a rare chronic disease was worse in comparison to more prevalent chronic disorders, both at physical and psychosocial level. In this study, questionnaires to 206 patients (representing 72 rare diseases) from an existing panel of 2 500 chronically ill patients were analysed. People with a rare chronic disorder experienced more problems in care and daily life than people with more common chronic disorders like cardiovascular diseases, respiratory diseases and diabetes. Forty five per cent had complaints of gloominess, tenseness or anxiety. Finally, almost 25% would like to have emotional support, e.g. from physicians, psychosocial workers or through contacts with fellow-sufferers. Patients with a rare disorder also use more medical care.

A more recent and extensive survey by Eurordis was held to fill the void of the experience and the needs of patients in terms of offer for care by future centres of expertise. The survey was part of the Rare Disease Patient Solidarity Project (RAPSODY) supported by the European Commission. In the survey patients’ experience and expectations concerning
access to health services were compared for 16 rare diseases\(^2\) in 22 European countries.\(^92,93\) In total, the study involved 130 patient organizations and 5 995 patients.\(^94\) Important findings were that “the average patient required more than nine different medical services, over the two-year period preceding the survey”. Other difficulties that were mentioned were difficult to impossible access to services (26%). With regard to social services: more than one-third of patients met a social worker with difficulty or could not meet one at all. Social services were rated by half of the respondents as not or somewhat meeting their expectations. Around one third reported that he/she or another member in the family had to reduce or stop professional activity as a result of the disease. Finally, “18% of respondents experienced rejection by a health care professional. The majority of patients reported a reluctance of professionals to treat them due to the complexity of their disease.”

It is expected that the need for access to care will be even higher in some countries. Improving the infrastructure for medical and psychosocial care for rare diseases could diminish the burden of disease for many patients. This would be beneficial for all patients but might be even more critical when there is no short-term hope to find a treatment.

6. **Which actions have been/are being undertaken to reduce the rare disease burden?**

6.1 **Europe**

Since 2004, several reports have been issued with detailed information on initiatives and incentives at EU and Member State (MS) level. Focus is on the three European Commission Directorates-General (Health and Consumers; Research and Innovation; Enterprise and Industry) that have a major influence on rare disease and orphan drug policy and other rare disease initiatives. Below we have included a concise description of actions at community (European) level.\(^97\)

6.1.1 **Actions at a (European) Community level**

For more than two decades, the European Commission (EC) has been addressing the problems of rare diseases, thereby contributing to the reduction of the burden of rare disease patients. An important legislative action that has already been mentioned above has been the introduction of specific legislation to stimulate the development of therapies for rare diseases.

Through its consecutive Programmes of Community Actions in the Field of Health and Framework Programmes for Research and Technological Development,\(^106,95\) the EU has paid a special attention to rare diseases. Initially, a strong focus existed on exchange of information, networks and funding fundamental research. However, more recently funding

\(^2\) alternating hemiplegia, Aniridia, Ataxias, Chromosome 11q disorders, Cystic fibrosis, Ehlers-Danlos syndrome, Epidermolysis bullosa, Fragile X syndrome, Huntington disease, Marfan syndrome, Myasthenia, Osteogenesis imperfecta, Prader-Willi syndrome, Pulmonary arterial hypertension, Tuberous sclerosis and Williams syndrome
also focussed on translational research and pre-clinical and clinical development of orphan drugs for prevention, diagnosis or treatment of rare diseases.

As stated by the EC on its website, focus of actions at Community level is on:

- improving recognition and visibility of rare diseases
- ensuring that rare diseases are adequately coded and traceable in all health information systems
- supporting national plans for rare diseases in EU Member States
- strengthening European-level cooperation and coordination
- creating European reference networks linking centres of expertise and professionals in different countries to share knowledge and identify where patients should go when expertise is unavailable in their home country
- encouraging more research into rare diseases
- evaluating current screening population practices
- supporting rare diseases registries and providing a European Platform for rare diseases registration.

### 6.1.2 Coordinating activities

An important action by the European Commission has been the launch of the Rare Disease Taskforce (RDTF) in 2004. The RDTF consisted of experts from Member States, representatives of the European Commission (DG SANCO, RTD, ENTR and EUROSTAT), EMA, and WHO-Europe. Their mandate was to improve information exchange between relevant authorities, to contribute to accurate and relevant indicators to a harmonized EU health data system and to assist the EC in setting priorities for information and knowledge on major and rare diseases. On 30 November 2009, the Rare Disease Taskforce was replaced by the establishment of the European Union Committee of Experts on Rare Diseases (EUCERD; see below).

On 11 November 2008, the European Commission published its ‘Communication on Rare Diseases: Europe’s Challenges’. The Communication focused on the improvement of recognition and visibility of rare diseases, support for policies on rare diseases of member states for a coherent overall strategy and the development of cooperation, coordination and regulation for rare diseases at EU level. This communication led to the adoption of the European Council Recommendation on an Action in the Field of rare diseases in June 2009.

The Recommendation notably focuses on national plans and strategies of Member States which should be adopted by 2013 to improve recognition of rare diseases, encourage research in the field of rare diseases and forging links between Member States through the creation of European reference networks in order to share knowledge and expertise.

The EUCERD was established to aid the European Commission with the preparation and implementation of Community activities in the field of rare diseases. The EUCERD consists of 51 members, which includes one representative from each government agency or ministry responsible for rare diseases of each Member state, four representatives from patient organisations, four representatives from the pharmaceutical industry, nine representatives from ongoing and/or past Community projects financed by the health programmes (including three members of the pilot European Reference Networks on rare diseases), six representatives of ongoing and/or past rare diseases project financed by the Community
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Framework Programmes for Research and Technical Development, and one representative of the European Centre for Diseases Prevention and Control.\textsuperscript{103}

The EUCERD publishes an annual overview of initiatives and incentives in the area of rare diseases by the EU and individual Member states.\textsuperscript{57} This also includes an overview of DG Research and Innovation’s fifth, sixth and seventh Framework Programmes for research, technological development and demonstration activities related to rare diseases.

6.1.3 Community Actions in the Field of Health (Health programmes)\textsuperscript{104}

‘Programmes of Community Action in the Field of Health’ are the main instrument the European Commission uses to implement the EU Health Strategy. Rare diseases have been included in these Community Actions for over a decade. In 1999 a ‘Programme of Community Action on Rare Diseases’ within the framework for action in the field of public health was established (1999-2003) with a budget of 6.5 million euro.\textsuperscript{105} This programme aimed for the development of a European network on rare diseases, information, education and updating on professionals knowledge, creation of transnational collaborations and networks and creation of systems improving collection, analysis and dissemination of knowledge in the field of rare diseases. In this community action programme 24 projects were funded.\textsuperscript{12}

The following ‘Programme of Community Action in the Field of Health’ (2003-2008) with a total budget of 312 million euro, was based on three general objectives: improving information and knowledge, enhancing a rapid reaction in a coordinated fashion to health threats and promoting health and preventing disease.\textsuperscript{13} The programme replaced a series of eight EU programmes that each focused on individual health issues, such as cancer, AIDS and other communicable diseases, rare diseases and drug abuse. Rare diseases were mentioned under the second objective.

The ‘Second Programme of Community Action in the Field of Public Health’ (2008-2013) with a total budget of 3 215 million euro was based on three general objectives: improving citizens’ health security, promoting health, which involves reducing inequalities in this area and generating and disseminating health information and knowledge. Rare diseases were mentioned under the second objective. For the years 2008-2011, a total of 21 434 895 euro was awarded to rare disease-related projects. An additional €4.5 million was planned for 2012.\textsuperscript{14}

Recently, an overview of eight projects was published, which receive(d) funding from the EU through Community Actions in the Field of Health, and which illustrate some of the actions that have been undertaken at Community level to reduce the burden of rare diseases.\textsuperscript{15}

Of course, the aforementioned projects are examples of many projects and other initiatives that have been funded by the EC.
Table 6.19.2: Projects to illustrate some of the actions that have been undertaken at Community level to reduce the burden of rare diseases

<table>
<thead>
<tr>
<th>Project</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eurordis</td>
<td>Patient advocacy and support organisation that promotes cooperation between rare disease patient organisations across the EU, with a myriad of educational and advisory activities that promote the empowerment of patients.</td>
</tr>
<tr>
<td>Orphanet</td>
<td>Improves the recognition and visibility of rare diseases by offering patients and health care professionals up-to-date, relevant information on rare diseases, orphan drugs and expert services.</td>
</tr>
<tr>
<td>ECORN-CF Care-NMD</td>
<td>The creation of European Reference Networks, linking centres of expertise and professionals in different countries, is essential to both share knowledge and to identify where patients should go when expertise is unavailable in their home country. ECORN-CF and CARE-NMD are two projects where treatment recommendations and a consensus in clinical care are being promoted for cystic fibrosis and Duchenne muscular dystrophy respectively.</td>
</tr>
<tr>
<td>Eurocat RareCare</td>
<td>Many EU-funded projects encourage more research into rare diseases. Understanding the scale and scope of rare diseases is often an issue, particularly when clinicians and patients struggle to find the right diagnosis and treatment. Two projects EUROCAT and RARECARE present detailed European epidemiological data on congenital anomalies and rare cancers respectively.</td>
</tr>
<tr>
<td>Eurocat European Newborn Screening</td>
<td>Projects like EUROCAT promote wide-ranging networks of expert knowledge to better understand rare diseases and support evidence-based action. For example, the review of European Newborn Screening practices will guide future European policy, enabling the appropriate diagnostic and preventive measures to be put into action in all Member States.</td>
</tr>
</tbody>
</table>


6.1.4 Framework programmes

At European level, research on rare diseases has been addressed as one of the priority areas in the health field under the EU Framework Programmes for Research and Technological Development since the early 1990’s.106

The aforementioned EUCERD annual overview of initiatives and incentives in the area of rare diseases by the EU and individual member states also includes an overview of DG Research and Innovation’s fifth, sixth and seventh Framework Programmes for research, technological development and demonstration activities related to rare diseases.

During the fifth framework programme for research support was provided for multinational research into rare diseases. Forty seven projects were funded for about €64 million in total.57
An example of a project funded by FP5 is the EuroBioBank with 1.2 million euro for 36 months that stimulated the infrastructure of rare diseases.\textsuperscript{107} This bank is the first of biological banks in Europe providing human biological material (DNA, tissues, cells) for research on rare diseases on a large scale. The consortium was originally composed of 16 partners from eight European countries, 12 academic or private banks, 2 computer services companies (software designer and developer), one biotechnology company and EURORDIS who initiated the project. A total of approximately 65 000 DNA samples and 15 000 tissue samples are available via the 12 banks of the consortium.

During the Sixth Framework Programme for Research (FP6 2002-2006), one of the seven thematic areas focused on “Life sciences genomics and biotechnology for health”. FP6 saw a significant increase in the funding for rare disease projects; around €230 million for a total of 59 projects, one of which was an ERA-Net Project.\textsuperscript{57} The outcomes of this funding was mobilization of research to tackle fragmentation of research, better coordination at EU level and the fostering of dialogue with stakeholders.

The Seventh Framework programme (FP7 2007-2013) encompasses four main programmes: “Cooperation”, “Idea”, “People” and “Capacities”. The Cooperation programme supports collaborative research and is subdivided into 10 themes, including the ‘Health Theme’, under which most research on rare diseases falls. The emphasis of rare disease research is on studies of natural history, pathophysiology, and the development of preventive, diagnostic and therapeutic interventions.\textsuperscript{58} Special attention has been given to communicating research outcomes and engaging in dialogue with civil society, in particular with patient groups.\textsuperscript{108}

The European Commission has already published several calls for proposals covering research on rare diseases in various thematic areas of FP7. Between the period of 2007-2010, 50 research projects on rare diseases have been supported. Approximately 17 of these projects are fundamental research, whilst eight projects cover preclinical and clinical development of orphan drugs. One of the projects funded by FP7 has been the Orphan Platform, which was a three year (2008-2011) project, aimed to help develop a platform for researchers in rare diseases to quickly and efficiently set up multidisciplinary teams and exchange information within EU Member States. It also produced an inventory of publicly funded projects in the field of rare diseases and orphan drugs.\textsuperscript{58}

6.1.5 Actions at Member State level

Apart from Programmes of Community Actions for Public Health and Framework Programmes at EU level, individual EU Member states have also addressed the burden of rare diseases in the last decade. As mentioned above, the EUCERD provides an extensive annual overview of initiatives and incentives in the area of rare diseases by the EU and individual Member States.\textsuperscript{57} Initiatives and incentives by individual member states cover extensive categories in relation to rare diseases. Examples are: national plans or strategies for rare diseases and related actions; presence of centres of expertise; neonatal screening policy; National alliances of patient organisations and patient representation and research activities.

Although Member States fund rare disease research, specific rare disease research programmes at Member State level are limited. Moreover, some countries have dedicated centres of expertise for certain rare diseases, others have not.
However, as mentioned above, the 27 EU Member States have committed to adopt National Plans/Strategies for responding to rare diseases before the end of 2013\textsuperscript{101} in their European Council Recommendation on an Action in the Field of rare diseases, adopted in June 2009.\textsuperscript{101} The collaborative EU-level Recommendation document aims to guide actions in rare diseases within the Member States’ health and social systems. To facilitate the process of developing complementary and effective plans, the European Commission funded the European Project for Rare Disease National Plan Development (EUROPLAN) between 2008-2011 and extended to 2015.\textsuperscript{109} The EU member states are currently in the process of adopting and implementing national plans and strategies for responding to rare diseases. The plans should ensure that rare disease patients have access to high quality care and if possible access to effective orphan drugs.\textsuperscript{109,110,111} France was the first EU country to adopt, at the end of 2004, a national rare disease plan (see Box 6.19.1).

Plans can be reviewed on the EUROPLAN website (www.europlanproject.eu), which shows the current stage of development of national plans or strategies for rare diseases in the EU.

**Box 6.19.1: National rare disease plan in France**

France’s first initiative in rare diseases was the creation of a French programme in 2002 with specific funds from public and charities. For the creation and/or development of 59 networks for rare diseases and promotion of 27 multidisciplinary research projects a budget of 7.9 million euro was made available for 2002 and 2003. Next to this funding programme, the development of partnerships and infrastructure was started, e.g. a partnership with the French Mouse Clinical Institute to generate mouse models for rare diseases. The programme formed the basis for the adoption of a national rare disease plan at the end of 2004. France was the first EU country to define a specific strategy on how to deal with the problems associated with rare diseases at a national level. The second national plan was elaborated by the Ministry of Health. The second plan was launched on 28\textsuperscript{th} February 2011 with a budget of €180 million. Before the end of 2013 a third plan will be discussed.

### 6.2 The Rest of the World

#### 6.2.1 United States of America (USA)

Within the USA, rare disease research has been given a stimulus with the Rare Diseases Acts of 2001-2002.\textsuperscript{112} The Rare Diseases Act of 2001 (S. 1379; S.R. 107-239) started two initiatives and was split later into two separate acts, the Rare Diseases Act of 2002 (H.R. 4013) and the Rare Diseases Orphan Product Act of 2002 (H.R. 4014), that were passed in November 2002.\textsuperscript{113,114} Emphasis was given in 2003 to the building of rare disease regional centres of excellence for clinical research into, training in, and demonstration of diagnostic, preventive, control, and treatment methods for rare diseases.\textsuperscript{114}

The Rare Diseases Act of 2002 (H.R. 4013, Public Law 107-280) has provided the National Institutes of Health (NIH) Office of Rare Diseases Research (ORDR) a statutory authorisation to increase the national investment in the development of diagnostics and treatments for
patients with rare disorders.\textsuperscript{14} Since then several programmes have been initiated in the area of rare diseases:

a) Undiagnosed Diseases Program\textsuperscript{15}
As mentioned above some patients wait years for a definitive diagnosis. Using a unique combination of scientific and medical expertise and resources at the NIH, the Undiagnosed Diseases Program aims to provide answers to patients with mysterious conditions that have long eluded diagnosis. Moreover, a second objective is to advance medical knowledge about rare and common diseases.

b) Therapeutics for Rare and Neglected Diseases program (TRND)\textsuperscript{16}
TRND is a collaborative drug discovery and development program with a $24 million budget per fiscal year since 2009.

c) Rare disease Bench-to-Bedside Awards\textsuperscript{17}
As part of the Bedside-to-Bench (B2B) Program in 2012 seven B2B awards were granted for rare disease-specific projects.\textsuperscript{18} The aim of the B2B Program is to fund projects that focus on translation of basic scientific findings into therapeutic interventions for patients and to increase understanding of important disease processes. A B2B award provides up to $135 000 a year for two years.

d) Rare Diseases Clinical Research Network (RDCRN)
The Rare Diseases Act of 2002 also resulted in the establishment of rare disease regional centres of excellence for clinical research into, training in, and demonstration of diagnostic, preventive, control, and treatment methods for rare diseases. On October 2009, the NIH funded rare diseases clinical research consortia\textsuperscript{3} and one Data Management Coordinating Center. This cooperative program should facilitate many advances including the identification of biomarkers for disease risk, disease severity/activity, and clinical outcome and encourage development of new approaches to prevention, diagnosis, and treatment of many rare diseases beyond those being studied. The easy and free availability of data from the Data and Technology Coordinating Center should also spawn many new research ideas and subsequent applications to NIH Institutes and Centers.\textsuperscript{19}

The Office of Orphan Products Development (OOPD) at the U.S. Food & Drug Administration (FDA) has been dedicated to promoting the development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions since it was created in 1982.\textsuperscript{120} OOPD interacts with the medical and research communities, professional organizations, academia, and the pharmaceutical industry, as well as rare disease groups. The OOPD is the administrative body for the Orphan Products Development Grant Program. The objective of this OOPD grant program is to fund trials that will result in new products or data to be used in the treatment of rare diseases. The products studied can be drugs, biologics, medical devices, or medical foods, but in practice they are primarily

\begin{itemize}
  \item Spinocerebellar ataxias, urea cycle disorders, primary immune deficiency, porphyria, mitochondrial disease, salivary gland carcinomas, nervous system channelopathies, dystonia, mucociliary clearance, nephrotic syndrome, graft versus host diseases, vasculitis, hereditary causes of nephrolithiasis and kidney failure, Angelman syndrome/Rett syndrome/Prader-Willi syndrome, autonomic rare disease, inherited neuropathies, sterol and isoprenoid diseases, lysosomal disease and brain vascular malformation
\end{itemize}
drugs and biologics. The current annual budget for funding grants is now approximately $14 million due to the Rare Disease Orphan Product Development Act of 2002 (H.R. 4014). Clinical trials are awarded grants from US$ 100 000 to US$ 200 000 per year in direct costs for up to three years. This program has led to increased research and development of orphan products at academic institutions and other responsible organisations: public, private, non-profit, or for-profit. The grants (over 500 until now) have enabled scientists to develop the preliminary scientific data necessary to prove that a new treatment warrants commercial development and FDA approval. These grants helped to bring more than 45 products to market approval.

The USA has a treatment IND protocol that can applied to rare disease patients. The IND treatment protocol is used when no satisfactory alternative treatment exists, for a life-threatening and debilitating illnesses, the patient can access promising therapeutic agents which have not yet been market approved. The treatment IND is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. The only countries in Europe with similar protocols are France and Italy.

Additionally, the U.S. Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) and accompanying PDUFA Reauthorization Performance Goals and Procedures for Fiscal Years 2013 through 2017 provide for several regulatory science initiatives to enhance the development of drugs for rare diseases by improving existing processes and creating new ones. Center for Drug Evaluation and Research (CDER) will increase staffing for the Rare Disease Program by five and create a new rare disease liaison position in the Center for Biologics Evaluation and Research (CBER) Office of the Center Director. FDA further aims to address development challenges for drugs targeting rare diseases by instructing FDA to specifically consider the issues arising under the Accelerated Approval and Fast Track provisions for such products including the chance to qualify for classification as a “breakthrough therapy” (FDASIA §901, §902). When approving a rare disease drug under its new Accelerated Approval authorities, FDA is asked to consider broader information in the assessment of benefit/risk, such as the severity and rarity of the condition and the lack of alternative treatments. FDA will seek input from external rare disease experts and patient advocates by holding public meetings and developing a list of such experts to serve as advisors for rare disease drug development (FDASIA §903). Finally, the law offers priority review vouchers as an incentive for novel pediatric rare disease drugs (§908) and amends the humanitarian device exemption (FDASIA §613).

6.2.2 Japan

Japan has the oldest programme for rare disease research and care in the world. The Specified Rare Diseases Treatment Research Programme was established in Japan in 1972 with the support of the Ministry of Health, Labour and Welfare. One-hundred and thirty diseases have so far been the subject of research programmes and research grants form government sources. In 2010, the government expanded the budget to 10 billion yen.

6.2.3 China

Due to China’s large population there is a large pool of rare disease patients. This has allowed China to conduct large genome studies on rare disease. Recently Beijing Genome
Institute has launched the “1000 Mendelian Disorder Projects”. These research studies have greatly developed China’s research interests in studies to better understand the genetic background of rare diseases. So far the Mendelian Disorders Project has initiated genetic studies covering more than 150 diseases. There are no national network for rare diseases in China and diagnosis of rare diseases is only possible in large cities within the country. This means that much of the needs of China’s rare disease patients are not met. Additionally there is very limited development of drugs for rare diseases in China because no policies for incentives have been adopted. China included the development of orphan drugs in a national programme for innovative new drugs in 2010. A definition of rare disease was proposed by a group of medical experts in 2010 and an initial list of 23 rare diseases has been proposed.

### 6.3 International collaboration

In the field of rare disease research maximising scarce resources and coordinating research efforts is key. In order to address this issue the International Rare Diseases Research Consortium (IRDiRC) was launched in 2011 at the initiative of the European Commission and the United States National Institutes of Health with the aim of fostering international collaboration in rare diseases research. The goal is to pool resources and work beyond borders in order to get a better understanding of rare diseases and find adequate treatments. Apart from the EC and the NIH, private as well as public organisations from EU Member States, Australia, Canada and the USA have joined the IRDiRC as funding body. The IRDiRC teams up researchers and organisations investing in rare diseases research. It has two main objectives: to deliver 200 new therapies for rare diseases and means to diagnose most rare diseases by 2020. Recently, the European Commission announced that it will provide €144 million of new funding for 26 research projects. Over 300 participants from 29 countries in Europe and beyond will be brought together in the selected projects, including teams from leading academic institutions, smaller businesses and patients’ groups. The 26 new projects cover an array of rare diseases including cardiovascular, metabolic and immunological disorders.

#### 6.3.1 Funding by patients

The role of rare disease patients in rare disease research and orphan drug development is enormous and at all stages of the drug innovation cycle. Rare disease patients or their parents initiate research, provide the necessary funding, provide input to research agendas, own patents, initiate product development programs, maintain registries and biobanks, and even start their own companies. The National Organization for Rare Disorders (NORD), a non-profit, voluntary health agency exists to serve rare-disease patients and their families in the USA. The Research Grant Program of NORD provides seed money in small grants to academic scientists studying new treatments or diagnostics for rare diseases. The clinical researchers supported by NORD’s research grants provide preliminary data indicating that a treatment (drug, device, or medical food) may be safe and effective when used for a larger number of patients. Researchers can then use the preliminary data to apply for larger multi-year government grants or to attract a commercial sponsor.

With regard to orphan drug development, apart from well-established sources of funding like governmental grants and venture capital, patient-initiated research foundations can also represent an important source of funding. Funding of translational research as well as (pre-
clinical proof of concept studies is not only directed to academic institutes, but also academic spin-offs/start-up companies and more mature SMEs. The French Muscular Dystrophy Association (AFM) serves as a good example in this respect with the creation of Genethon, a company that focuses on gene therapy. In 2012 the new innovative cystic fibrosis product Kalydeco™ was approved by the FDA. Although the product has been developed by Vertex Pharmaceuticals, its development was to a large extent funded by the Cystic Fibrosis Foundation. In France, Lysogene, a company founded by a parent of a child with Sanfilippo syndrome type IIIA (mucopolysaccharidosis IIIA), is working on a gene therapy product. Another example is the AKU society that is collaborating with academia and industry to study the potential clinical effect nitisinone, a product approved for tyrosinemia type I (orfadin), may have in alkaptonuria. This has been made possible by EU funding, and it was the patients’ group that was the driving force behind setting up the consortium, designing the programme and applying for the funding. These are only a few examples.

7. 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?

In the last decade considerable attention has been paid worldwide to stimulate the research, development and bringing to the market of orphan medicinal products by the pharmaceutical industry. In the USA and the EU over 400 and 70 OMPs have been approved as therapy for a rare disease. Many orphan medicinal products are innovative, biotechnological products that have been the start for several small biotech-companies. Apart from treatments coming available, the introduction of various (research) programmes and networks has advanced understanding and diagnosis of several rare diseases as well.

However, despite the growing number of approved orphan drugs and enhanced rare disease understanding in the last decade, many gaps remain related to the development of treatments and care for patients with a rare disease. Being a complex and heterogeneous mosaic of an estimated 5 000-8 000 conditions, it has become clear that the (research) need can differ considerably between (groups of) rare diseases:

Lack of disease understanding: need for fundamental research into disease process

For many rare diseases basic knowledge, like diagnosis, cause of the disease, pathophysiology, natural course of the disease and epidemiological data that would allow for development of preventive, diagnostic and/or therapeutic approaches is limited or worse missing. This significantly hampers the ability to both diagnose and treat these diseases. For those diseases funding of fundamental biomedical research is necessary. Genomic research will result in the recognition of more rare genetic diseases or subclasses. Proteomic research will result in more insight in protein function and structure of proteins that are deficient or are accumulated in rare diseases. Ongoing fundamental research into the disease process will result in more targets for pharmaceutical intervention or healthcare innovation for rare diseases. While only a small number of pharmaceutical companies are engaged in investing
in fundamental research in rare diseases, public research is of utmost importance, and will help increase public-private partnerships in view of new therapy development.

To support the development of scientific knowledge ultimately useful to patients, investments in fundamental research in disease process need to go hand in hand with investments in dedicated rare disease infrastructure and pan-European or even global networks. Where needed these network will also provide effective medical education and opportunities to train health professionals on rare diseases.

The availability of a rare disease classification system is equally important to make rare diseases more visible in health information systems. This will be an important step to help generate reliable epidemiological data. Such a system will constitute a useful basis for further research into the natural history and etiology of rare diseases, allows monitoring safety and clinical effectiveness of therapies and measuring quality of care. Several systems are currently considered suitable for coding rare diseases diagnosis: International Classification of Diseases-11 (ICD11; currently in Beta phase), the Orphanet classification, OMIM and SNOMED CT. Each system has its advantages and disadvantages, and important questions remain unanswered with regard to funding and maintenance of such a system.

Translation of disease understanding into product development or healthcare innovation is hampered.

As aforementioned, the majority of designated and approved orphan drugs in the USA and EU were intended for treatment of rare diseases in the field of oncology followed by metabolism. The latter indicates that translation of rare disease research into an orphan drug development is not equally spread across disease classes, which was confirmed by Heemstra et al.

Consequently, a lack of treatment remains for many rare disorders, which is a clear pharmacological gap. Although the development of orphan drugs is in essence the primary responsibility of the pharmaceutical industry, public funding could focus on proof of concept studies and act as a catalyst to translate rare disease research into orphan drug development. In the EU at Member State level translational research programmes are limited.

Apart from treatment, disease understanding may also translate into healthcare innovations. Beyond focusing on finding a cure, research should also focus on providing easy and accurate diagnosis and on prevention strategies. As has been shown above for PKU, some interventions to avoid organ damages require early diagnosis (e.g. newborn screening) to be effective and decrease the reliance on curative interventions.

Most OMP designations are for pharmaceuticals intended to treat rare diseases. The OMP designation system covers diagnosis and prevention in its criteria as well, but is less adequate to stimulate diagnosis and prevention. Products and techniques for diagnosis most of the time do not require a marketing authorisation and the technical development follow a different cycle than drugs. Prevention can be understood in two different ways either prevention of disease occurrence or prevention of symptoms or relapse of symptoms. Prevention of disease occurrence relies on adapted behaviors and in case of rare genetic disorders also on proper genetic counselling. Prevention of symptoms and organ damage are
related to the timing of a treatment or intervention hence the importance of early diagnosis. It is therefore not unusual that nearly all the approved orphan drugs in the EU are intended for treatment of rare diseases and not for diagnosis or prevention. However, diagnosis and prevention strategies represent important tools in reducing the burden of rare diseases. Specific incentives for researchers and industry to tackle these two dimensions of care more prominently are welcome.

For some rare diseases translation of research into product development or healthcare innovation has taken place, but further development is hampered.

7.1 Clinical trials

A key issue with rare diseases is that they present with fundamentally different challenges than more common diseases, like asthma or diabetes. This is most apparent during the clinical development stage where rarity significantly complicate the developers task: too small a number of patients geographically dispersed throughout the world, logistics, ethics (e.g. use of placebo), lack of validated biomarkers and surrogate end-points, poor diagnostics, limited clinical expertise and expert centres, high administrative requirements which vary from country to country, and from clinical trial site to clinical trial site.

Clinical trial-funding programmes (e.g. orphan products grant program) remain essential for orphan drug development for rare diseases that receive less attention from the pharmaceutical industry (e.g. less prevalent).

Critical for marketing authorization and reimbursement is the acceptance of the evidence generated with methods adapted to small to very small population. Further development and/or optimization of alternative methodologies in clinical investigation in small populations to meet the criteria for marketing authorization and to provide information for pricing or reimbursement decisions are desirable (See Chapter and Background paper 8.3). Regulatory authorities, which have gained extensive experience with small-sized clinical trials, can represent an added-value in this respect.

Similar to fundamental research, large multidisciplinary networks should be funded to stimulate collaboration between all interested parties bringing together medical experts, reference centers, and patients’ groups for rare diseases. This infrastructure is necessary for developing clinical guidelines that can help the physicians in the diagnosis and therapeutic decision tree, reinforcing the performance of clinical trials and subsequent monitoring of the new products through (public-private) registries.

7.2 Innovative therapies

The first clinical proof of concept study of alipogene tiparvovec (Glybera®), the first gene therapy product approved in the EU, was partially funded through a translational research programme of the Netherlands Organisation for Health Research and Development (ZonMw).

Alipogene tiparvovec is an excellent example of a whole new generation of more targeted therapies, like stem cell therapies, gene therapies or therapeutic gene modulations (exon skipping, antisense drugs, RNA interference). To allow these targeted therapies for smaller
patient groups to become more common practice in the future, it is critical to continue funding the research and development of these highly innovative therapies through specific budgets or public-private partnership (PPP) programs.

7.3 **Innovative drug delivery methods**

Innovative drug delivery methods are discussed in depth in Chapter 7.4 of this report. The use of (other) delivery methods for existing orphan drugs would be of significant benefit for patients with rare diseases. These methods entail an improved pharmacokinetic profile of existing orphan drugs, and consequently an improved efficacy, safety profile or contribution to patient care. For rare disease patients the ability to measure the added value these innovative drug delivery methods bring to patients and/or the health care system will be critical to justify the additional developments costs for industry. The reason why innovative drug delivery systems remain underused in the area of orphan drugs is unclear. Increased patient involvement will certainly increase demand for more convenient administration schemes and devices. Some examples of innovative drug delivery systems are:

1) **Alternatives for intravenous administration**

For example enzyme replacement therapy for several lysosomal disorders (Gaucher disease, Fabry disease) is given intravenously, either in the hospital or at home. The frequency of these infusions, that take about two hours per infusion, may vary widely from three times a week to once a month. It would be a great advantage for these patients when the supplemented enzyme could be given in another way, e.g. via a tablet or capsule.

2) **Controlled delivery systems**

Another example of patients with a rare disease that could benefit from an improved delivery method are Addison patients. Many Addison patients are substituted with corticosteroids due to an adrenal cortical insufficiency. The capsules are taken three times a day. However, it would be much better for the patients to mimic the natural situation as much as possible by a controlled delivery of the corticosteroids in the body.

3) **Site-specific drug delivery**

Another important issue is the delivery of drugs across the blood brain barrier. Many patients with rare diseases have neurological symptoms. It would be a major breakthrough for the treatment of these diseases when large molecules could be targeted across the blood brain barrier.

7.4 **Drug repurposing**

Another opportunity for research in pharmacological intervention for rare diseases is the use of molecules that are running out of patent protection. Some of these molecules could be further developed for new indications e.g. rare disorder. This is known as drug repurposing. The advantage is that these molecules have obtained a marketing approval or have gone through considerable clinical testing for another indication. Consequently, preclinical and safety data is available with sometimes clinical experience (off label use) in the targeted indication. The new molecule will still need to be developed for registration in the new indication to define dose, safety, efficacy and even if relevant how to optimize delivery. In this case also clinical readiness is critical to expedite development (diagnosis, epidemiology, natural history, endpoints to study, rare disease patients ready for enrollement). Review of
the EU Register of Orphan Medicinal Products indicates that several companies exist that have built their business model around the concept of drug repurposing. Regulatory requirements and market access arrangements for new use of out of patent molecules may however still present some significant hurdles.

Although slightly different the screening of available public and private drug libraries for potential leads for rare diseases may also hold great promise in the discovery and subsequent development of novel therapies for specific rare diseases.

8. CONCLUSION

In the area of rare diseases there are many opportunities for the EU to build on the successful programmes, projects and networks that have been supported since 2000. The most important ones that should continue to be supported are:

- Networks of excellence that focus on research infrastructure (e.g. registries) as well as provision of disease-related information at EU level and beyond (guidelines, diagnosis, patient experience)
- Initiatives that focus on rare disease classification
- Fundamental research into the disease process to increase rare disease understanding
- Incentives for development of therapeutics (e.g. clinical trial-funding programmes)
- Assessment methods adapted to small and very small patient populations (e.g. marketing authorisation and reimbursement).

In addition, more support is needed for:

- Translational research to increase translation of disease understanding into drug development or healthcare innovation (e.g. NIH bench to bed grants)
- Innovative diagnostic methods of rare diseases to enable early intervention
- Research, infrastructure as well as implementing guidelines for medical and psychosocial care for rare diseases. This would be especially beneficial for those patients for whom underlying treatment is not yet available.
- Incentives for development of preventive strategies and validated diagnostic techniques
- Incentives to leverage existing knowledge and optimize the use of existing drugs (innovative drug delivery systems and drug repurposing).
- Giving easy access to available healthcare (diagnostic, medical, pharmacological or other types of care) to patients regardless of where they live.

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## Annex

### Annex 6.19.1: Orphan drug policies in different countries

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<th>Program established</th>
<th>United States</th>
<th>Japan</th>
<th>Taiwan</th>
<th>Australia</th>
<th>EU</th>
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</table>

<table>
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<tr>
<th>Prevalence criterion for rare disease</th>
<th>United States</th>
<th>Japan</th>
<th>Taiwan</th>
<th>Australia</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 200 000 patients in USA (&lt;7.5:10 000)</td>
<td>Less than 50,000 patients in Japan (&lt;4.1: 10 000)</td>
<td>Less than 1 person in 10 000.</td>
<td>Less than 2 000 patients in Australia (&lt;1.1:10 000)</td>
<td>Life-threatening or chronically debilitating disorder that affects less than 5:10 000 in EU</td>
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</tbody>
</table>

<table>
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<tr>
<th>Requirements for designation</th>
<th>United States</th>
<th>Japan</th>
<th>Taiwan</th>
<th>Australia</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare disease or R&amp;D costs cannot be recovered in seven years</td>
<td>Rare and serious disease; no other treatment available, must be a high health care priority</td>
<td>Drugs with major indications for the prevention, diagnosis and treatment of rare diseases</td>
<td>Rare disease or product is not commercially viable</td>
<td>Rare disease, or product unlikely to be developed without incentives or new product will be of significant benefit</td>
<td></td>
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</table>

<table>
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<tr>
<th>Products eligible for orphan designation</th>
<th>United States</th>
<th>Japan</th>
<th>Taiwan</th>
<th>Australia</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs and biologicals (including vaccines and in vivo diagnostics)</td>
<td>Drugs, biologicals and medical devices</td>
<td>Drugs and biological and special nutrient foods</td>
<td>Drugs, vaccines or in vivo diagnostic agents</td>
<td>Drugs and biologicals (including vaccines and in vivo diagnostics)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Market exclusivity</th>
<th>United States</th>
<th>Japan</th>
<th>Taiwan</th>
<th>Australia</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seven years; prevents same product being approved for the same indication unless clinical superiority is shown</td>
<td>Re-examination period extended from four to 10 years</td>
<td>Ten years. During this period, no applications for registration and market approval of pharmaceuticals of the same kind will be approved</td>
<td>None; second product with the same active ingredient will not be designated unless clinical superiority is shown</td>
<td>Ten years; can be reduced to six if orphan criteria no longer met</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other benefits</th>
<th>United States</th>
<th>Japan</th>
<th>Taiwan</th>
<th>Australia</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory fee waivers, 50% tax credit on clinical research after designation; grants for clinical research (pharma and academia eligible); protocol assistance; faster review if indication warrants; research grants for medical devices and medical food.</td>
<td>Application fee reduced (?); grants for clinical and non-clinical studies (only pharma eligible) up to 50% of yearly R&amp;D costs available up to three years; 6% tax reductions for (pre) clinical research; protocol assistance on request; faster review if indication warrants.</td>
<td>Patients ailments are now included in National Health Insurance coverage for major diseases and injuries and whose co-payment can be waived.</td>
<td>Regulatory fee waivers; no grants, no tax credits, protocol assistance on request; priority review</td>
<td>Regulatory fees can be reduced or waived, access to centralized procedure, protocol assistance. Individual Member States have to implement measures to stimulate the development of orphan medicinal products (Article 9 of Regulation)</td>
<td></td>
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Source: reference 28,50,119-123
Update on 2004 Background Paper

Background Paper 6.20
Diarrhoea

By Shuichi Suzuki, MPH, BSPharm

February 2013
Update on 2004 Background Paper, BP 6.20 Diarrhoea

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<th>Description</th>
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<tr>
<td>CHNRI</td>
<td>Child Health and Nutrition Research Initiative</td>
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<td>DALY</td>
<td>Disability-adjusted life year</td>
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<td>DFID</td>
<td>The United Kingdom Department for International Development</td>
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<td>E. coli</td>
<td><em>Escherichia coli</em></td>
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<tr>
<td>EC</td>
<td>European Commission</td>
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<tr>
<td>EDCTP</td>
<td>European and Developing Countries Clinical Trials Partnership</td>
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<tr>
<td>ETEC</td>
<td>Enterotoxigenic <em>E. coli</em></td>
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<tr>
<td>GAVI</td>
<td>Global Alliance for Vaccines and Immunization</td>
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<td>GBD</td>
<td>Global burden of disease</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<td>HUS</td>
<td>Haemolytic uraemic syndrome</td>
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<tr>
<td>IHME</td>
<td>Health Metrics and Evaluation</td>
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<td>IMCI</td>
<td>Integrated management of childhood illness</td>
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<tr>
<td>MDG</td>
<td>Millennium Development Goal</td>
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<tr>
<td>NIH</td>
<td>US National Institutes of Health</td>
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<tr>
<td>OCV</td>
<td>Oral cholera vaccine</td>
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<td>ORS</td>
<td>Oral rehydration salts</td>
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<td>ORT</td>
<td>Oral rehydration therapy</td>
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<td>PAHO</td>
<td>Pan American Health Organization</td>
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<td>PDP</td>
<td>Product development partnership</td>
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<td>RR</td>
<td>Relative risk</td>
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<td>RV</td>
<td>Rotavirus</td>
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<td>Sd1</td>
<td><em>Shigella dysenteriae</em> type</td>
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<td>STEC</td>
<td>Shiga toxin-secreting <em>E. coli</em></td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WRAIR</td>
<td>Walter Reed Army Institute of Research</td>
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Update on 2004 Background Paper, BP 6.20 Diarrhoea

Executive Summary

Although diarrhoea is a preventable disease, it remains the second leading cause of death (after pneumonia) among children aged under five years worldwide. It is estimated that in 2010, diarrhoeal diseases accounted for 60.1 million disability-adjusted life years (DALYs) and for 666,000 deaths among children aged under five years - down from 70.6 million DALYs and 782,000 deaths in 2005. The risk factors for diarrhoeal diseases include childhood underweight, suboptimal breastfeeding, unsafe drinking water and sanitation, vitamin A deficiency, and zinc deficiency. At highest risk of diarrhoeal diseases are the poorest and most vulnerable children in communities lacking basic human needs such as safe drinking water, adequate sanitation, and optimal nutrition. Around 50% of deaths among children under five occur in sub-Saharan Africa and 40% in South Asia.

Diarrhoeal diseases are caused by a variety of pathogens including viruses (for example, rotavirus), bacteria (cholera, Shigella and enterotoxigenic Escherichia coli (ETEC)) and protozoa (Cryptosporidium and Entamoeba histolytica). Most pathogens are transmitted from the stool of one person to the mouth of another via contaminated food or water (faecal-oral transmission). Improvements in the supply of drinking water and sanitation, and optimal nutrition can prevent diarrhoea efficiently, and studies have shown that interventions targeting those areas are also cost-effective. Licensed vaccines are available against rotavirus and cholera. The rotavirus vaccine has been recommended by the WHO since 2006 for use in routine childhood immunization programmes.

Diarrhoeal disease can be treated by using low-osmolarity oral rehydration salts (ORS) together with continued feeding and zinc treatment. Although these treatments are not expensive, the percentage of children with diarrhoea who have access to ORS has only slightly increased over the past decade. While antimicrobials are not recommended for routine use, it is recognized that some pathogens, such as Shigella, should be treated with antibiotics. However, there has been an increase in cases of multi-resistance to antibiotics, especially for Shigella. Diagnosis of diarrhoea relies on assessment for dehydration, type of diarrhoea (watery diarrhoea, bloody diarrhoea and persistent diarrhoea), malnutrition, and non-intestinal infection. Diagnostics for point-of-care, such as a rapid diagnostic tool to identify the specific pathogen involved, are not yet available.

From the perspective of the cost-effectiveness of interventions to improve water and sanitation compared with vaccination in endemic areas, the environmental interventions should be prioritized for investment. Access to existing treatment is also highly cost-effective. However, vaccines can greatly reduce the burden of disease and appear to be very effective in areas where access to safe water and sanitation cannot be guaranteed. There are no vaccines available to protect against several pathogens, such as Shigella and ETEC, and more research is needed to develop new vaccines against these pathogens. The development of affordable and easy-to-use diagnostic tools would change the treatment protocol and enable health care workers to provide pathogen-specific treatment.

In April 2013, a Global Action Plan for Prevention and Control of Pneumonia and Diarrhoea was issued jointly by UNICEF and the WHO. This plan sets specific goals for a reduction in the number of deaths and the incidence of diarrhoea by 2025. To address these issues, it sets targets for vaccine coverage, case management, and environmental interventions.
There are a number of promising vaccine candidates against rotavirus, *Shigella* and ETEC, including some in Phase II clinical trials. Meanwhile, candidate vaccines against *Campylobacter* are currently in the preclinical phase. The need for further research on rotavirus vaccines largely depends on the outcome of current vaccines in terms of their efficacy in endemic regions and their ability to provide cross-protection against a range of rotavirus strains. There are currently fewer medicines in the pipeline, compared with vaccines. However, since 2006, OneWorld Health, a product development partnership (PDP), has been developing new anti-secretory medicines for the treatment of cholera and other diarrhoeal diseases, with funding from the Bill & Melinda Gates Foundation. As a result, a new antidiarrhoeal medicine was approved by the U.S. Food and Drug Administration (FDA) to relieve symptoms of diarrhoea in HIV/AIDS patients on antiretroviral therapy (ART). Two additional medicine candidates are in Phase I trials. Meanwhile, a new diagnostic test which can distinguish between the different pathogens that cause diarrhoeal diseases is also in early development. One of the examples is a disposable diagnostic instrument with microfluidic cards for immunological detection of pathogens.

Among the handful of funders supporting the R&D efforts against diarrhoea, the European Commission (EC) has been funding about 100 projects, involving basic science, pharmaceuticals, vaccines, and diagnostics under the Sixth and Seventh Framework Programmes.

According to the G-FINDER survey (which provides information on global R&D funding for 31 neglected diseases), global R&D funding for diarrhoea was an estimated US$ 113.9 million in 2007 and US$ 152.2 million in 2011, with a peak of US$ 180.4 million in 2009 (2009 and 2011 data adjusted for inflation based on 2007). In 2011, R&D in diarrhoeal diseases accounted for 5% of the total funds available for research. The majority of diarrhoea R&D funding in 2011 addressed three disease areas: 33.9% for rotavirus (US$ 51.7 million), 17.1% for cholera (US$ 26 million) and 15.7% for *Shigella* (US$ 23.9 million). The fact that a number of vaccine and medicine candidates are in Phase I and II trials indicates that more funding is critically needed to bring these candidates into larger scale clinical trials.

**What is new since 2004**

- Global and European diarrhoeal incidences and deaths are declining.
- There have been several huge outbreaks of diarrhoeal diseases, including the one in Haiti in 2010.
- (The Global Action Plan will be launched in April 2013)
- In 2004, UNICEF and WHO issued treatment recommendations for low-income countries, encouraging oral rehydration therapy (ORT) with solutions made of low-osmolarity oral rehydration salts (ORS).
- The 2004 WHO and UNICEF joint statement also recommended zinc treatment along with low-osmolarity ORS.
- Two rotavirus vaccines, Rotarix® and RotaTeq® became available on the market, mostly in developed countries. Clinical trials are underway in developing countries.
- The first anti-diarrhoeal medicine, Fulyzaq™, was approved in 2012 by FDA for the treatment of diarrhoea for HIV positive children.
- There have been a growing number of candidates in the portfolios, especially of vaccines.
1. **Introduction**

1.1 **Background**

In 2004, the Priority Medicines for Europe and the World report was written by Warren Kaplan and Richard Laing and published by the World Health Organization (WHO). This chapter (6.20) and background paper on diarrhoea are newly added to the 2013 update report, since diarrhoeal burden of disease is one of the highest globally.

Diarrhoea is defined as “having loose or watery stools at least three times per day, or more frequently than normal for an individual”. Diarrhoeal diseases are caused by viruses, bacteria or protozoa. Most pathogens that cause diarrhoea mostly transmit from the stool of one person to the mouth of another via contaminated food or water, which is known as faecal-oral transmission. The number of organisms needed to cause clinical illness varies amongst pathogens.

Rotavirus (RV), a double-stranded RNA virus of the family Reoviridae, is the leading cause of acute diarrhoea, which is responsible for about 40 per cent of all hospital admissions due to diarrhoea among children under the age of five globally. The outermost shell of the virus contains two important proteins for cell-mediated immunity; VP7 (G-protein), and VP4 (P-protein). The most common strains globally were G1P [8], G9P [8] and G2P [4] in 2001-2007, though their proportion varied depending on the regions. In fact, nearly half of the specimens of the infecting strain were not identified at the period in the African and Eastern Mediterranean regions. However, understanding of existing strain in the region has a great impact on vaccination programme. Rotavirus is very stable and able to stay viable in the environment for weeks or months if not disinfected. The virus has an incubation period, usually less than 48 hours. The symptom varies between the first infection and reinfection. The first infection after three months of age appears to be the most severe. The infection may cause watery diarrhoea, severe dehydrating diarrhoea with fever and vomiting. Up to 30% of infected children may have a temperature greater than 39°C. The gastrointestinal symptoms last around three to seven days.

Cholera is an acute infection of the gut, which is caused by intake of contaminated food or water with the bacterium *Vibrio cholerae* O1 or O139. *V. cholerae* O139 is a new strain which emerged in the Bay of Bengal in 1992 and has been confined to South-East Asia. Approximately 75% of people infected with *Vibrio cholerae* O1 or O139 do not develop any symptoms. Amongst the people who develop cholera, 80% have mild or moderate diarrhoea, although the bacterium exists in their faeces for 7-14 days. Cholera has a short incubation period and produces an enterotoxin that causes voluminous, painless, watery diarrhoea. Vomiting also occurs in most patients. The infection can lead to rapid dehydration if not treated. Recently, newly evolved strains have also been reported from several parts of the world, such as several African countries, Asia and Hispaniola. These variant El Tor strains exhibit the toxin produced by classical strains, and are expected to be more virulent.

*Shigella*, which is Gram-negative, non-motile bacilli, is characterized by the acute bloody diarrhoea. The genus is named after Japanese bacteriologist, Kiyoshi Shiga, who first discovered it in the end of 19th century. The *Shigella* species are categorized by four
serotypes: serogroup A (S. dysenteriae), B (S. flexneri), C (S. boydii) and D (S. sonnei). S. sonnei and S. boydii cause relatively mild illness with watery or bloody diarrhoea. S. flexneri is the main cause of endemic shigellosis in developing countries. Shigella dysenteriae type 1 (Sd1), also known as the Shiga bacillus, exhibit different clinical features; production of a potent cytotoxin (Shiga toxin), more severe, prolonged, and frequent symptoms, higher fatality, greater potency to acquire resistance to antimicrobials. Immunity is serotype-specific. Shigella can spread by direct contact with an infected person, or faecal-oral transmission or flies. The infective dose is as low as 200 viable organisms. The incubation period is one to four days. Common symptoms include bloody diarrhoea, abdominal cramps and tenesmus, fever and anorexia. The case-fatality rate is estimated to be less than one per cent if the symptoms are not severe. However, it becomes as high as 15% among patients with Sd1 who require hospital admission.

Several types of Escherichia coli (E. coli) strains are diarrhoeagenic, such as enterotoxigenic E. coli (ETEC) and Shiga toxin-secreting E. coli (STEC). ETEC is transmitted via contaminated foods or water, and produces toxins, known as verotoxins or Shiga-like toxins, which have a similar structure with the toxins produced by Shigella dysenteriae. ETEC is destroyed by thorough cooking of foods until all parts reach a temperature of 70°C or higher. One of the most important serotype is E. coli O157:H7 from the public health aspect. The incubation period is three to eight days. Symptoms caused by ETEC include abdominal cramps, diarrhoea that may result in bloody diarrhoea in severe cases. Fever and vomiting may also occur. Most patients recover within 10 days, but in a small proportion of patients suffer a life-threatening disease including haemolytic uraemic syndrome (HUS). Especially among children, 20% of paediatric patients results in serious sequelae.

Cryptosporidium parasite is the most commonly isolated protozoan pathogen among children visiting health facilities and is frequently found among HIV-positive patients. The genus Cryptosporidium has about 13 species, and human infections are largely caused by C. hominis and the cattle genotype of C. parvum. Humans and livestock, especially young animals, are the most typical source of infection. Calves can excrete 10 billion oocysts per day. Cryptosporidium is transmitted via the faecal–oral route, mostly person-to-person contact. In addition, the intake of contaminated food and water, and direct contact with infected farm animals or domestic pets can cause infection. Infection with Cryptosporidium can cause watery diarrhoea lasting for a week, but death is extremely rare. It also causes nausea, vomiting and fever, which usually resolves within a week in healthy individuals. Cryptosporidiosis outbreaks have brought a public health impact, exemplified by 1993 outbreak in Milwaukee, USA.

Amoeba, especially Entamoeba histolytica, is another prevalent protozoan pathogen causing diarrhoea. Humans are the prime reservoir of the pathogen with key sources of infection being chronic cases and asymptomatic carriers who excrete the cysts of E. histolytica. The pathogen can exist in sewage and contaminated water for long periods of time, especially because cysts remain viable in suitable aquatic environments for several months at low temperature. Around 90% of infections with E. histolytica are asymptomatic. The incubation period is one to 14 weeks. Approximately 10% of infected individuals result in dysentery or colitis. Symptoms of amoebic dysentery are characterized by the presence of blood and mucus in the stool as well as cramping, lower abdominal pain and low-grade fever. In addition, E. histolytica can invade other parts of the body, such as the liver, lungs and brain, which sometimes causes fatal outcome.
Giardia is a protozoan pathogen that parasitizes the gastrointestinal tract of humans and certain animals. The most common route of transmission includes person-to-person contact and intake of contaminated water and food. Less than ten cysts of Giardia can cause an infection. Symptoms generally include diarrhoea and abdominal cramps. In severe cases malabsorption deficiencies in the small intestine may be present, mostly among young children.

Other major bacterial pathogens include Campylobacter and Salmonella.

There are three main forms of acute childhood diarrhoea. All of these have a potential to kill the patients and require different case management:

- **Acute watery diarrhoea**: causes significant fluid loss and rapid dehydration in infected persons. It usually lasts for several hours or days. The pathogens include V. cholerae or E. coli, or rotavirus.
- **Bloody diarrhoea** (dysentery): is characterised by visible blood in the faeces. It is associated with intestinal damage and nutrient losses in an infected individual. The common cause of pathogens is Shigella, which is also the most common cause of severe cases. Another common pathogen causing dysentery is E. histolytica (protozoan dysentery).
- **Persistent diarrhoea**: lasts at least 14 days, with or without blood in the stool. It is more common among undernourished children and those with other illnesses, such as AIDS. Diarrhoea also tends to deteriorate their condition.

Diarrhoea is a common clinical symptom among HIV patients in both adults and children. For adults, it is usually due to compromised immune system late in the HIV disease cycle. For children with HIV, it is often a consequence of frequently aggressive common childhood infections by Campylobacter, E. coli, Salmonella, Shigella or rotavirus. More than 14 days of unexplained persistent diarrhoea in children is one of the indicators of clinical stage 3 HIV infections according to WHO guidelines, and requires further evaluation and antiretroviral treatment. Persistent diarrhoea is frequently observed among HIV-infected children, and is associated with 11 times higher mortality than uninfected children. Causes of persistent diarrhoea in HIV-positive children include HIV-related malabsorption, gut manifestation of tuberculosis, gut infections and infestations of pathogens such as Cryptosporidium parvum, Cyclospora cayetanensis, Isospora belli, Microsporidia and Cytomegalovirus.

Diarrhoea is one of the most common causes of death associated with measles worldwide. Measles is an acute viral infection, which is often self-limiting. However, some undernourished or immune-compromised children are likely to suffer diarrhoea due to serious side effects.

### 1.2 Risk factors

Risk factors of diarrhoeal illness includes childhood underweight, suboptimal breastfeeding, unimproved water and sanitation, vitamin A deficiency and zinc deficiency (Figure 6.20.1).
Undernourished children are at higher risk of severe, prolonged and often frequent episodes of diarrhoea. Undernutrition also includes a lack of micronutrient, such as vitamin A and Zinc. Nutrient deficiency causes impaired resistance to infection due to a lack of immune responses, which is resulted from impaired antibody formation and reduced number of lymphocytes. Repeated attacks of diarrhoea put children at a greater risk of deteriorating nutritional status because of reduced food intake and nutrient absorption. As a result, diarrhoea often causes stunting in children. Breastfeeding is quite important for child nutritional status as well as the immunity. Breast milk provides infants all the nutrients they need for healthy development as well as antibodies to protect from pathogens. Unimproved water and sanitation allow contaminated water to stay longer in the living environment, which put young children as well as adult at higher risk of contracting pathogens causing diarrhoea.

2. Epidemiological Trends for Europe and the World

2.1 Global diarrhoeal burden (including Europe)

Diarrhoea is one of the second leading causes of death among children under five globally, followed by pneumonia (Figure 6.20.2). According to the research from the Institute for Health Metrics and Evaluation (IHME), it was estimated that diarrhoeal illnesses were
responsible for 60.1 million DALYs (disability-adjusted life years) and 666,000 deaths among children under the age of five annually in 2010, which decreased from 70.6 million DALYs and 782,000 deaths in 2005. According to the 2012 study by Liu L et al., the number of child death under five due to diarrhoea was estimated to be 801,000 in 2010, which was 4.0% reduction from 2000 with 1.160 million deaths per year in the same age population. Even in considering whole age groups, diarrhoeal burden is one of the highest, being the second leading cause of death in the low-income countries (8.2%), and fifth in the middle-income countries (4.4%) and globally (4.3%) according to WHO 2008 data. According to the research from IHME, males suffered from diarrhoea slightly more than females when they were young (Figure 6.20.3). Diarrhoea disproportionately affects the poorest population: around 90 per cent of deaths due to diarrhoea occur in the poorest regions such as in sub-Saharan Africa and South Asia (Table 6.20.1). Countries with the highest death tolls are mostly poor and populous, such as India (237,500 deaths in 2008), Nigeria (201,400), Democratic Republic of the Congo (102,700), Afghanistan (89,700), Pakistan (74,000) and Ethiopia (73,300). There is also the huge child survival gap with countries. It is reported that the poorest and most vulnerable children within countries are more likely to be exposed to pathogens which cause diarrhoea due to poor sanitation and/or inadequate water supplies, and develop severe illness due to malnutrition.

**Figure 6.20.2: Global causes of child deaths in 2010**

Note: Data are separated into deaths of neonates aged 0–27 days and children aged 1–59 months. Causes under 1% of deaths are not depicted.
**Update on 2004 Background Paper, BP 6.20 Diarrhoea**

Figure 6.20.3: Absolute DALYs caused by diarrhoea in the world, by gender and age group in 2010

![Absolute DALYs caused by diarrhoea in the world, by gender and age group](image)


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Table 6.20.1: Deaths among children under age five due to diarrhoea, 2010

<table>
<thead>
<tr>
<th>UNICEF regions24</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>430 000</td>
<td>54</td>
</tr>
<tr>
<td>South Asia</td>
<td>300 000</td>
<td>37</td>
</tr>
<tr>
<td>East Asia and Pacific</td>
<td>34 000</td>
<td>4</td>
</tr>
<tr>
<td>Middle East and North Africa</td>
<td>36 000</td>
<td>4</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td>12 000</td>
<td>1</td>
</tr>
<tr>
<td>Central and Eastern Europe and the Commonwealth of Independent States</td>
<td>6 000</td>
<td>1</td>
</tr>
<tr>
<td>Least developed countries</td>
<td>350 000</td>
<td>44</td>
</tr>
<tr>
<td>Developing countries</td>
<td>801 000</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Industrialized countries</td>
<td>&lt;1 000</td>
<td>&lt;1</td>
</tr>
<tr>
<td>World</td>
<td>801 000</td>
<td>100</td>
</tr>
</tbody>
</table>


Note: Due to rounding, regional values may not sum to the world total, percentages may not sum to 100.
Rotavirus is the leading cause of acute diarrhoea. As of January 2012, the WHO estimates that globally 453 000 child deaths occurred during 2008 due to rotavirus infection.\textsuperscript{25} India was the highest in the number of deaths (98 621 deaths), representing 22\% of all rotavirus deaths under five. The cause-specific mortality rate (rotavirus deaths under age five per 100 000 population under age five) was the highest in Afghanistan (474 per 100 000). Chad, Somalia and Burundi also had rotavirus cause-specific mortality rate of greater than 300 per 100 000.

For cholera, it is estimated that around 1.4 billion people are at risk of cholera in endemic countries.\textsuperscript{26} An estimated 2.8 million cholera cases with about 91 000 deaths occurred annually in endemic countries between 2000 and 2008, and an estimated 87 000 cases with about 2 500 deaths occurred in non-endemic countries.\textsuperscript{26} Children under the age of five accounted for about half the cases and deaths. The burden of cholera is greatest in Africa and southern Asia (Annex 6.20.1, 2). The number of cholera cases under five has declined from 11 million, whose data came from the study between 1990 - 2002.\textsuperscript{27} However, different methodologies were used to estimate the cases in those two reports. Endemic cholera accounts for a majority of share in the global disease burden and is often under-detected and under-reported.\textsuperscript{21} Epidemic cholera also has a great impact on local health care management, as exemplified by large, recent outbreaks in Haiti and Viet Nam, Zimbabwe and Sierra Leone.\textsuperscript{26,28} Like rotavirus, cholera does not pose a threat to people in a region with minimum standards of hygiene, but it still remains a challenge to many places where there is a lack of access to safe drinking water and adequate sanitation.\textsuperscript{6}

Recent estimates about Shigella burden showed that Shigella was responsible for 90 million cases with 108 000 deaths annually worldwide.\textsuperscript{9} Mostly, Shigella cases occurred in developing countries, and the majority of cases and deaths occurred among children under five.\textsuperscript{7} Furthermore, Shigella dysenteriae type 1 (sd1) epidemics also affect all age groups.\textsuperscript{8} Also, about half a million cases of shigellosis occurred among military personnel and travelers from industrialized countries each year.\textsuperscript{9}

Global child death under the age of five due to Cryptosporidium was estimated to be 80 000 in 2010.\textsuperscript{15} According to the informal consultation from the WHO/Pan American Health Organization (PAHO) in 1991, over 58 million cases annually of diarrhoea detected in children are associated to intestinal protozoa infections.\textsuperscript{29} In Costa Rica, 4.3 \% of child diarrhoea was due to Cryptosporidium and 10.8 \% in Venezuela. The latest data in 2011 reported that an estimated 748 000 cases of cryptosporidiosis occurred annually in the United States.\textsuperscript{30}

Global burden of disease due to diarrhoea, sorted by pathogens and age group, is summarized in the Figure 4, based on the dataset from IHME.\textsuperscript{15,16} Rotavirus is a leading cause of burden (DALYs) followed by Cryptosporidium, ETEC and Campylobacter.
Figure 6.20.4: Absolute DALYs caused by diarrhoea in the world, by pathogen and age group in 2010

Diarrhoea is a leading cause of death during complex emergencies and natural disasters.\(^1\) Temporary, overcrowded living environment is often associated with polluted water sources, a lack of sanitation and hygiene practices, contaminated food/water and malnutrition.\(^1\) All of them attribute to the spread and severity of diarrhoea. Also, inadequate health services and transport prevent individuals from access to a prompt and appropriate treatment of diarrhoea.\(^1\) When 500,000 to 800,000 Rwandan refugees escaped into the Democratic Republic of the Congo in 1994, it was estimated that 50,000 deaths in the first month were mostly due to diarrhoea.\(^31\)

Especially, the cholera outbreak in Haiti on October 2010 has been considered as the worst outbreak in the recent years.\(^32,33\) It was the first cholera epidemic in over 100 years in Haiti, with over 470,000 cases and 6,000 deaths. The epidemic occurred ten months after a catastrophic earthquake brought substantial damages to Haiti with more than 200,000 deaths and displaced one million residents, who were forced to stay in tents and slums with poor or no sanitation. A lack of sanitation after the earthquake allowed *V. cholerae* to spread rapidly through water system. Water levels in rivers increased due to long-lasting rains, which also accelerated the spread of the pathogen. Then, interventions were focusing on improved sanitation and treatment of cases. The following graph describes cholera incidence from October 20 to December 3 2010 (Figure 6.20.5).\(^34\)
2.2 Diarrhoeal burden in Europe

It was estimated that 3.6 million episodes of rotavirus disease occurred annually out of the 23.6 million children under five in the EU from 2000-2003. Every year, rotavirus accounts for 231 deaths, 87,000 hospitalizations and almost 700,000 outpatient visits (Annex 6.20.3).

Campylobacteriosis remains the most commonly reported infectious gastrointestinal disease in European countries. The rate of confirmed cases of campylobacteriosis kept stable during 2006 – 2009 with approximately 50 cases per 100,000 population (Annex 6.20.4). Campylobacteriosis was more frequently found in children under five, with a confirmed case rate for males of 144.34 cases and for females of 114.71 cases per 100,000 population in 2009. Most cases were reported during summer seasons. Campylobacter jejuni was the most frequently reported species in 2009 (36.4 %).

Salmonellosis is one of the most common gastrointestinal infections in the EU/EEA, while the confirmed case rates have been decreasing for over the last four years. The reported case rates are very high in children, especially under five (124 per 100,000 population). The Czech Republic (100.1 cases per 100,000), Slovakia (77.3), Lithuania (61.6) and Hungary (58.5) reported the highest confirmed case rates (Annex 6.20.5). Most cases were reported during summer seasons. In 2009, 1,722 outbreaks were reported by the EU/EEA countries, out of which 324 were verified with 4,500 cases.
Update on 2004 Background Paper, BP 6.20 Diarrhoea

Cholera is a rare disease in Europe, with 19 confirmed cases in 2009 (Annex 6.20.6). All reported cases were imported from outside the EU/EEA area. A cholera outbreak in Ukraine in 2011 resulted in 33 cholera cases with no death.\textsuperscript{5}

In 2009, the confirmed case rate of cryptosporidiosis was 2.74 per 100,000 population.\textsuperscript{36} It slightly increased from the previous three years, but greatly decreased from the late 1990s with around 5 cases per 100,000.\textsuperscript{38} The highest confirmed case rate was reported in Ireland (10.0 per 100,000 population in 2009), the United Kingdom (9.3 per 100,000) and Belgium (4.1 per 100,000) (Annex 6.20.7).\textsuperscript{36} The disease is likely to be underdiagnosed and underreported in several EU countries. Reports were provided by 21 out of 31 EU and EEA/EFTA countries.\textsuperscript{36}

The rate of confirmed giardiasis cases has been relatively stable between 2006 and 2009, with a rate of 5.6 per 100,000 in 2009 (Annex 8).\textsuperscript{36} Over 80\% of cases were reported from Romania, but there was uncertainty regarding with laboratory confirmation and case definition.\textsuperscript{36}

The confirmed case rate of shigellosis was 1.63 cases per 100,000 population in 2009 (Annex 6.20.9).\textsuperscript{36} Shigellosis is most prevalent in children under five. In the early summer in 2009, there were shigellosis outbreaks in Denmark, Norway and Sweden due to sugar peas imported from Kenya, with over 70 cases.\textsuperscript{39,40,41} Travel-associated cases, predominantly to regions outside of European countries, were more frequently reported than indigenous cases.\textsuperscript{36}

In 2009, 3,689 confirmed cases of enterotoxigenic \textit{E. coli} (ETEC) were reported by 27 EU and EEA countries. The overall notification rate was 0.86 cases per 100,000 (Annex 6.20.10). United Kingdom, Germany, Netherlands, Ireland and Sweden accounted for over 80\% of the total number of confirmed cases reported in 2009. The number of cases in Netherlands increased three times from 2008 (92 in 2008 to 313 in 2009) due to a nationwide outbreak associated with contaminated raw meat (steak tartare) with O:157.\textsuperscript{42}

Absolute DALYs caused by diarrhoea, sorted by European region and age group in 2010 is described in Figure 6.20.6, based on the dataset from IHME.\textsuperscript{15,16} Globally, the burden of diarrhoea is high in children under five. In the Western Europe, however, the absolute DALYs among elderly were also high, making a second peak in the age of over 80.
3. Control Strategy

3.1 Vaccination

Immunizations decrease the burden of diarrhoea in two ways: by preventing infections that cause diarrhoea directly, such as rotavirus, and by preventing infections that can lead to diarrhoea as a complication of an illness, such as measles.\(^1\) To date, there is no licensed vaccine against \textit{Shigella} or ETEC, but the vaccine research targeting those pathogens is underway.\(^43\)

The WHO listed 25 vaccine-preventable infections in 2012, two of which (rotavirus and cholera) cause diarrhoea.\(^44\)

3.1.1 Rotavirus

Rotavirus vaccine has been recommended by the WHO since 2006 and introduced into the routine immunization programme in 11 countries.\(^3,45\) There are two licensed live attenuated rotavirus vaccines available globally; monovalent human vaccine RV1 (Rotarix\(^\text{®}\)), manufactured by GlaxoSmithKline and pentavalent bovine–human reassortant vaccine RV5 (RotaTeq\(^\text{®}\)) by Merck.\(^2\) They have shown efficacy of 85–98\% against severe rotavirus diarrhoea in trials conducted in WHO’s Region of the Americas and the European Region, but 51 to 64 \% in developing countries in Africa and Asia.\(^2,45,46,47\) Both live attenuated
rotavirus vaccines are given orally but differ in the number of doses given and target different rotavirus strains. Generally in lower income countries, RV5 is given in three doses at six weeks, 10 weeks, and 14 weeks of age, and RV1 is given in two doses at 10 weeks and 14 weeks of age. In middle- and upper-income countries, RV5 is given in three doses at two months, four months, and six months of age, RV1 is given in two doses at two months and four months of age. As of target strains, RV1’s indication is only G1P1A strain, while RV5 addresses five distinctive strains (G1-G4, and P[8]). In addition, Lanzhou lamb rotavirus vaccine, which has been used only in China, showed effectiveness of 44.3% (95% confidence interval (CI), 28.4–56.7%) for children 9–11 months old in the latest study in 2012.

As a limitation of rotavirus vaccines, they should not be administered to children older than eight months old. Labeled maximum age for RV1 is 24 weeks, and 32 weeks for RV5. In addition, immune-compromised patients, such as infants with HIV/AIDS have a higher risk of vaccine-acquired rotavirus infection. The latest study in Mexico and Brazil (2011) showed that RV1 was associated with a short-term risk of intussusception (a form of bowel obstruction) in one out of every 51,000 to 68,000 vaccinated infants. Incidence ratio of intussusception occurred one to seven days after the first dose of RV1 was 5.3 (95% CI, 3.0–9.3) among infants in Mexico. In fact, the serious side effect resulted in the first rotavirus vaccine (Rotashield®) being withdrawn from the market in the USA in 1998.

3.1.2 Cholera

Several oral cholera vaccines are available and proved to be safe and effective. Currently, only two of these are being marketed. One of them is whole-cell recombinant B subunit (WC/rBS) vaccine (Dukoral, Crucell, Leiden, Netherlands) made of killed whole-cell V. cholerae O1 with purified recombinant B subunit of cholera toxoid. Due to the cross reaction with heat-labile toxin excreted by enterotoxigenic Escherichia coli (ETEC), the vaccine also provide short-term protection against ETEC. The vaccine has shown safety and efficacy with 85%–90% protection against cholera for four to six months in all age groups according to field trials in Bangladesh and Peru. The protective efficacy reduces after six months amongst young children, but remains around 60% against classical cholera and around 40% against El Tor cholera after two years in older children. This vaccine is currently administered in a three-doses schedule to 2-6 year old children, with a booster dose every six months, or as a two-dose regimen to older children and adults with a booster every other year. It is prequalified for purchase by United Nations agencies and has been used in several mass vaccination campaigns with WHO support. It is also licensed for travellers visiting cholera-endemic areas.

Variant WC/rBS (mOrvac and Shanchol™) is also a licensed vaccine by VaBiotech (Viet Nam), Shantha Biotechnics (India) and BioFarma (Indonesia), consisting of serogroups O1 and O139, without containing a recombinant B subunit. Unlike previously mentioned vaccine, these do not need to be administered with a buffer to neutralize stomach acidity. Shanchol™ was granted WHO prequalification in September 2011.

The WHO has never recommended the use of the parenteral cholera vaccine due to the lesser protective efficacy (45% for three months) and the unsuitability for public health purposes. The previously licensed oral live attenuated single-dose vaccine (CVD 103-HgR) is currently not being produced.
During a recent WHO ad hoc meeting regarding the integrated response to cholera outbreaks during large-scale humanitarian crises, it was agreed that cholera vaccines should be given reactively in regions where other interventions cannot be operated effectively. Providing access to safe drinking-water, and improving basic sanitation, hygiene and social mobilization should be prioritized and should not be hampered by vaccination programmes.

3.2 Other preventive approaches (hygiene, sanitation and nutrition)

Risk factors for diarrhoeal illness includes childhood underweight, suboptimal breastfeeding, unimproved water and sanitation, vitamin A deficiency and zinc deficiency. Reduction of childhood diarrhoea needs interventions to decrease those risk factors. Improved nutrition and overall health status reduce a child’s susceptibility to diarrhoea and dehydration. Clean living circumstances are less likely to transmit disease and children are less likely to be exposed to pathogens which cause diarrhoea.

Sanitation and hygiene programmes include various kinds of interventions, such as disposing of human excreta in a sanitary manner, washing hands with soap, increasing access to safe water, improving water quality at the source, and treating household water and storing it in a safe manner. Improving sanitation facilities has been associated with an estimated median reduction in diarrhoea incidence of 36 per cent according to reviewed studies in 1991. However, scaling up sanitation facilities to the level where they cover a whole community is a major challenge. Washing hands with soap is another important and cost-effective public health intervention to reduce transmission. A Cochrane study showed that hand washing with soap could reduce the diarrhoeal incidence. Accessible and plentiful water has also been shown to promote better hygiene and hand washing, and result in the reduction of diarrhoea, depending on the water sources and the quality of the water. In order to reduce the risk of diarrhoea due to *Giardia* and *Cryptosporidium*, filtration is a necessary process with the aid of coagulation and flocculation followed by disinfection (disinfection is the most commonly used and very effective process to kill bacteria and inactivate viruses). Impacts on diarrhoeal disease reduction by intervention area are summarized in Table 6.20.2 below.

<table>
<thead>
<tr>
<th>Intervention area</th>
<th>Reduction in diarrhoea frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hygiene</td>
<td>37%</td>
</tr>
<tr>
<td>Sanitation</td>
<td>32%</td>
</tr>
<tr>
<td>Water supply</td>
<td>25%</td>
</tr>
<tr>
<td>Water quality</td>
<td>31%</td>
</tr>
<tr>
<td>Multiple</td>
<td>33%</td>
</tr>
</tbody>
</table>

Adequate nutrition can reduce the risk of suffering from diarrhoea, especially from severe cases. Diarrhoea control, particularly in the first six months of life, may also help to reduce stunting prevalence among children. Breast milk is a good source of nutrition for babies. It also contains the antioxidants, hormones and antibodies to keep a baby healthy. Infants who are exclusively breastfed for the first six months of life and continue to be breastfed until the age of two and beyond develop fewer infections and have less severe illnesses than those who are not. It was also found that infants who are not breastfed have a six-times greater risk of death due to infectious diseases in the first two months of life, such as from diarrhoea, than those who are breastfed.

Micronutrient supplementation is also an effective approach to prevent diarrhoea among children. According to the latest Cochrane study (2010), vitamin A supplementation reduced the risk of all-cause mortality by 24% among children aged six months to five years old, compared with control group (Relative risk (RR) = 0.76 (95% CI 0.69 to 0.83). It also showed that mortality rate due to diarrhoea decreased by 28% in the same age group (RR = 0.72 (95% CI 0.57 to 0.91)). However, another Cochrane study (2011) found that vitamin A supplementation among infants younger than six months old did not result in mortality reduction due to diarrhoea (59 402 participants, nine studies, RR = 0.97 (95% CI 0.83 to 1.12)). In addition, several trials regarding to zinc supplementation have shown that adequate zinc resulted in a decline of diarrhoea cases among children. Cochrane studies regarding effectiveness on preventive interventions for diarrhoea are summarized in Figure 6.20.7 (Outcome: morbidity) and Figure 6.20.8 (mortality). Only point estimates were available in terms of effectiveness on mortality due to "a household-based water treatment", "disinfectant-only water treatment" and "disposal of human excreta".
Figure 6.20.7: Effect of preventive interventions on morbidity caused by diarrhoea.

**Effect of preventive interventions on morbidity**

- **Water quality under five** (1) 1905 children, 6 trials
- **Water quality all ages** (2)
- **Hand washing (Institution-based)** (3)
- **Hand washing (Community-based)** (4)
- **Vit A among infants from 6 months to 5 years** (5)
- **Vit A among infants younger than 6 months** (6)

*(1) Interventions to improve water quality for preventing diarrhoea, 1 905 children, 6 trials*
*(2) Interventions to improve water quality for preventing diarrhoea, 18 328 participants, 10 trials*
*(3) Hand washing for preventing diarrhoea, 7 711 children, 8 trials*
*(4) Hand washing for preventing diarrhoea, 4 trials*
*(5) Vitamin A supplementation for preventing morbidity and mortality in children from 6 months to 5 years of age, 24 135 children, 13 trials*
*(6) Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age, 59 402 children, 9 trials*

Source: Cochrane studies
Figure 6.20.8: Effect of preventive interventions on mortality.

Effect of preventive interventions on mortality

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Participants</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>A household-based water treatment</td>
<td>6,650</td>
<td>1 study</td>
</tr>
<tr>
<td>Disinfectant-only water treatment</td>
<td>6,650</td>
<td>1 study</td>
</tr>
<tr>
<td>Disposal of human excreta</td>
<td>1,260</td>
<td>1 study</td>
</tr>
<tr>
<td>Vitamin A supplementation</td>
<td>56,090</td>
<td>7 trials</td>
</tr>
<tr>
<td>Vitamin A supplementation for infants</td>
<td>59,402</td>
<td>9 studies</td>
</tr>
</tbody>
</table>

Source: Cochrane studies

3.3 Diagnosis

Diagnosis of diarrhoea relies on assessment of dehydration, the type of diarrhoea (watery diarrhoea, bloody diarrhoea and persistent diarrhoea) and the presence of malnutrition and non-intestinal infection. Methodology of the clinical assessment includes asking a patient history of the symptom and clinical observations of physical condition, such as sunken eyes, looking for a loss of elasticity of skin and thirst.

Determining the degree of dehydration is important to decide a treatment plan. The degree of dehydration is established based on on clinical signs and symptoms that reflect the amount of fluid lost:
- In the early stages of dehydration, there are no signs or symptoms.
- As dehydration increases, signs and symptoms start to develop. Initial signs include thirst, restless or irritable behaviour, decreased skin turgor, sunken eyes, and sunken fontanelle (in infants).
Update on 2004 Background Paper, BP 6.20 Diarrhoea

- In severe dehydration, these effects become more pronounced and the patient may develop evidence of hypovolaemic shock, including: diminished consciousness, lack of urine output, cool moist extremities, a rapid and feeble pulse (the radial pulse may be undetectable), low or undetectable blood pressure, and peripheral cyanosis. Death follows soon if rehydration is not started quickly.

Estimation of the fluid deficit helps when estimating the fluid requirements. The estimate is calculated from the degree of dehydration and child body weight. Assessment of diarrhoea patients for dehydration and choice of treatment are summarized in Table 6.20.3. See also reference 64.

Other important factors to consider in diagnosis are to distinguish between dysentery diarrhoea and persistent diarrhoea, as these two types of diarrhoea require different case control approaches. Dysentery diarrhoea is diagnosed by the stool containing red blood. *Shigella* accounts for about 60% of dysentery cases observed in clinics and almost all cases of life-threatening dysentery. If the diarrhoea continues longer than two weeks, it is diagnosed as persistent diarrhoea.64

<table>
<thead>
<tr>
<th>SIGNs</th>
<th>CLASSIFY AS</th>
<th>IDENTIFY TREATMENT (Urgent pre-referral treatments are in bold print.)</th>
</tr>
</thead>
</table>
| Two of the following signs: | SEVERE DEHYDRATION | ➤ If child has no other severe classification:  
— Give fluid for severe dehydration (Plan C).  
OR  
If child also has another severe classification:  
— Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way.  
Advise the mother to continue breastfeeding  
➤ If child is two years or older and there is cholera in the area, give antibiotic for cholera. |
| ● Lethargic or unconscious  
● Sunken eyes  
● Not able to drink or drinking poorly  
● Skin pinch goes back very slowly | | |
| Two of the following signs: | SOME DEHYDRATION | ➤ Give fluid and food for some dehydration (Plan B).  
➤ If child also has a severe classification:  
— Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way.  
Advise the mother to continue breastfeeding  
➤ Advise mother when to return immediately.  
➤ Follow-up in five days if not improving. |
| ● Restless, irritable  
● Sunken eyes  
● Drinks eagerly, thirsty  
● Skin pinch goes back slowly | | |
| Not enough signs to classify as some or severe dehydration. | NO DEHYDRATION | ➤Give fluid and food to treat diarrhoea at home (Plan A).  
➤Advise mother when to return immediately  
➤Follow-up in five days if not improving. |


Note: Urgent pre-referral treatments are described in bold print.
Usage of diagnostic tool is not practical in clinical settings, because a patient can be simply diagnosed based on epidemiologic data and the clinical presentation of the patient. Also, the quality of laboratory testing is often not high enough to detect the cause of the diarrhoea and a diagnostic cell culture is costly and takes several days to identify the pathogens. Furthermore, antibiotics are not administered routinely for the treatment of diarrhoea except for the case of Shigella. However, diagnostic methods exist. Bacterial cultures with selective agars provide information of specific Salmonella, Shigella, Vibrio, Yersinia and Campylobacter species, regarding sensitivity to antimicrobial agents, information on strains, virulence factors or toxins during investigations of outbreaks. Molecular diagnostic techniques can detect bacterial genes, but the usage is limited to research and outbreak investigations. Historically, light microscopy was used to identify ova and parasites. Currently, ELISA is used to detect protozoa. Sensitive ELISA and latex agglutination analyses are currently used to rapidly determine the presence of a rotavirus infection. However, these two methods are not sufficient to identify specific genotypes.

When diarrhoea is suspected to be caused by a pathogen which produces toxins, such as V. cholerae and E. coli, identifying the toxins is more important than the pathogen. Multiplex genetic assays (a type of PCR assay) can be used to detect different toxins, pathogens and species or genotypes. However, the molecular techniques are not accessible and affordable for the primary care clinics and community health centers, especially in low income countries.

3.4 Treatment

In 2004, UNICEF and WHO issued the latest diarrhoea treatment recommendations for low-income countries, encouraging oral rehydration therapy (ORT) with solutions made of low-osmolarity oral rehydration salts (ORS) containing lower concentrations of glucose (75 mmol/l) and salt (75 mEq/l) and continued feeding and zinc treatment for children with acute diarrhoea. Early and appropriate fluid replacement is a key intervention to prevent child death due to diarrhoea. See also reference 64 and 69.

ORS solutions are the ‘gold standard’ therapy for diarrhoea, and the new formulation, low-osmolarity ORS, was proved to improve overall outcomes with a reduced incidence of vomiting and reduced stool volume compared with previous standard WHO ORS solution. ORS is available in smaller packet sizes (200 grams) and assorted flavours to improve compliance among children.

Treatment regimen depends on the degree of dehydration of a child. When a child has no signs of dehydration, home therapy should be provided to prevent dehydration and malnutrition (Treatment Plan A). When a child has signs of dehydration, he/she should receive ORT with ORS in a health care facility following Treatment Plan B. The amount of ORS solution given to the child depends on the age, weight and the degree of dehydration. When the child develops signs of severe dehydration, he should receive Treatment Plan C, which includes intravenous rehydration. Detailed information about the Treatment Plans is described in “The Treatment of Diarrhoea, A manual for physicians and other senior health workers” by the WHO (2005).

Other fluids such as sugar-salt solutions, cereal-based drinks and breast milk can also help prevent dehydration as a substitute for ORS solution, though they are not effective enough to
treat dehydrated children. Food intake is important not only because of the fluid replacement it contains, but also due to its effect in supporting fluid absorption from the gut into the bloodstream. However, food should not be provided during the initial four-hour rehydration period. Children continued on Treatment Plan B more than four hours should be given some food every three to four hours as with Treatment Plan A. All children over six months should be given some food before leaving for home.

The 2004 WHO and UNICEF joint statement recommended zinc treatment for 10–14 days, along with low-osmolarity ORS, as a supportive therapy to reduce the length and severity of a diarrhoea episode, to reduce stool volume and the need for advanced medical care.

Treatment of diarrhoea for HIV positive children follows the regimens for non-HIV patients. However, HIV positive children are more likely to have lactose and monosaccharide intolerances. At the end of 2012, the first anti-diarrhoeal medicine, Fulyzaq™ (crofelemer), to relieve symptoms of diarrhoea in HIV/AIDS patients taking antiretroviral therapy was approved by US Food and Drug Administration (US FDA). Crofelemer works by blocking chloride ions secretion reducing with the high volume of water loss in diarrhoea, and by normalizing the flow of chloride ions and water into the gastrointestinal tract. In a clinical trial, a significantly larger proportion of patients receiving crofelemer experienced clinical response (less than or equal to two watery bowel movements per week during at least two of the four weeks) compared with placebo group (17.6% versus 8.0%, 1-sided p < 0.01). The new medicine is contraindicated in a patient with diarrhoea caused by an infection or a gastrointestinal disease. As a preventive intervention for HIV positive patients, the latest WHO recommendation (2010) includes Vitamin A supplementation among children aged six months to five years and co-trimoxazole prophylaxis.

Antimicrobials are not recommended to be used routinely against diarrhoea. First, many of the pathogens causing diarrhoea are unresponsive to antimicrobials and identifying the pathogens is quite challenging. Selection of an effective antimicrobial often needs the data about the sensitivity of the medicine against the pathogens and such information is usually unavailable. Use of antimicrobials causes the cost of treatment to be increased, adverse reactions and the opportunity to develop resistant strains. However, antimicrobials are reliably helpful for children with bloody diarrhoea, suspected cholera with severe dehydration, and serious non-intestinal infections such as pneumonia. Anti/protozoal drugs are rarely indicated. The usage of antimicrobials to treat specific causes of diarrhoea is summarized in Table 6.20.4.

Antidiarrhoeal medicines have no practical benefits for children with acute or persistent diarrhoea and do not prevent dehydration. Some cause dangerous, and sometimes fatal, adverse reactions, so should never be given to children under five. For instance, codeine (antidiarrhoeal medicine) is used in the symptomatic relief of uncomplicated, acute diarrhoea in adults, but is contraindicated in young children. Codeine acts on opioid receptors in the gut wall and decreases bowel motility.
Table 6.20.4: Antimicrobials used to treat specific causes of diarrhoea

<table>
<thead>
<tr>
<th>Cause</th>
<th>Antibiotics</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholera&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>Doxycycline (Adults only) or Tetracycline</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Shigella dysentery&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ciprofloxacin</td>
<td>Pivmecillinam Ceftriaxone</td>
</tr>
<tr>
<td>Amoebiasis</td>
<td>Metronidazole</td>
<td></td>
</tr>
<tr>
<td>Giardiasis</td>
<td>Metronidazole or Tinidazole</td>
<td></td>
</tr>
</tbody>
</table>


Note: a. Selection of an antimicrobial should be based on sensitivity patterns of strains of Vibrio cholerae O1 or O139, or Shigella recently isolated in the area.
b. An antimicrobial is recommended for patients older than two years with suspected cholera and severe dehydration.

Careseeking behaviors for suspected diarrhoea were studied in several regions. In rural Burkina Faso (2010), 54.9% of the caregivers of children under five looked for care outside the home, mostly by consulting care providers in public sector health clinics. Around 80% of those who sought health care were given some form of treatment. Traditional therapies, such as amulets or medicines made from plants, were most commonly administered (29.5%). Around one quarter of children received ORS solutions. Other medications, such as antibiotics (13.6%) and unidentified drugs (27.6%) were also administered. In rural Niger (2009), 70.4% sought care at a health structure, and amongst those who sought health care 80.4% received ORS. In rural China (2012) among children under three, most of the caretakers sought care outside the home (91.25%). Of these 37% sought high-level care at township or county level, while 40% sought village level care.

### 3.5 Diarrhoea control during outbreaks

Diarrhoea control is a prime concern in complex emergencies such as war and civil disturbance. The scarcity of clean water is the main cause for the outbreak. Also, malnutrition becomes common and substantially increases when feeding practices are disordered and sanitation is disrupted. Priority interventions include distribution of safe water in adequate quantities, establishment of appropriate sanitation facilities, launching health services to detect and treat cases swiftly, and encouraging hygiene practices. In recent years, there has been progress in implementing community-based interventions to respond emergencies, such as promoting exclusive breastfeeding, micronutrient supplementation, point-of-use water treatment, hand washing with soap, and treating cases with ORS or appropriate homemade fluids.
3.6 Integrated global action plan for diarrhoea and pneumonia

In April 2013, the Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) was issued jointly by UNICEF and the WHO. This plan sets specific goals by 2025 for a reduction in the number of deaths and the incidence of diarrhoea as well as pneumonia, which are both the leading killers among children under five. The plan also goes beyond the Millennium Development Goal for 2015 on child survival, and is contributed to by the United Nations Global Strategy for Women’s and Children’s Health launched in 2010 and the Global Vaccine Action Plan. In the UN global strategy in 2012, there was a call to action to reduce child mortality to 20 or fewer child deaths per 1 000 live births in each country by 2035.

To address the issues, GAPPD set specific goals for 2025:

- reduce mortality from pneumonia in children less than five years of age to fewer than three per 1 000 live births;
- reduce mortality from diarrhoea in children less than five years of age to fewer than one per 1 000 live births;
- reduce the incidence of severe pneumonia by 75% in children less than five years of age compared to 2010 levels;
- reduce the incidence of severe diarrhoea by 75% in children less than five years of age compared to 2010 levels;
- reduce by 40% the global number of children less than five years of age who are stunted compared to 2010 levels.

The GAPPD also provides a diarrhoea-pneumonia integrated framework for prevention, protection and treatment. Complementarity between diarrhoea and pneumonia interventions is summarized in Figure 4, page 14 of the GAPPD report.

4. Affordability, feasibility, and sustainability of the control strategy

There are several cost-effectiveness studies regarding rotavirus vaccination. A national rotavirus immunization program in Egypt resulted in a cost-effectiveness ratio of US$ 363 per DALY. Rheingans et al. showed the cost-effectiveness of various health interventions in Latin America as depicted in Table 6.20. See also reference 81.
Table 6.20.5: Comparison of the cost-effectiveness of various health interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Location</th>
<th>Cost-effectiveness ratio (US$/DALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrheal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus vaccination (US$ 24/course)</td>
<td>8 Latin American countries</td>
<td>269 to 10 656</td>
</tr>
<tr>
<td>Rotavirus vaccination (US$ 16/course)</td>
<td>8 Latin American countries</td>
<td>161 to 4 437</td>
</tr>
<tr>
<td>Oral rehydration therapy expansion to 50%</td>
<td>Latin America (low mortality)(^{b})</td>
<td>1 085</td>
</tr>
<tr>
<td>Point of use water treatment</td>
<td>Latin America (low mortality)(^{b})</td>
<td>1 092</td>
</tr>
<tr>
<td>Water supply and sanitation</td>
<td>Global</td>
<td>13 00</td>
</tr>
<tr>
<td>Hygiene education</td>
<td>Global</td>
<td>9 to 160</td>
</tr>
<tr>
<td>Breast-feeding promotion</td>
<td>Brazil, Honduras, Mexico</td>
<td>12 to 19</td>
</tr>
<tr>
<td>Child health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc supplementation (children &lt; 5 yr)</td>
<td>Latin America (low mortality)(^{b})</td>
<td>102</td>
</tr>
<tr>
<td>Vitamin A supplementation</td>
<td>Latin America (low mortality)(^{b})</td>
<td>521</td>
</tr>
<tr>
<td>Integrated management of childhood illness</td>
<td>Global</td>
<td>40 to 140</td>
</tr>
</tbody>
</table>


Note: a Costs have been converted to 2003 US$ for comparison; DALY = disability-adjusted life year.

\(^{b}\) Countries are classified by the World Health Organization according to region and mortality stratum. All eight countries selected for this study are classified as having low child and low adult mortality. Within Latin America, the following countries are classified as having high child and high adult mortality: Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, and Peru.

The cost effectiveness of cholera vaccines was examined in cholera endemic areas and in stable refugee populations where there were epidemics.\(^{82}\) The results are shown in Table 6. In a population with endemic cholera, the net costs per DALY averted due to vaccination are higher than the net cost per DALY averted due to the other interventions. Meanwhile, in a stable refugee population at risk for epidemic cholera, the net cost per DALY averted due to vaccination is almost the same as the interventions regarding with sanitation and drinking water. Murray J et al. mentioned that the reason of the cost reduction in a stable refugee population was that attack rates were higher and access to health care facilities was assumed to be 100%.\(^{82}\) Outpatient treatment and inpatient treatment were more cost effective than the other interventions against endemic cholera and epidemics in the stable refugee population. In addition, the recent study in Zanzibar (2012) showed that US$ 30 000 per DALY was averted in an oral cholera mass vaccination campaign against endemic cholera.\(^{83}\) The author concluded that mass vaccination campaigns in Zanzibar to control endemic cholera becomes cost-effectiveness, especially in high-incidence areas and when OCV prices are less than US$ 1.30.\(^{83}\)
### Table 6.20.6: Costs per DALY averted, by intervention type, for cholera and simple diarrhoea in a population at risk for endemic cholera (above) and In a stable refugee population at risk for epidemic cholera (below)

#### In a population at risk for endemic cholera

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Net cost (US$)</th>
<th>Cholera cases averted (r)</th>
<th>Simple diarrhoea cases averted (r)</th>
<th>Cholera deaths averted (r)</th>
<th>Simple diarrhoea deaths averted (r)</th>
<th>DALYs averted (n)</th>
<th>Net cost per DALY averted (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>573 845</td>
<td>40</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>193</td>
<td>2973</td>
</tr>
<tr>
<td>Drinking-water and sanitation</td>
<td>1 954 700</td>
<td>43</td>
<td>18 360</td>
<td>9</td>
<td>104</td>
<td>4 133</td>
<td>433</td>
</tr>
<tr>
<td>Outpatient treatment</td>
<td>317 107</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>78</td>
<td>2 023</td>
<td>157</td>
</tr>
<tr>
<td>Inpatient treatment</td>
<td>9 551</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>49</td>
<td>1 294</td>
<td>7</td>
</tr>
<tr>
<td>Drinking-water and sanitation + vaccine</td>
<td>2 529 000</td>
<td>67</td>
<td>18 360</td>
<td>14</td>
<td>104</td>
<td>4 253</td>
<td>556</td>
</tr>
<tr>
<td>Drinking-water and sanitation + treatment</td>
<td>2 281 458</td>
<td>43</td>
<td>18 360</td>
<td>15</td>
<td>196</td>
<td>6 439</td>
<td>327</td>
</tr>
</tbody>
</table>

#### In a stable refugee population at risk for epidemic cholera

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Net cost (US$)</th>
<th>Cholera cases averted (r)</th>
<th>Simple diarrhoea cases averted (r)</th>
<th>Cholera deaths averted (r)</th>
<th>Simple diarrhoea deaths averted (r)</th>
<th>DALYs averted (n)</th>
<th>Net cost per DALY averted (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>688 000</td>
<td>422</td>
<td>0</td>
<td>85</td>
<td>0</td>
<td>2 562</td>
<td>269</td>
</tr>
<tr>
<td>Drinking-water and sanitation</td>
<td>1 704 860</td>
<td>320</td>
<td>18 360</td>
<td>64</td>
<td>104</td>
<td>5 846</td>
<td>276</td>
</tr>
<tr>
<td>Outpatient treatment</td>
<td>320 021</td>
<td>0</td>
<td>0</td>
<td>79</td>
<td>97</td>
<td>4 416</td>
<td>72</td>
</tr>
<tr>
<td>Inpatient treatment</td>
<td>12 782</td>
<td>0</td>
<td>0</td>
<td>79</td>
<td>97</td>
<td>4 416</td>
<td>3</td>
</tr>
<tr>
<td>Drinking-water and sanitation + vaccine</td>
<td>2 393 400</td>
<td>573</td>
<td>18 360</td>
<td>114</td>
<td>104</td>
<td>7 356</td>
<td>313</td>
</tr>
<tr>
<td>Drinking-water and sanitation + treatment</td>
<td>2 075 973</td>
<td>320</td>
<td>18 360</td>
<td>158</td>
<td>244</td>
<td>11 679</td>
<td>170</td>
</tr>
</tbody>
</table>


A WHO study (2008) showed the cost effectiveness of interventions regarding with water sources and sanitation.\(^{57}\) According to the study, an investment of US$ 11.3 billion per year is needed to meet the drinking water and sanitation target of the Millennium Development Goals (MDGs), which resulted in a payback of US$ 84 billion a year.\(^{57}\) Benefit–cost ratios by intervention area in developing regions and Eurasia are summarized in Table 6.20.7.\(^{57}\) It shows intervention on universal access to improved water and sanitation services costs more, but annual benefits are higher than smaller scale of intervention which do not cover all the population in the region. The benefit-cost ratio of universal access to a regulated piped water supply and sewage connection becomes less cost-effective than the other interventions, but still creates four-fold more benefits than the cost.
Table 6.20.7: Benefit–cost ratios by intervention area in developing regions and Eurasia

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Annual benefits in US$ millions</th>
<th>Benefit–cost ratio by intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halving the proportion of people without access to improved water sources by 2015</td>
<td>18 143</td>
<td>9</td>
</tr>
<tr>
<td>Halving the proportion of people without access to improved water sources and improved sanitation by 2015</td>
<td>84 400</td>
<td>8</td>
</tr>
<tr>
<td>Universal access to improved water and sanitation services by 2015</td>
<td>262 879</td>
<td>10</td>
</tr>
<tr>
<td>Universal access to improved water and improved sanitation and water disinfected at the point of use by 2015</td>
<td>344 106</td>
<td>12</td>
</tr>
<tr>
<td>Universal access to a regulated piped water supply and sewage connection by 2015</td>
<td>555 901</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: To calculate a benefit–cost ratio, the total benefits are divided by the total costs. Projects with a benefit–cost ratio greater than one have greater benefits than costs. The higher the ratio, the greater the benefits relative to the costs.

5. Reasons why the disease burden persists

5.1 Is there a pharmaceutical ‘gap’?

To some extent, yes. Pharmaceutical gaps include:

- There are vaccines against rotavirus and cholera on the market, but several other pathogens also caused substantial burden due to diarrhoea.
- Rotavirus vaccine has not yet proved to be effective in many developing countries, in areas such as Africa and Asia.
- There is only limited information on the efficacy on epidemic and reactive usage of the cholera vaccine.
- There have been occurrences of drug resistant strains, including Sd1 strain resistance to fluoroquinolones, which were seen in outbreaks in India and Bangladesh in 2000.

However, accessibility to and availability of existing pharmaceuticals and preventive interventions are largely addressed.

5.2 Access to control strategy

Other than pharmaceutical gaps, the underlying reason as to why the disease burden persists is a ‘rich-poor’ gap in the access to preventive measures and treatment. For instance, existing vaccines against rotavirus and cholera are underutilized, and especially in low income countries the rotavirus vaccines are largely unavailable. However, in the case of rotavirus, a total of 14 low-income countries in regions where vaccine efficacy has been proven are
eligible for financial support from the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunization) for the purchase of rotavirus vaccine. If current trials in Africa and Asia can show sufficient efficacy, it is expected that the support would be expanded to the other 58 countries. Generally, lower efficacy of oral vaccines is common in countries with high rates of poverty and death, which is due to the effect of maternal antibodies, micronutrient deficiencies, and persistent exposure to pathogens. Despite lower efficacy, the availability and use of rotavirus vaccines globally contributes greatly to the achievement of the Millennium Development Goals in terms of childhood mortality.

Also, many people are still struggling to access to safe water, nutrition and medicine. For the last decade, percentage of children under five with diarrhoea receiving ORS only slightly increased from 30% in 2000 to 32% in 2010 (Figure 6.20.9). For zinc accessibility, information is limited, but it is suggested that coverage is still low (Table 6.20.8). Coverage gaps also persist between countries, as well as within countries. Since 1990 over two billion people have gained access to an improved drinking water source, but many of the poorest households are still missing this access (Figure 6.20.10). Coverage gaps between the rich and the poor are larger in sub-Saharan Africa, East Asia and Pacific and Latin America and the Caribbean. In fact, most of those who cannot access to safe water live in rural areas. In 2010, 783 million people did not have access to an improved drinking water source, and 83 per cent are from a rural area.

Figure 6.20.9: Percentage of children under age five with diarrhoea receiving ORS (ORS packet or prepackaged ORS fluids), by region, around 2000 and around 2010

Note: a. Excludes China. Note: Estimates are based on a subset of 65 countries with available data covering 74 per cent of the under-five population in developing countries(excluding China, for which comparable data are not available) and at least50 per cent of the under-five population in each region. Data coverage was insufficient to calculate the regional average for CEE/CIS, Latin America and the Caribbean, and industrialized countries.
Table 6.20.8: Share of children under age 5 with diarrhoea receiving zinc treatment, countries with data, 2006–2011 (per cent)

<table>
<thead>
<tr>
<th>Country</th>
<th>Per cent</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albania</td>
<td>5</td>
<td>DHS 2008–2009</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>23</td>
<td>DHS 2007</td>
</tr>
<tr>
<td>Bhutan</td>
<td>1</td>
<td>MICS 2010</td>
</tr>
<tr>
<td>Cambodia</td>
<td>2</td>
<td>DHS 2010</td>
</tr>
<tr>
<td>Chad</td>
<td>&lt;1</td>
<td>MICS 2010</td>
</tr>
<tr>
<td>Democratic People’s Republic of Korea</td>
<td>19</td>
<td>MICS 2009</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>2</td>
<td>MICS 2010</td>
</tr>
<tr>
<td>El Salvador</td>
<td>12</td>
<td>Other 2008</td>
</tr>
<tr>
<td>Ghana</td>
<td>2</td>
<td>DHS 2008</td>
</tr>
<tr>
<td>Guyana</td>
<td>1</td>
<td>DHS 2009</td>
</tr>
<tr>
<td>India</td>
<td>&lt;1</td>
<td>DHS 2005–2006</td>
</tr>
<tr>
<td>Kenya</td>
<td>&lt;1</td>
<td>DHS 2008–2009</td>
</tr>
<tr>
<td>Liberia</td>
<td>&lt;1</td>
<td>DHS 2007</td>
</tr>
<tr>
<td>Madagascar</td>
<td>1</td>
<td>DHS 2008–2009</td>
</tr>
<tr>
<td>Malawi</td>
<td>&lt;1</td>
<td>DHS 2010</td>
</tr>
<tr>
<td>Nepal</td>
<td>6</td>
<td>DHS 2011</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1</td>
<td>DHS 2008</td>
</tr>
<tr>
<td>Philippines</td>
<td>2</td>
<td>DHS 2008</td>
</tr>
<tr>
<td>Rwanda</td>
<td>&lt;1</td>
<td>DHS 2007–2008</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>2</td>
<td>DHS 2008</td>
</tr>
<tr>
<td>Timor-Leste</td>
<td>6</td>
<td>DHS 2009–2010</td>
</tr>
<tr>
<td>Uganda</td>
<td>1</td>
<td>DHS 2006</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>5</td>
<td>DHS 2010</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>&lt;1</td>
<td>DHS 2010–2011</td>
</tr>
</tbody>
</table>

Figure 6.20.10: Share of population using an improved drinking water source, by household wealth quantile and region, 2004–2009 (per cent)

Note: a. Excludes China. b. Unweighted average of 10 countries in the region with available data. c. Available data cover 51 per cent of the region’s population and exclude Algeria and Turkey. d. Available data cover 59 per cent of the region’s population and exclude the Russian Federation. The asset index used to classify households into wealth quintiles has not been adjusted for the drinking water variable that is part of the index.

6. Research and Development

6.1 Research priorities

Research priorities to decrease global mortality due to childhood diarrhoea by 2015 was investigated in 2009 by the Department of Child and Adolescent Health and Development (CAH) in WHO using the Child Health and Nutrition Research Initiative (CHNRI) methodology. In brief, the CHNRI method provides a score for each research topic based on the full spectrum of research investment options, the potential risks and benefits from investments, and possibilities to reduce the persisting burden and disability through investments. The 15 proposed research questions with the highest overall research priority score with average expert agreement are listed below. See also reference 85 for the methodology and more detailed information.

1. What is the acceptability and effectiveness of the new reduced osmolarity ORS in clinic as well as in the community?
2. What is the effectiveness of zinc supplementation on the outcome and incidence of diarrhoea in the community?
3. What are the barriers against appropriate use of ORT?
4. Design locally adapted training programmes to orient health workers on integrated management of childhood illness (IMCI)
5. What is the impact of IMCI in different population groups on timely identification and treatment of acute diarrhoeas?
6. Identify cost-effective, sustainable methods for community-based promotion and support for early initiation and continuation of breastfeeding during first six months of life and prolonged breastfeeding
7. Test indicators to determine effectiveness of IMCI in treatment of diarrhoea and in terms of reducing disease burden
8. Assess cost-effectiveness of outpatient treatment of diarrhoea with zinc and ORS
9. Assess proportion of cases with diarrhoea who get appropriate outpatient treatment
10. What is the impact of IMCI in different population groups on administration and promotion of zinc therapy for acute and persistent diarrhoeas?
11. Assess integration of zinc treatment for diarrhoea and the use of zinc in prevention
12. Identify means to make community promotion of breastfeeding sustainable
13. Assess effectiveness of delivery strategies to provide zinc and ORT
14. Assess optimal dose and duration of zinc for diarrhoea treatment
15. What is the acceptability/adherence to zinc supplementation for the management of diarrhoea in various settings (urban, rural)?

Research questions with the higher research priority score are more likely to focus on “health systems and policy research” and “epidemiological research” rather than “research to develop new interventions” or “research to improve the existing interventions”. That is because, as Fontaine O et al. mentioned, those research questions with higher scores benefitted by the CHNRI study settings of quick win research situations with a short time frame by 2015. Other limitations of this study include overlaps of concept between several questions and repeated variations of questions in the list, for instance, there were 30 questions regarding zinc.

Because of the long lead time for development of new vaccines and medicines, a long term commitment will be needed for: 
- Basic research for cholera, *Shigella* and *Cryptosporidium*
- Vaccines for *E. coli* (ETEC), cholera, *Shigella* and *Cryptosporidium*
- New pharmaceuticals for the treatment of cholera, *Shigella* and *Cryptosporidium*, including ones against drug resistant strains (see Chapter 6.1)
- Diagnostics (point of care)

### 6.2 Vaccines

In a global vaccine action plan, the Decade of Vaccines (2011–2020) collaboration listed several pathogens as an example of vaccine targets towards the licensure and launch of a vaccine programme. These pathogens are not currently vaccine-preventable agents, such as *Cytomegalovirus*, dengue virus, group A *Streptococcus*, hepatitis C virus, hookworm, *Leishmania* and respiratory syncytial virus. For diarrhoeal diseases, vaccines against rotavirus and cholera exist, while there is no vaccine against several pathogens including *Shigella*, enterotoxigenic *E. coli* and *Cryptosporidium*. 
6.2.1 Rotavirus

Several candidate vaccines have been found to be immunogenic in preclinical trials and/or clinical trials. Whether they will further proceed into the late-stage clinical trials will depend on the outcomes of the current live oral RV vaccines, including pricing and efficacy in endemic countries especially in Africa.9 Another issue to consider carefully is a cross protection against the full range of RV strains, including serotype G9, which is becoming important in Asian countries, and G8, which is wide-spread across Africa.9

Vaccines which were licensed for use in industrialized countries require more time to make them available in developing countries. PATH’s Rotavirus Vaccine Program (RVP) was established in 2003 partnering with the USA CDC and WHO along with funding by the GAVI Alliance (GAVI).87 It was to announced to accelerate the licensing and availability of rotavirus vaccines in the developing countries and reduce the time lag. Also, it has been creating and disseminating information about vaccine efficacy, safety and cost-effectiveness of rotavirus vaccines.87

Candidate vaccines against rotavirus include:

- Live attenuated RV strains, RV3 (P2[6]-G3), is a candidate live oral vaccine, which showed protective efficacy 54% against rotavirus epidemic in an early Phase II trial.88

- There are several candidates of live reassortant RV strains. Human-animal reassortant RV strains containing the VP7 or VP4 RNA segment from a human RV strain has shown to provide the required antigenicity.89 A multivalent bovine-human reassortant oral vaccine, developed by the National Institute of Allergy and Infectious Diseases, addresses the five most common RV serotypes in humans, G1-G4, G8 and G9.90 The Phase II study showed a good immune response and no adverse drug interaction with concomitantly administered childhood vaccines.90 A tetravalent rhesus-human reassortant RV vaccine (Rotashield™) with the simian RRV strain (G3) mixed with three human-simian reassortant strains of G types 1, 2, and 4, was on the market from 1998 until withdrawal due to an adverse intestinal event, intussusception.9

- A naturally occurring human-bovine, neonate-derived RV strain, 116E (P[10]-G9), which was isolated from a nosocomial outbreak of asymptomatic infection in New-Delhi, is under development by Bharat Biotech Ltd in India.89 A Phase I trial placebo controlled study showed safety and good tolerance among eight-week-old infants.89

- Other RV vaccine approaches include an inactivated virus vaccine (formalin-inactivated rhesus rotavirus), DNA vaccines, a VP6 subunit vaccine and virus-like particles expressed in a baculovirus system.9

6.2.2 Shigella

In 1992, the WHO published a paper titled “New strategies for accelerating Shigella vaccine development.”91 This paper described what had been done and the many challenges faced in developing Shigella vaccines. The need for Shigella vaccines is clearly justified by the high global burden of disease as well as increasing multi-resistance to antibiotics.92 There have been two approaches to Shigella vaccines, live attenuated vaccines and lipopolysaccharide
Update on 2004 Background Paper, BP 6.20 Diarrhoea

(LPS)-conjugate vaccine for several decades. Both of them are mostly focusing on S. flexneri 2a and S. sonnei, as well as on Sd1. To date, both approaches have shown to be promising, with efficacy studied in human clinical trials.

Various live, attenuated Shigella vaccine candidates are under development. A S. flexneri 2a vaccine strain SC602 and an attenuated S. dysenteriae type 1 strain (SC599) carrying mutations in their icsA, iuc, iut and stxA genes were developed at the Pasteur Institute. SC602 was manufactured by the Walter Reed Army Institute of Research as a lyophilized vaccine product. Clinical studies have shown 75% of immunogenicity among 24 inpatient volunteers (North American) and 30% of reactogenicity rate. However, Phase I clinical trials of SC602 in Bangladesh resulted in no consistent increase in serum antibody against S. flexneri 2a LPS in any group. For SC599, a Phase I clinical trial of a single escalating dose for safety and immunogenicity showed good tolerance without significant side effects reported. However, serum antibody responses were modest or absent, because SC599 was highly attenuated.

Other live, attenuated vaccine candidates are being researched by Walter Reed Army Institute of Research (WRAIR). A Phase I, dose-escalating trial of SSRW1 in Israel showed immunogenicity and clinical acceptability. A Phase I study on strain WRSd1 resulted in modest immunogenic effect in human volunteers. In addition, a new S. flexneri vaccine candidate strain, WRSf2G11, is also under development.

The Center for Vaccine Development (CVD) in Maryland, USA has been working on attenuating S. flexneri 2a by targeted deletion of virulence genes. A Phase I clinical trial on S. flexneri 2a vaccine (CVD 1203) showed dose-dependence on reactogenicity and immunogenicity. Vaccine strain CVD 1207 showed good tolerance with a modest immunogenicity. Vaccine strains CVD 1204 and CVD 1208 were also under development. The CVD has also been working on a multivalent Shigella vaccine that can protect broadly against several Shigella strains. The technology is applied to live vectors for the expression of ETEC antigens, in order to express fimbrial and large T antigens.

In addition, the live, attenuated Salmonella typhi vaccine strain Ty21a as a carrier for Shigella LPS antigens was also investigated, but has been found to have only limited efficacy so far.

Another approach on vaccine research includes the development of conjugate vaccines, such as detoxified O-specific polysaccharide protein conjugate vaccines. The conjugate vaccines have been tested in clinical trials and found to be safe and highly immunogenic among young adults. In addition, antibody levels remained at high levels at two years and at were still raised (40–50%) levels up to four -five years after vaccination.

Also, WRAIR has been developing a Shigella flexneri Invaplex 50, which is a macromolecular complex containing several antigens extracted from virulent Shigella. A Phase I clinical study showed that the vaccine was well tolerated, safe and encouraging mucosal immune responses. Also, the International Vaccine Institute and WRAIR has been developing subunit Shigella vaccines, including a parenteral nuclear protein/ribosomal vaccine.

An inactivated whole-cell vaccine made of S. sonnei is under development at the Johns Hopkins University in Baltimore, MD, USA. A Phase I trial has been showing to be well tolerated with protective efficacy against diarrhoea, dysentery or fever was 36%. Also,
Antex (USA) is developing a *Shigella* inactivated whole-cell vaccine and an oral vaccine for travellers' diarrhoea (Activax™) containing antigens from *Campylobacter, Shigella* and ETEC.¹⁰

Supporting researches are also necessary to make vaccine development more successful. First, epidemiological data regarding with serotype distribution of shigellosis in the world are essential to conduct clinical trials properly.¹² Second, animal models relevant to human bacillary dysentery also facilitate R&D of *Shigella* vaccines.⁹⁷

### 6.2.3 Enterotoxigenic E coli (ETEC)

Historically immunogenicity of ETEC has been expected because of decreased rates of ETEC diarrhoea and lower ratios of symptomatic to asymptomatic ETEC infections with increasing age. Scientific research revealed that pathogenesis seemed to be related with specific proteins, such as colonization factor antigens (CFAs).⁹

The cholera vaccine (Dukoral™) was found to prevent 23% of all diarrhoea episodes and 52% of episodes due to ETEC in Finnish tourists visiting Morocco, but the protection did not last more than a few months.⁹⁸ A retrospective study in Spain showed that Dukoral™ reduced the risk of travelers’ diarrhoea by 43%.⁹⁹

One of the promising ETEC vaccines, a killed oral whole-cell ETEC vaccine, has been developed by the University of Göteborg, Sweden.⁹ A pilot efficacy trial of the vaccine among European tourists travelling to developing countries resulted in 80% protection against ETEC diarrhoea.¹⁰⁰ The Phase II studies conducted in Bangladesh, Egypt, Israel, Nicaragua, the USA and Europe have also shown the safety and immunogenicity to date.⁹ Other oral killed vaccines are also being investigated, such as *E. coli* bacteria K12 over-expressing CFA/I.⁹

Pierrel Research USA. Inc and Johns Hopkins University have been developing an oral, live attenuated, three-strain recombinant bacterial vaccine, ACE527, which is currently in Phase IIb and III trials.⁸⁶,¹⁰¹ To date, it was found to be safe and well tolerated, but showed mild reduction (27%) in episodes of moderate to severe diarrhoea.¹⁰¹

Two live attenuated ETEC strains, PTL002 and PTL003, were tested in a Phase I trial. Due to the superior immunogenicity, PTL003 will be developed further.⁹ In addition, another live attenuated oral vaccine (ACAM 2010) was found to be well tolerated and has shown 73% immunogenic among human volunteers, which will be developed as by Acambis, UK.⁹

The Center for Vaccine Development (CVD), University of Maryland, USA, and WRAIR have been researching usage of a live attenuated *Shigella* vectors for expression of ETEC fimbrial and large T antigens.⁹ To date, several strains have been tested in preclinical trials.⁹ Similarly, Microscience, UK has been investigating a usage of oral live attenuated typhoid vaccine as a vector for the delivery of ETEC antigens.¹⁰² The vaccine is expected to provide protection against ETEC diarrhoea and typhoid fever as well. The Peru15pCTB live attenuated oral cholera vaccine has been developed by AVANT. The candidate is expected to protect against both *V. cholerae* and ETEC.⁹
6.2.4 Campylobacter

There is no vaccine available in the market to date, but the latest preclinical research using mice showed that vaccination of with flagella-secreted protein FspA1 resulted in 63.8% protection with adjuvant against C. jejuni. Immunity to Campylobacter has been understood to be strain-specific.

6.2.5 Gaps between current vaccine pipelines and needs for vaccines

One of the major pathogens without vaccine candidates in clinical or preclinical trials is Cryptosporidium. Basic research including lead generation and lead optimization in these areas is also essential to feed scientific knowledge to encourage vaccine development against this organism in the future.

6.3 Pharmaceuticals

In 2006, OneWorld Health, a product development partnership (PDP), received a grant from the Bill & Melinda Gates Foundation to develop new anti-secretory drugs for the treatment of cholera and other diarrhoeal diseases to be used as an adjunct to ORT. With support from Roche, 40 new drug leads were identified for further study. Work with Novartis Institutes for BioMedical Research resulted in selection of promising drug candidates ready for pre-clinical testing. In 2011, the FDA approved Phase I trials of the drug candidates (iOWH032) designed to reduce or prevent secretory diarrhoea caused by cholera and other diarrhoeal diseases. OneWorld Health also partnered with Anacor Pharmaceuticals to discover antibacterial compounds for treating bloody diarrhoea (shigellosis), and with Center for World Health and Medicine at St. Louis University to develop new drugs to combat diarrhoea in 2011.

Pharmaceutical pipeline is described in Table 6.20.9.

In February 2013, a zinc dispersible tablet (ZinCfant®), produced by the France-based Nutriset/Laboratoire Pharmaceutique Rodael, gained a WHO prequalification. This encourages international aid programmes and countries with weak pharmaceutical regulation to procure and distribute the medicine with proper quality. Furthermore, higher availability of dispersible zinc tablets would result in the higher compliance among infants as well as easier inventory management compared with liquid formula.
Table 6.20.9: Pharmaceutical pipeline against diarrhoea

<table>
<thead>
<tr>
<th>Product/Research Program</th>
<th>Target &amp; Indications</th>
<th>Developers</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKT10081</td>
<td>Antimicrobial peptide (Cholera, Shigellosis, EPEC, TB)</td>
<td>Akthelia Pharmaceuticals</td>
<td>Phase I</td>
</tr>
<tr>
<td>iOWH032</td>
<td>Chloride channel inhibitor (Secretory diarrhoeas; cholera and other watery diarrhoea)</td>
<td>Galapagos NV OneWorld Health Roche</td>
<td>Phase I</td>
</tr>
<tr>
<td>Second-generation synthetic CFTR chloride channel inhibitors</td>
<td>Ion channels (Infectious diarrhoea)</td>
<td>Napo Pharmaceuticals, Inc.</td>
<td>Preclinical</td>
</tr>
<tr>
<td>MBX-500</td>
<td>hybrid antibiotics (toxigenic C. difficile)</td>
<td>Microbiotix, Inc</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Discovery program for anti-diarrhoeal agents</td>
<td>Ion channels</td>
<td>Anacor Pharmaceuticals Novartis AG OneWorld Health Roche</td>
<td>Discovery</td>
</tr>
</tbody>
</table>

Source: Diarrhoeal Diseases. BIO Ventures for Global Health.

6.4 Diagnostics

A new diagnostic test which can distinguish between pathogens causing diarrhoeal diseases is also in early development. Disposable enterics card (DEC) system is under development as a rapid diagnostic test (RDT), which will be able to distinguish between *Shigella dysenteriae* serotype 1, *Escherichia coli* O157:H7, *Campylobacter jejuni*, and *Salmonella* in stool samples.\(^\text{107}\) It has been developed by Micronics, PATH and the University of Washington.\(^\text{105}\) BIO Ventures for Global Health reported that “a rapid test to differentially diagnose the cause of diarrhoea, particularly between bacterial, viral or parasitic causes, currently in early-stage development, has the potential to change the treatment paradigm for this class of diseases.”\(^\text{105}\)

6.5 EC Framework Programme

There have been roughly 100 projects on diarrhoea funded by the EC Framework Programme since 2004 (the Fifth EC Framework Programme (FP5) to the Seventh EC Framework Programme (FP7)).\(^\text{108}\) Nine projects were related to discovery, preclinical and clinical trials on diarrhoeal treatments, vaccines and diagnostics. The remaining projects were related to basic scientific research, epidemiological studies and food safety to prevent diarrhoea. The list of projects funded EC Framework Programme since 2004 regarding with treatment, vaccine and diagnostics are listed below, sorted by area of research.
Treatment (four projects)
- Development of a novel treatment for *Clostridium difficile* (FP5, for nosocomial diarrhoea)
- Global antibiotic resistance by bacteria is becoming an increasing public health concern, and the race is on to discover new antibacterials (Bax et al., 2000). (FP5)
- Effects of antibiotic administration on the composition of the human intestinal microbiota, the prevalence of antibiotic resistant bacteria and the development of antibiotic-associated diarrhoea. (FP7)
- The development of a next generation probiotic supplement for treatment and prevention of antibiotic associated diarrhoea. (FP6 and FP7)

Vaccine (three projects)
- Novel strategies for a safe rotavirus vaccine. (FP5)
- Herpesvirus-based vaccines against rotavirus infections. (FP6)
- Vaccination against *Shigella* and ETEC: novel antigens, novel approaches. (FP7)

Diagnostics (two projects)
- EACH CHILD - a European-Asian challenge to childhood diarrhoea: design of a rapid diagnostic test for the most severe forms of childhood diarrhoea for use in peripheral health care centres in developing countries. (FP5)
- European approach to combat outbreaks of clostridium difficult associated diarrhoea by development of new diagnostic tests. (FP6)

7. Existing Resource Flows

7.1 Finance for research and development

According to the G-FINDER survey from 2007 to 2011, which provide global R&D funding information on basic research, diagnostics, pharmaceuticals and preventive and therapeutic vaccines for 31 neglected diseases, it is estimated that diarrhoea research received US$ 113.9 million in 2007 and US$ 152.2 million in 2011, with a peak of US$ 180.4 million in 2009 (2009 and 2011 data have been adjusted for inflation based on 2007). The share of overall funding in diarrhoeal diseases in 2011 was 5.0%. The estimate does 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 webpage does not include funding information on diarrhoeal projects during 2004-2010, but as is stated in previous session, European Commission has been supporting many diarrhoeal projects. An overview of the diarrhoeal R&D funding in 2011 is depicted in Table 6.20.11. The majority of diarrhoea R&D funding in 2011 addressed three disease areas: rotavirus (US$ 51.7m, 33.9%), cholera (US$ 26.0m, 17.1%) and *Shigella* (US$ 23.9m, 15.7%). Funding profiles varied among diseases. For cholera, 70% of funding was allocated to basic research, while vaccine research received nearly half of the funding for *Shigella.*
Large scale clinical trials of vaccines and medicines in Phase II and Phase III require substantial funding. With the unmet needs for vaccines against Shigella, ETEC and other pathogens as well as a number of vaccine candidates in Phase I and Phase II trials in those areas; additional and continued funding will be necessary.

### Table 6.20.11: Funding for diarrhoeal disease R&D 2011 (thousand US$), by diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Basic Research</th>
<th>Medicines</th>
<th>Vaccines</th>
<th>Diagnostics</th>
<th>Unspecified</th>
<th>Total US$ (,000)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus</td>
<td>-</td>
<td>-</td>
<td>51 089</td>
<td>-</td>
<td>563</td>
<td>51 652</td>
<td>33.9</td>
</tr>
<tr>
<td>Cholera</td>
<td>18 290</td>
<td>1 562</td>
<td>4 040</td>
<td>582</td>
<td>1 494</td>
<td>25 968</td>
<td>17.1</td>
</tr>
<tr>
<td>Shigella</td>
<td>8 254</td>
<td>2 010</td>
<td>11 307</td>
<td>882</td>
<td>1 420</td>
<td>23 873</td>
<td>15.7</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>2 053</td>
<td>2 684</td>
<td>154</td>
<td>2 473</td>
<td>-</td>
<td>7 363</td>
<td>4.8</td>
</tr>
<tr>
<td>Enterotoxigenic E.coli (ETEC)</td>
<td>-</td>
<td>-</td>
<td>4 080</td>
<td>2 272</td>
<td>340</td>
<td>6 693</td>
<td>4.4</td>
</tr>
<tr>
<td>Giardia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>508</td>
<td>-</td>
<td>508</td>
<td>0.3</td>
</tr>
<tr>
<td>Enteroaggregative E.coli (EAggEC)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>186</td>
<td>-</td>
<td>186</td>
<td>0.1</td>
</tr>
<tr>
<td>Multiple diarrhoeal diseases</td>
<td>5 058</td>
<td>5 034</td>
<td>13 584</td>
<td>4 962</td>
<td>7 362</td>
<td>36 000</td>
<td>23.6</td>
</tr>
<tr>
<td>Total</td>
<td>33 655</td>
<td>11 290</td>
<td>84 253</td>
<td>11 865</td>
<td>11 179</td>
<td>152 243</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Source: Adapted from Neglected disease R&D: A five-year review (2012) Policy Cures.

Note: 2008-2011 funding data has been adjusted for inflation and is reported in 2007 US dollars (US$).

"-" means G-FINDER didn't include such categories.

The top 10 funders of diarrhoea R&D during the period 2007-2011 were described in Table 6.20.12.86,109

Most funding was supplied by the US NIH, Bill & Melinda Gates Foundation, and the pharmaceutical/biotechnological industry, which together accounted for over 60% of global diarrhoea R&D funding. Average annual funding from European Commission during 2007-2010 was US$ 660,000, which was mostly allocated for vaccine research. An overview of the global diarrhoea R&D funding by funder type is illustrated in Figure 6.20.13. The decline in private sector investment is due to the reductions in funding from multinational pharmaceutical company for rotavirus vaccines, down from US$ 30.8 million in 2009 to US$ 16.6 million in 2011.86 The reduction of funding from philanthropic organizations in 2009 to 2011 results from Bill & Melinda Gates Foundation. Meanwhile, public funding has doubled from US$ 43.1 million in 2007 to US$ 87.6 million in 2011.86
## Table 6.20.12: top 10 funders of diarrhoea R&D during the period 2007 - 2011 (thousand US$)

<table>
<thead>
<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>US National Institutes of Health (NIH)</td>
<td>USA</td>
<td></td>
<td>31.0</td>
<td>39.5</td>
<td>60.9</td>
<td>50.4</td>
<td>52.6</td>
<td>181.9</td>
</tr>
<tr>
<td>Bill &amp; Melinda Gates Foundation</td>
<td>USA</td>
<td></td>
<td>44.3</td>
<td>26.7</td>
<td>46.8</td>
<td>44.9</td>
<td>30.8</td>
<td>162.7</td>
</tr>
<tr>
<td>Aggregate Pharmaceutical and Biotechnology Company Respondents</td>
<td></td>
<td></td>
<td>13.7</td>
<td>24.1</td>
<td>37.2</td>
<td>31.6</td>
<td>26.0</td>
<td>106.5</td>
</tr>
<tr>
<td>US Department of Defense (DOD) including DOD Defense Advanced Research Projects Agency (DARPA)</td>
<td>USA</td>
<td></td>
<td>5.4</td>
<td>5.9</td>
<td>11.0</td>
<td>5.9</td>
<td>4.8</td>
<td>28.2</td>
</tr>
<tr>
<td>Global Alliance for Vaccines and Immunizations (GAVI)</td>
<td></td>
<td></td>
<td>10.1*</td>
<td>14.8*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>24.9</td>
</tr>
<tr>
<td>Institut Pasteur</td>
<td>France</td>
<td></td>
<td>3.4</td>
<td>3.8</td>
<td>5.2</td>
<td>4.3</td>
<td>4.2</td>
<td>16.7</td>
</tr>
<tr>
<td>Indian Council of Medical Research (ICMR)</td>
<td>India</td>
<td></td>
<td>*</td>
<td>3.7</td>
<td>3.5</td>
<td>3.6</td>
<td>2.2</td>
<td>10.8</td>
</tr>
<tr>
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<td>France</td>
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<td>0.3</td>
<td>0.3</td>
<td>1.5</td>
<td>1.7</td>
<td>8.5</td>
<td>3.8</td>
</tr>
<tr>
<td>UK Department for International Development (DFID)</td>
<td>UK</td>
<td></td>
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<td>-</td>
<td>2.7</td>
<td>5.4</td>
<td>3.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Undisclosed participants</td>
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<td></td>
<td>0.5</td>
<td>0.9</td>
<td>0.5</td>
<td>1.8</td>
<td>5.9</td>
<td>3.7</td>
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<tr>
<td>Grand Total</td>
<td></td>
<td></td>
<td>113.9</td>
<td>132.2</td>
<td>180.4</td>
<td>158.9</td>
<td>152.2</td>
<td>737.7</td>
</tr>
</tbody>
</table>

Source: Adapted from Neglected disease R&D: A five-year review (2012) Policy Cures.
Note: 2008- 2011 funding data has been adjusted for inflation and is reported in 2007 US dollars (US$).

"*" means G-FINDER didn’t include such categories. * means no available data from the survey: any contributions listed come from data reported by funding recipients, so that they may be incomplete.

## Figure 6.20.13: Diarrhoea annual R&D funding (million US$), by funder type.

![Diarrhoea R&D Funding by Funder Type](image)
8. Challenges

- Further research and development is vital to make promising vaccine candidates available on the market.
- The lack of basic scientific knowledge supporting preclinical and clinical research also needs to be addressed.
- Although the global diarrhoeal burden has been declining since 2004, there are still many children suffering from diarrhoea. The poorest and most vulnerable children within countries are more likely to be suffering from diarrhoea due to a lack of sanitation and/or inadequate water supplies, and develop severe illness due to malnutrition.
- There have been many outbreaks causing acute diarrhoea in developing countries as well as developed countries. The cholera outbreak in Haiti (2010) resulted in over 470,000 cases and 6,000 deaths.
- The underlying reason why the disease burden persists is mostly due to a ‘rich-poor’ gap in the access to preventive measures and treatment.
- Pharmaceutical gaps exist; no vaccine exists against several pathogens such as *Shigella* and ETEC; research time lag between developed countries and developing countries; limited information on vaccine efficacy on epidemic and reactive usage of existing vaccines; growing resistance to antibiotics.
- Current molecular technologies to identify pathogens and toxins causing diarrhoea are neither available nor affordable in many of primary care settings, especially in developing countries.
- Vaccines portfolios include a number of candidates, but there is long term committed to facilitate research and development efficiently, most likely through PDP.

9. Conclusions

Diarrhoea is a preventable disease. Basic human needs, such as improved water, sanitation and optimal nutrition can prevent diarrhoea efficiently. Studies have shown that interventions targeting those areas are not a luxury, but fundamental and cost-effective, but diarrhoea is still the second leading cause of children’s death in the world. The poorest and most vulnerable children within countries are more likely to be suffering from diarrhoea due to a lack of those basic human needs. Treatment of diarrhoeal disease is not expensive, but percentage of children with diarrhoea who can access to ORS has just slightly increased since a decade ago. Access to zinc tablets is also limited. Recently approved rotavirus vaccine is not yet available in many developing countries. Clinical trials to prove the safety and effectiveness of other vaccines are under way.

When considering the cost effectiveness of the interventions to water and sanitation compared with vaccination in endemic areas, those environmental interventions should be prioritized for investment. Access to existing treatment is also highly cost effective. However, it is also true that vaccines can greatly reduce the burden of disease and appears to be very effective in places where access to improved water and sanitation cannot be guaranteed. Existing rotavirus vaccines seems to be less effective in endemic countries in Africa and Asia,
and there is no vaccine against several pathogens, such as *Shigella* and ETEC. Therefore, more research is needed especially to introduce new vaccines. Arrival of affordable and easy-to-use diagnostic tools would change the treatment protocol and enable health care workers to provide pathogen-specific treatment.

Research and development of new pharmaceuticals including vaccines require a long time and long-term support. Continued and increased support from the European Commission is vital to ensure that diarrhoea can be prevented throughout the world.

**References**


Update on 2004 Background Paper, BP 6.20 Diarrhoea


Update on 2004 Background Paper, BP 6.20 Diarrhoea


Gogia S, Sachdev HS. Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less. Cochrane database of systematic reviews (Online), 2011, (10):CD007480.


Prescribing information Fulyzaq™ (crofelemer). Salix Pharmaceuticals, Inc.


Updade on 2004 Background Paper, BP 6.20 Diarrhoea


Annexes

Annex 6.20.1: Population at risk, estimated number of cholera cases and estimated annual incidence in endemic countries, by age group and World Health Organization (WHO) mortality stratum

Annex 6.20.2: Estimated number of cholera deaths and annual mortality rate in endemic countries, by age group and World Health Organization (WHO) mortality stratum

Annex 6.20.3: Annual incidence of rotavirus disease in children younger than five years of age in Europe, 2000 - 03

Annex 6.20.4: Number and rate of campylobacteriosis cases reported in EU and EEA/EFTA countries, 2006–09

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Annex 6.20.8: Number and rate of giardiasis cases reported in EU and EEA/EFTA countries, 2006–09

Annex 6.20.9: Number and rate of shigellosis cases reported in EU and EEA/EFTA countries, 2006–09

Annex 6.20.10: Number and rate of ETEC cases reported in EU and EEA/EFTA countries, 2006–09
Annex 6.20.1: Population at risk, estimated number of cholera cases and estimated annual incidence in endemic countries, by age group and World Health Organization (WHO) mortality stratum


<table>
<thead>
<tr>
<th>WHO stratum</th>
<th>Total population at risk</th>
<th>Age group (in years)</th>
<th>Incidence (per 1 000 at risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR-D</td>
<td>196 462 691</td>
<td>&lt; 1</td>
<td>392 929</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1–4</td>
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<td></td>
<td></td>
<td>5–14</td>
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<td></td>
<td></td>
<td>15+</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>All</td>
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</tr>
<tr>
<td>AFR-E</td>
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<td></td>
<td></td>
<td>1–4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–14</td>
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<td></td>
<td>15+</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All</td>
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</tr>
<tr>
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<td>&lt; 1</td>
<td>1 174</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1–4</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>All</td>
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</tr>
<tr>
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<td></td>
<td>1–4</td>
<td>1 909</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–14</td>
<td>46 951</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15+</td>
<td>187 619</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All</td>
<td>2 836 669</td>
</tr>
<tr>
<td>SEAR-B</td>
<td>50 443 558</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a Provinces of Indonesia included West Java, Irian Jaya, Sumatra, Jakarta, Banten, Tangerang, Bogor and Maluku.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b States and territories of India included Andhra Pradesh, Assam, Goa, Gujarat, Haryana, Himachal Pradesh, Karnataka, Kerala, Madhya Pradesh, Maharashtra, Orissa, Punjab, Tamil Nadu, Uttar Pradesh, West Bengal, Andaman &amp; Nicobar Island, Chandigarh and Delhi.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c Provinces of China included Guandong, Zhejiang, Shanghai, Fujian and Hainan.</td>
<td></td>
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</tr>
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<td>SEAR-D</td>
<td>694 832 590</td>
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<td>1–4</td>
<td>120 1 682</td>
</tr>
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<td>All</td>
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<td></td>
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</tr>
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<td></td>
<td>All</td>
<td>2 836 669</td>
</tr>
<tr>
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<td>&lt; 1</td>
<td>2 836 669</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1–4</td>
<td>7</td>
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<tr>
<td></td>
<td></td>
<td>5–14</td>
<td>2.2</td>
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<td></td>
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<td>15+</td>
<td>0.9</td>
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<tr>
<td></td>
<td></td>
<td>All</td>
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AFR-D, African Region, stratum D; AFR-E, African Region, stratum E; EMR-B, Eastern Mediterranean Region, stratum B; EMR-D, Eastern Mediterranean Region, stratum D; SEAR-B, South-East Asia Region, stratum B; SEAR-D, South-East Asia Region, stratum D; WPR-B, Western Pacific Region, stratum B.
### Annex 6.20.2: Estimated number of cholera deaths and annual mortality rate in endemic countries, by age group and World Health Organization (WHO) mortality stratum


<table>
<thead>
<tr>
<th>WHO stratum</th>
<th>Age group (years)</th>
<th>Mortality (Deaths per 100 000)</th>
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</thead>
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<tr>
<td></td>
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<td>EMR-B</td>
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<tr>
<td>EMR-D</td>
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<tr>
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<tr>
<td>SEAR-D</td>
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<td>WPR-B</td>
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<tr>
<td>Total</td>
<td>9 382</td>
<td>34 086</td>
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</table>

| Mortality (Deaths per 100 000) | 24.1 | 23.2 | 7 | 2.7 | 6.3 | – |

AFR-D, African Region, stratum D; AFR-E, African Region, stratum E; EMR-B, Eastern Mediterranean Region, stratum B; EMR-D, Eastern Mediterranean Region, stratum D; SEAR-B, South-East Asia Region, stratum B; SEAR-D, South-East Asia Region, stratum D; WER, WPR-B, Western Pacific Region, stratum B.
## Annex 6.20.3: Annual Incidence of Rotavirus Disease in Children Younger Than 5 Years of Age in Europe, 2000 - 03


<table>
<thead>
<tr>
<th>Country</th>
<th>Income Group</th>
<th>Home</th>
<th>Physician Visit</th>
<th>Hospitalizations</th>
<th>Deaths</th>
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<td>Austria</td>
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<td>11,222</td>
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<td>2107</td>
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<tr>
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<td>1</td>
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<td>13,851</td>
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<td>5916</td>
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</tr>
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<td>1195</td>
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<tr>
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<td>7685</td>
<td>1921</td>
<td>240</td>
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<tr>
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<td>1</td>
<td>33,591</td>
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<td>113,975</td>
<td>14,247</td>
<td>14</td>
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<tr>
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<td>13,573</td>
<td>13</td>
</tr>
<tr>
<td>Greece</td>
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<td>1890</td>
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<td>57,299</td>
<td>14,302</td>
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<td><strong>Total</strong></td>
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<td>698,501</td>
<td>87,313</td>
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</table>

*Proportional to Germany: 1, high GNI; 2, high-middle GNI.
Annex 6.20.4: Number and rate of campylobacteriosis cases reported in EU and EEA/EFTA countries, 2006–09

Source: Annual epidemiological report Reporting on 2009 surveillance data and 2010 epidemic intelligence data.

<table>
<thead>
<tr>
<th>Country</th>
<th>Reports coverage</th>
<th>Reports type</th>
<th>Total confirmed cases</th>
<th>Cases 2009</th>
<th>Rate 2009</th>
<th>Cases 2008</th>
<th>Rate 2008</th>
<th>Cases 2007</th>
<th>Rate 2007</th>
<th>Cases 2006</th>
<th>Rate 2006</th>
</tr>
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<td>5697</td>
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<td>26</td>
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<td>58</td>
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Y: Yes; N: No; A: Aggregated data report; C: Case-based report; -: No report; U: Unspecified.
### Annex 6.20.5: Number and rate of salmonellosis cases reported in EU and EEA/EFTA countries, 2006–09

Source: Annual epidemiological report Reporting on 2009 surveillance data and 2010 epidemic intelligence data.

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Annex 6.20.6: Number and rate of cholera cases reported in EU and EEA/EFTA countries, 2006–09

Source: Annual epidemiological report Reporting on 2009 surveillance data and 2010 epidemic intelligence data.

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| Liechtenstein         | -     | -    | -     | -    | -     | -    | -     | -    |
| Norway                | Y     | C    | 0     | 0.00 | 0     | 0.00 | 1     | 0.02 |

| **Total**             | -     | -    | 22    | 0.01 | 26    | 0.01 | 17    | 0.00 |

Y: Yes; N: No; A: Aggregated data report; C: Case-based report; -: No report; U: Unspecified.
Annex 6.20.7: Number and rate of cryptosporidiosis cases reported in EU and EEA/EFTA countries, 2006–09

Source: Annual epidemiological report Reporting on 2009 surveillance data and 2010 epidemic intelligence data.

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Y: Yes; N: No; A: Aggregated data report; C: Case-based report; –: No report; U: Unspecified.
**Annex 6.20.8: Number and rate of giardiasis cases reported in EU and EEA/EFTA countries, 2006–09**

Source: Annual epidemiological report Reporting on 2009 surveillance data and 2010 epidemic intelligence data.

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Y: Yes; N: No; A: Aggregated data report; C: Case-based report; –: No report; U: Unspecified.
Annex 6.20.9: Number and rate of shigellosis cases reported in EU and EEA/EFTA countries, 2006–09

Source: Annual epidemiological report Reporting on 2009 surveillance data and 2010 epidemic intelligence data.

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Y: Yes; N: No; A: Aggregated data report; C: Case-based report; –: No report; U: Unspecified. (a) Surveillance system changed to full national coverage in 2009 compared to previously estimated coverage of 25% of the population. (b) Rates calculated excluding the Spanish data.
Annex 6.20.10: Number and rate of ETEC cases reported in EU and EEA/EFTA countries, 2006–09

Source: Annual epidemiological report Reporting on 2009 surveillance data and 2010 epidemic intelligence data.

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Y: Yes; N: No; A: Aggregated data report; C: Case-based report; –: No report; U: Unspecified.
Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

Background Paper 6.21
Hearing Loss

By Béatrice Duthey, Ph.D

20 February 2013
Update on 2004 Background Paper, BP 6.21 Hearing Loss

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Executive Summary

The World Health Organization (WHO) estimated in 2008 that over 360 million persons have disabling hearing loss which represents 5.3% of the world population. Eighty per cent of these people reside in low- or middle-income countries (LMIC). In Europe, about 52 million people are affected and more than 50% of European adults beyond 65 years old present slight to severe hearing loss according 2010 estimates. Epidemiological surveys are scarce and particularly in low-income countries as a result of difficulty field testing of hearing levels, poor diagnosis and reporting as well as lack of awareness of the problem leading to shortage of funding to conduct surveys. With the aging of the world population these numbers are expected to rise substantially.

Hearing loss is an important public health concern with substantial economic and societal costs. In infants and children hearing impairment retards developmental language and educational progress. In adults, it causes difficulties in both professional and social life as well as stigmatization. Apart from consequences to the individual person, hearing loss also leads to high costs to society.

Hearing impairment can be caused by a number of factors including infections during childhood such as measles, mumps and meningitis, chronic otitis media, exposure to excessive or prolonged noise, head/neck injuries, use of ototoxic medications such as certain types of chemotherapies and antibiotics, industrial solvents, congenital abnormalities and infections and perinatal problems, certain nutritional deficiencies, genetic disorders and aging.

Use of hearing devices such as aids and cochlear implants as well as sign language, lip reading and special amplification systems in schools are strategies to help affected people manage their communication. Although the prevalence of hearing impairment is high, very little research towards pharmaceutical treatment has been made in the previous decades.

Within the past few years, exciting research on genetic manipulation, gene therapy, and stem cell transplantation as well pharmaceutical agents, suggest that a therapeutic treatment for hearing loss may eventually be possible in the future.
1. Introduction

In 2004, Warren Kaplan and Richard Laing wrote the Priority Medicines for Europe and the World Report. This report did not address hearing loss, but by 2012 the burden of disease caused by hearing loss justified an in-depth study.

The ability to hear is critical to understanding the world around us as well as interacting with each other. Hearing impairment is the most frequent sensory deficit in human populations and affects newborns, children, adults and elderly.\(^1\)

In children, hearing loss can be inherited, or acquired as sequelae of viral or bacterial infections during pregnancy, childhood or complications during birth, also due to ototoxic drugs, excessive noise and specific nutritional deficiencies. In adults, the major causes of hearing loss are presbycusis which is related to ageing, excessive and prolonged exposure to noise, acoustic and physical trauma, and use of ototoxic drugs such as certain types of chemotherapies, antibiotics, and industrial chemicals.

This background report reviews global data on hearing loss among children and adults in Europe and the world and provides estimates on disability prevalence and costs of management. In addition this report reviews scientific progress and identifies gaps and opportunities for research interventions towards prevention or cure.

There has been exciting research performed recently on a possible preventive treatment of hearing loss caused by ototoxic medications or high level of noise. Following the success of research from animal experiments, several promising clinical trials have been launched. These trials offer exciting possibilities not only for prevention of hearing loss but also for a possible treatment to restore auditory functions.

1.1 Hearing Loss definitions

Hearing is the ability to perceive sounds. Sound occurs over a wide spectrum of frequencies. The human ear is sensitive to a frequency band within that spectrum expressed in decibels (dB). Frequencies capable of being heard by humans are called audio or sonic. The range is typically considered to be between 20 Hz and 20,000 Hz (Hertz). Frequencies higher than audio are referred to as ultrasonic, while frequencies below audio are referred to as infrasonic.\(^1\) Loss of the ability to hear sound frequencies in the normal range of hearing is called hearing impairment.

There is a diversity of definitions of hearing impairment, thus, comparison among studies is difficult and may be invalid. The definition used by any study should always be checked before attempting to make such comparisons. The World Health Organization (WHO) defines disabling hearing impairment in adults as a permanent unaided hearing threshold level (average for frequencies 0.5, 1, 2, 4 kHz (kiloHertz)) for the better ear of 41 dB or greater (WHO, 2001).\(^2\) In children under 15 years of age, disabling hearing impairment is defined as permanent unaided hearing threshold level (average for frequencies 0.5, 1, 2, 4 kHz) for the better ear of 31 dB or greater. The WHO classifies hearing impairment into five grades, as shown in Table 6.21.1. Categories of hearing impairment range from “no impairment” to
“profound impairment” according to the threshold. Thus, for both adults and children “disabling hearing impairment” means the same as moderate or worse hearing impairment.

Table 6.21.1. WHO grades of hearing impairment

<table>
<thead>
<tr>
<th>Grade of Impairment</th>
<th>Audiometric ISO value (average of 500, 1000, 2000, 4000 Hz)</th>
<th>Impairment description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (no impairment)</td>
<td>25 dBHL or less (better ear)</td>
<td>No or very slight hearing problems. Able to hear whispers</td>
</tr>
<tr>
<td>1 (Slight impairment)</td>
<td>26-40 dBHL (better ear)</td>
<td>Able to hear and repeat words spoken in normal voice at 1 metre</td>
</tr>
<tr>
<td>2 (Moderate impairment)</td>
<td>41-50 dBHL (better ear)</td>
<td>Able to hear and repeat words using raised voice at 1 metre</td>
</tr>
<tr>
<td>3 (Severe impairment)</td>
<td>61-80 dBHL (better ear)</td>
<td>Able to hear some words when shouted into better ear</td>
</tr>
<tr>
<td>4 (Profound impairment including deafness)</td>
<td>81 dBHL or greater (better ear)</td>
<td>Unable to hear and understand even a shouted voice</td>
</tr>
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</table>


The auditory pathway comprises the external ear, the middle ear and the inner ear, followed by the auditory nerve ending up in the auditory centres in the auditory cortex.

- The external ear consists of the pinna, ear canal and eardrum. Sound travels down the ear canal, striking the eardrum and causing it to move or vibrate.
- The middle ear is a space behind the eardrum that contains three small bones called ossicles. This chain of tiny bones is connected to the eardrum at one end and to the oval window at the other end which connects to the inner ear. Vibrations from the eardrum cause the ossicles to vibrate which, in turn, creates movement of the fluid in the inner ear.
- Movement of the fluid in the inner ear, or cochlea, causes changes in tiny structures called hair cells. This movement of the hair cells sends electric signals from the inner ear up the auditory nerve (also known as the hearing nerve) to the brain.

The brain then interprets these electrical signals as sound. Figure 6.21.1 shows the different compartment of the ear described above.
There are three basic types of hearing loss: conductive hearing loss, sensorineural hearing loss and mixed hearing loss based on which part of the auditory system is damaged.

- Conductive hearing loss occurs when sound is not conducted efficiently through the external ear canal to the eardrum and the ossicles of the middle ear. This type of hearing loss usually involves a reduction in sound level or the ability to hear faint sounds and can be corrected medically or surgically.

- Sensorineural hearing loss (SNHL) occurs when there is damage to the inner ear (cochlea), or to the nerve pathways from the inner ear to the brain. Sensorineural hearing loss is the most common type of hearing loss and cannot be medically treated so far. Persons affected have difficulties in hearing faint sounds even when the speech is loud enough.

### 1.2 Possible Causes of hearing loss

#### 1.2.1 Ear infections

Hearing loss can be caused by viral, bacterial or parasitic infections. Middle ear infections are important causes of hearing impairment for many children in the world. For example chronic suppurative otitis media is the commonest cause of hearing loss in children in developing countries. Children are more prone to ear infections than adults as the Eustachian tube, the passage between the middle ear and the back of the throat is smaller and more horizontal than in adults. This allows it to be more easily blocked by inflammation from infections in the ear or adenoid and tonsillar enlargement which blocks the Eustachian tube and impairs the ventilation and drainage of the middle ear, thus preventing drainage of purulent fluids.
Chronic suppurative otitis media (CSOM), caused by chronic bacterial infections in the middle ear, is an important cause of hearing loss in low- and middle-income countries. Chronic otitis media is associated with perforation of the tympanic membrane and can lead to death from complications such as meningitis or brain abscess.  

According to the WHO “High rates of chronic otitis media have been attributed to overcrowding, inadequate housing, poor hygiene (through transmission of the pathogens by physical contact with a contaminated individual, inhalation of infected droplets, or contact with an infected surface), lack of breastfeeding, poor nutrition, passive smoking, anecdotally to wood-burning smoke, high rates of nasopharyngeal colonization with potentially pathogenic bacteria, and inadequate or unavailable health care. Poverty is a major risk factor in developing countries and certain neglected populations.”  

Because of availability of ear care facilities with appropriately trained staff together with topical and systemic antibiotic therapies, chronic otitis media has markedly decreased in high income countries. However, it is still a serious public health concern in many low- and middle-income countries.

1.2.2 Untreated infections during childhood

The difficulty of access to health care facilities and other factors such as poor personal hygiene and overcrowding cause many children in low- and middle-income countries to become deaf or hard of hearing following infections such as meningitis, measles, viral encephalitis, chicken pox, influenza, mumps or other viral infections. In the so-called “meningitis belt” in the sub-Saharan Sahelian region of Africa, epidemics of meningococcal meningitis happen regularly, and many survivors are left with sensori-neural hearing loss and other neurological sequelae.

1.2.3 Congenital hearing loss

The term congenital hearing loss means that hearing loss is present at birth. Congenital hearing loss can be caused by genetic or non-genetic (acquired) factors. Non-genetic factors that are known to cause congenital hearing loss are linked to pregnancy and birth delivery and include:

- Maternal infections during pregnancy, such as rubella (German measles), Cytomegalovirus, or herpes simplex virus
- Prematurity
- Low birth weight
- Cranio-facial abnormalities
- Birth injuries
- Toxins including certain drugs and alcohol consumed by the mother during pregnancy
- Complications associated with severe jaundice in the newborn baby often due to maternal-fetal blood type incompatibility
- Maternal diabetes
- Lack of oxygen (anoxia)

Hearing loss from genetic defects can be present at birth or develop later on in life. Most genetic hearing loss can be described as autosomal recessive or autosomal dominant, linked to X-chromosome or to mitochondrial inheritance patterns. In autosomal recessive hearing loss, both parents carry the recessive gene and pass it along to the child. Marriages between
cousins, especially first cousins, which occur in certain communities, favour this type of genetically inherited disorders.\(^9\)

Autosomal dominant hearing loss occurs when an abnormal gene from one parent is able to cause hearing loss even though the matching gene from the other parent is normal.

Other genetically inherited syndromes such as Down syndrome, Usher syndrome, Treacher Collins syndrome, Crouzon syndrome, Alport syndrome and Waardenburg syndrome include hearing loss as part of the syndrome.\(^9\)

### 1.2.4 Injury/trauma

Head injury, acoustic trauma, ear and brain tumors can induce a permanent sensori-neural hearing impairment. The auditory nerve is then not able to transfer signals to the brain.

### 1.2.5 Aging

Aging contributes substantially to damage and deterioration of the peripheral and central auditory system. Age related loss of audition is called presbyacusis. In humans, inner and outer hair cells present in the cochlea of the inner ear cannot self reconstitute, therefore a loss of or damage to these cells is irreversible and causes permanent hearing impairment. Neural loss and strial loss may also be factors. Frequency loss is progressive from high to low.

### 1.2.6 Exposure to prolonged or excessive noise

Exposure to high levels of noise is the most common cause of hearing loss in adults but presbycusis, which is potentiated by noise has the highest prevalence in older adults.\(^{10\ 11\ 12}\)

Exposure to excessive duration and intensity of noise causes progressive loss of outer and inner hair cells with damage and eventual death of the organ of Corti, ischemia of the inner ear, and increased metabolic activity leading to excessive reactive oxygen species (ROS) generation and lipid peroxidation.\(^{13\ 14\ 15}\)

Exposure to high level of noise such as during loud concerts or use of headphones contribute to hearing loss. Noise is also a particular concern for soldiers who are exposed to noise bombardments, hunters exposed to rifle fire, pilots and industrial workers especially in developing countries where there is more likely to be lack of available protection and the legislation to enforce it. This type of hearing loss can be either transient (called temporary threshold shift) or permanent (called permanent threshold shift). With the latter, the part of the cochlea where hair cell death occurs initially is related to the noise frequency that causes it, partly due to direct mechanical damage. The over-stimulation of hair cells also causes excessive generation of free radicals, which may continue for some time after the initial trauma.

### 1.2.7 Medications and other chemicals that are toxic to the ear

Certain medications are considered ototoxic as they may cause damage of hair cells in the inner ear. There are more than 200 known ototoxic medications (prescription and over-the-counter) on the market today. These include medicines used to treat serious infections, cancer and heart disease.\(^{15\ 16\ 17\ 18\ 19\ 20}\) Hearing loss caused by these drugs is often dose-dependent and with some drugs can sometimes be reversed when the drug therapy is
discontinued (e.g. loop diuretics, quinine, salicylates). Sometimes, however, the damage is permanent.

Ototoxic medications known to cause permanent damage include all commonly used aminoglycoside antibiotics, such as gentamicin (family history may increase susceptibility), streptomycin, amikacin, kanamycin and neomycin. They all affect the vestibular system (organ of balance) as well as the cochlea although streptomycin has a greater effect on the former and neomycin acts mainly on the latter.\textsuperscript{21} Increased sensitivity to deafness caused by aminoglycosides can be inherited maternally. Cancer chemotherapy drugs, such as cisplatin and carboplatin can cause effects on the cochlear similar to aminoglycosides. Elevations of audiometric thresholds have been reported in some studies in 75–100\% of patients treated with cisplatin.\textsuperscript{15} Cisplatin ototoxicity results from the production of reactive oxygen species (ROS) within the cochlea, overwhelming endogenous antioxidant mechanisms and causing irreversible free–radical-related apoptosis of cochlea outer hair cells, spiral ganglion cells, and the stria vascularis.\textsuperscript{16}

Hearing loss is usually bilateral and irreversible, and is particularly severe in young children with neuroblastoma, CNS malignancies, and in adults with head and neck cancers, in which the base of the skull or brain may be irradiated.\textsuperscript{16}

Aminoglycoside antibiotics are used in the treatment of gram-negative bacterial infections like tuberculosis; tularemia and other hospital acquired serious infections. Dose-limiting side effects include cochlear and/or vestibular toxicity and nephrotoxicity. Cochlear toxicity is primarily due to death of outer hair cells in the organ of Corti.\textsuperscript{17} The outer hair cells in the part of the cochlear where high frequencies are detected, die first but successively lower frequencies are then affected. Loss of inner hair cells follows after some delay.

Medications known to cause temporary damage include salicylate pain relievers (aspirin, used for pain relief and to treat heart conditions), macrolide antibiotics such as erythromycin, quinine (to treat malaria), and loop diuretics – furosemide, bumetanide or ethacrynic acid (used to treat certain heart and kidney conditions).\textsuperscript{20, 22, 23} A single dose of the last group which by itself would only cause completely reversible hearing loss, in combination with an aminoglycoside may cause rapid, profound permanent loss. Various industrial chemicals including toluene, p-xylene, ethylbenzene, styrene, trichloroethylene have been implicated in ototoxicity. The effects of solvents may be potentiated by exposure to high noise levels or noise induced hearing loss may become worse. Damage occurs particularly in the mid frequency range of hearing.\textsuperscript{24, 25, 26}

There is some evidence that excessive alcohol consumption may damage auditory centres in the brain and be ototoxic to the ear.

1.2.8 Nutritional Deficiency Causes

Iodine deficiency is common in certain parts of the world and is one of the leading causes of preventable mental handicaps worldwide, including cretinism, in which hearing loss is a feature. Maternal hypothyroidism results in congenital hypothyroidism which is fully treatable if detected soon after birth. If it is untreated the child will develop cretinism. Hypothyroidism may potentiate presbycusis in the elderly.
1.3 Diagnosis

Early diagnosis and early intervention is essential to prevent further damage and provide adaptive therapies.

1.3.1 Newborns and Infants Diagnosis

In high income countries, most hospitals screen all babies’ hearing shortly after they are born. Infant screening is very important because, without such programs, the average age of detection of significant hearing loss is approximately 14 months. When hearing loss is detected late, language development is delayed, affecting a child’s ability to learn and perform in school. The screening procedures for newborns and infants are simple and painless, and can be done while the infant is resting quietly. The two common screening methods used with infants are otoacoustic emissions (OAE) and auditory brainstem response (ABR). These tools can detect hearing loss averaging 30 to 40 decibels (dB) or more in the frequency region important for speech recognition, e.g., approximately 500–4000 Hertz (Hz).

Otoacoustic emissions (OAEs) are sounds given off by the inner ear when the cochlea is stimulated by a sound. When sound stimulates the cochlea, the outer hair cells vibrate. The vibration produces a nearly inaudible sound that echoes back into the middle ear. The sound can be measured with a small probe inserted into the ear canal. People with normal hearing produce emissions. Those with hearing loss greater than 25–30 decibels (dB) do not produce these very soft sounds. This test can detect blockage in the outer ear canal, as well as the presence of middle ear fluid and damage to the outer hair cells in the cochlea. The high cost of the electronic instrument may preclude use in low- and middle-income countries.

1.3.2 Children and Adult Diagnosis

Hearing can be measured by partially subjective tests using a pure-tone audiometer in children aged over four years. Electrophysiological tests of hearing can provide accurate objective measurements of hearing thresholds even in unconscious subjects. Such tests include auditory brainstem evoked potentials (ABR), otoacoustic emissions (OAE) and electrocochleography (EchoG). Technical advances in these tests have allowed hearing screening for infants to become widespread.

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

2.1 General

The WHO estimated that in 2008, over 360 million persons in the world have disabling hearing loss. This constitutes 5.3% of the world population, nearly 183 million adult males above 15 years old and 145 million females, which is 7.5% of the adult male population and approximately 6% of the adult female population respectively. With the ageing of the world population these numbers are expected to double by 2030-2050. Hearing impairment is considered the most prevalent impairment worldwide.
2.2 Prevalence

2.2.1 Prevalence in the world

Disabling hearing loss is unequally distributed across the world. Population based studies are rare particularly in developing countries where newborns and children are not systematically screened for hearing impairment.

Prevalence of child and adult hearing impairment appears to be substantially higher in middle- and low-income countries than in high-income countries, demonstrating the global need for attention to hearing impairment. Approximately 15% of the world's adult population has some degree of hearing loss. Fifty per cent of those who are affected, have disabling hearing loss. Figure 6.21.2 shows the distribution of hearing loss per selected world region. Table 6.21.2 shows the estimates of disabling hearing loss in adults and children in 2012.

South and East Asia and sub-Saharan Africa remain the world regions with the highest prevalence of hearing impairment in both adults and children. This can be explained by the high rates of pre- and post-natal childhood infections such as chronic otitis media, meningitis, rubella, measles, use of ototoxic drugs and excessive noise. High prevalences in adults are due to higher rates of infections such as chronic otitis media, and meningitis, excessive noise, ototoxic drugs and ageing populations in developing countries which increase the prevalence of presbyacusis.

The lack of a comprehensive health care system, especially ear and hearing care at primary and secondary levels, lack of trained personnel at all levels, poor personal hygiene and overcrowding, poor accessibility to medications and other interventions, lack of primary, secondary and tertiary prevention interventions, lack of national planning and programmes for ear and hearing care, low resource allocation in this field also account for these high prevalence rates of hearing impairment in low and middle income countries.

Figure 6.21.2. Distribution of disabling hearing loss per selected world region

*MBD, WHO, 2012 DHL estimates; DHL adult threshold is ≥41 dB, adults of 15 years or older.

Table 6.21.2. Region-wise estimate of disabling hearing loss, in adults 15 years or older and children 0-14 years in millions and percentage of population (by World Bank Regions).

<table>
<thead>
<tr>
<th>Selected Regions</th>
<th>Children (Both sexes)</th>
<th>Adults (Males)</th>
<th>Adults (Females)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>millions</td>
<td>prevalence (%)</td>
<td>millions</td>
</tr>
<tr>
<td>High-income</td>
<td>0.8</td>
<td>0.5%</td>
<td>19</td>
</tr>
<tr>
<td>Central/Eastern Europe and Central Asia</td>
<td>1.1</td>
<td>1.6%</td>
<td>14</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>6.8</td>
<td>1.9%</td>
<td>17</td>
</tr>
<tr>
<td>Middle East and North Africa</td>
<td>1.2</td>
<td>0.9%</td>
<td>6</td>
</tr>
<tr>
<td>South Asia</td>
<td>12.3</td>
<td>2.4%</td>
<td>52</td>
</tr>
<tr>
<td>Asia Pacific</td>
<td>3.4</td>
<td>2.0%</td>
<td>19</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td>2.6</td>
<td>1.6%</td>
<td>15</td>
</tr>
<tr>
<td>East Asia</td>
<td>3.6</td>
<td>1.3%</td>
<td>41</td>
</tr>
<tr>
<td>World</td>
<td>31.9</td>
<td>1.7%</td>
<td>183</td>
</tr>
</tbody>
</table>

*MBD, WHO, 2011 DHL estimates, where DHL adult threshold is ≥41 dB and children threshold is ≥31 dB. Children between 0 and 14 years old and Adults 15 years or older.

Source: World Health Organisation 2012 (Countries within regions are listed in Annex 6.2.1)

Figures 6.21.3, 6.21.4 and 6.21.5 show the prevalence rate of disabling hearing impairment per world region in children, adults and elderly respectively.

Figure 6.21.3. Prevalence of disabling hearing loss in children 0-14 years

*MBD, WHO, 2011 DHL estimates, children threshold is ≥31 dB (children 0 until 14 years old).

Source: Contribution from Disability Department, WHO, Geneva.
Figure 6.21.4: Prevalence of disabling hearing loss for adults of 15 years or older by selected regions.

![Bar chart showing prevalence of disabling hearing loss for adults by selected regions.]

*MBD, WHO, 2011, DHL estimates, where DHL adult threshold is $\geq 41$ dB HL.

Source: Contribution from Disability Department, WHO, Geneva.

Figure 5. Prevalence of disabling hearing loss for children, adults: 15-65 years and 65 years or older by selected regions (WHO 2011)

![Bar chart showing prevalence of disabling hearing loss for children and adults by selected regions.]

*MBD, WHO, 2011 DHL estimates, where DHL adult threshold is $\geq 41$ dB HL and children threshold is $\geq 31$ dB (children 0 until 14 years old).

Source: Contribution from Disability Department, WHO, Geneva.
Hearing loss prevalence increases as age increases, reaching its highest prevalence level for adults over the age of 65 years old (from 18% in high income region to almost 50% in the South Asia region).

The prevalence increase with age is more than five times for all the regions except high-income and Central/East Europe and Central Asia region.

A recent study (2011) led by Johns Hopkins University researchers showed that nearly a fifth of all Americans aged 12 years or older have hearing loss that may make communication difficult. Researchers stated that they used the World Health Organization’s definition for hearing loss (not being able to hear sounds of 25 decibels hearing level (dB HL) or greater in the speech frequencies). However the WHO definition is 26 dB HL or greater for any level of hearing loss so the results of this study are not completely comparable with other surveys using the WHO criteria, and would produce a slightly greater prevalence. They collected data from the National Health and Nutritional Examination Surveys (NHANES) and analyzed data from all participants age 12 and over whose hearing was tested during NHANES examinations from 2001 to 2008.

Researchers found that overall, about 30 million Americans, or 12.7 per cent of the population aged 12 years or older, had hearing loss in both ears and this figure increased to 48.1 million, or 20.3 per cent, when also including people who have hearing loss in one ear. The prevalence was lower in women than men, and in black than white individuals across nearly all age decades. The findings, thought to be the first nationally representative estimate of hearing loss that used audiometric hearing testing, suggest that many more people than previously thought are affected by hearing impairment. In high income countries, studies have usually been performed on children and elderly and data on adults are scarce.

### 2.2.2 Prevalence in Europe

The prevalence of hearing loss in Europe is not well defined, due in part to the use of countries own classification systems for hearing impairment. As a consequence, comparison of data from several studies is difficult. Moreover, the majority of studies have focused on prevalence among people aged 65 and over and there are few detailed reports on the prevalence of hearing impairment of different grades among adults or children. There is clearly a gap in knowledge and understanding of how hearing loss affects young people that needs to be addressed.

The need for standardized procedures when collecting and reporting epidemiological data on hearing loss is essential. In this regard, WHO provided a classification on hearing impairment and recommends countries to use standard audiometric measures in population based surveys. WHO has developed a survey protocol, the WHO Ear and Hearing Disorders Survey Protocol, in order to standardize other aspects of survey methodology in addition to hearing levels. At least 12 surveys have been conducted in developing countries using this protocol.

Report from Shield (2006) found that 19 per cent of the UK men and 13 per cent of UK women above 16 years of age report that they suffer from hearing loss. Most European countries studied were higher than the usual 10% of the population often considered the
Update on 2004 Background Paper, BP 6.21 Hearing Loss

general prevalence of the impairment. Shield presents specific facts on the prevalence of hearing impairment in Europe.

- The frequency in Germany may be as high as one in five.
- In Finland, one in seven suffers from varying degrees of hearing loss.
- In Italy, one in six are suffering from some form of hearing loss.
- One in 10 has hearing loss in Denmark and Sweden.

Figure 6.21.6 shows the repartition of hearing impairment according to gender, age range and level of impairment in Western Europe in 2010. Figures are from the World Health Organization from Stevens et al, unpublished data.

Figure 6.21.6. Level of impairment repartition of hearing loss according to gender, age range in Western Europe in 2010.

<table>
<thead>
<tr>
<th>Age range</th>
<th>Population</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per cent of population</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26-40 dBHL</td>
<td>41-60 dBHL</td>
<td>61-80 dBHL</td>
</tr>
<tr>
<td>0-1 years</td>
<td>2290</td>
<td>0.8 (0.6, 1.1)</td>
<td>0.1 (0.1, 0.2)</td>
</tr>
<tr>
<td>1-4 years</td>
<td>9061</td>
<td>0.8 (0.6, 1.2)</td>
<td>0.2 (0.1, 0.3)</td>
</tr>
<tr>
<td>5-14 years</td>
<td>22728</td>
<td>1.0 (0.7, 1.3)</td>
<td>0.2 (0.1, 0.3)</td>
</tr>
<tr>
<td>15-34 years</td>
<td>52683</td>
<td>2.1 (1.6, 3.0)</td>
<td>0.4 (0.3, 0.6)</td>
</tr>
<tr>
<td>35-44 years</td>
<td>31874</td>
<td>4.7 (3.5, 6.4)</td>
<td>0.9 (0.7, 1.3)</td>
</tr>
<tr>
<td>45-54 years</td>
<td>28887</td>
<td>8.0 (6.0, 10.7)</td>
<td>1.6 (1.2, 2.3)</td>
</tr>
<tr>
<td>55-64 years</td>
<td>24044</td>
<td>17.7 (14.2, 22.2)</td>
<td>4.2 (3.2, 5.7)</td>
</tr>
<tr>
<td>65-74 years</td>
<td>17629</td>
<td>31.7 (27.5, 35.8)</td>
<td>10.3 (7.9, 13.4)</td>
</tr>
<tr>
<td>75+ years</td>
<td>12775</td>
<td>39.1 (38.1, 39.9)</td>
<td>25.0 (20.6, 29.7)</td>
</tr>
</tbody>
</table>

Source: unpublished data (World Health Organization from Stevens et al).

People lose their hearing much earlier than in the past. This disconcerting trend is caused by the generally higher noise levels in today’s society.

In a systematic literature review, in which data were crudely averaged and interpolated, Roth et al. estimated that “roughly 55% of men and 45% of women in Europe were found to have a hearing loss of 30 dB HL or more by age 70 years.” Because of the ageing of the population in Europe these figures are expected to rise in the future.

Hearing loss prevalence estimates for 2025

According to Hear-it.com (2011); Professor Adrian Davis of the British MRC Institute of Hearing Research estimates that “the total number of people suffering from hearing loss of more than 25 dB will exceed 700 million worldwide by 2015. Davis’s statistics suggest that more than 900
All in all, the different surveys and estimates indicate that hearing loss is much more common than previously thought and that young adults and not only children and elderly people are affected.

3. What is the control Strategy?

3.1 Prevention Measures

3.1.1 Primordial Prevention

Preventing excessive exposure to noise

Noise-induced hearing loss is preventable but is often not prevented, especially in developing countries. The incidence of noise-induced hearing loss at the work place can be reduced or eliminated through the successful application of engineering controls and hearing conservation programs. Wearing ear plugs or special earmuffs when exposed to high level of noise, reducing the volume of headphones, designing less noisy machines, lowering noise pollution from auto traffic, trains, airplanes and industry are all measures that will make a difference. Countries should enact legislation to reduce noise pollution in the workplace and enable adequate compensation, and to reduce social and other environmental noise sources. Noise pollution needs to be monitored and sanctions enforced. Building design needs to consider the acoustic environment both for normal and hard of hearing persons. Older children and young adults should be made aware that high levels of noise such as in clubs and from personal stereos can permanently damage their hearing; ear plugs should be made readily available and role models such as rock musicians should lead the way to make prevention of noise-induced hearing loss fashionable.

Preventing hearing loss due to infectious diseases

Immunisation against vaccine preventable infections especially rubella, measles, meningitis contribute to reduce the burden of hearing loss as sequelae of these diseases are known to cause irreversible hearing damage. As Morris and Leach stated (2012) “the largest gains in the prevention of severe to profound sensorineural hearing loss have come from the measles and rubella vaccines, and the protein-conjugated bacterial meningitis vaccines (targeting Hemophilus influenzae type b (Hib), pneumococcal and meningococcal disease). Most of the mild and moderate conductive hearing loss in the world is associated with otitis media. To some extent, OM is a vaccine preventable disease. In the future, the development of otitis media vaccines (or combinations of vaccines) that reduce colonisation and protect against common respiratory bacterial and viral pathogens has the potential to dramatically reduce the frequency of mild and moderate hearing loss in young children.” The WHO’s original Expanded Programme of Immunization (EPI) started in 1974 includes measles vaccine and BCG, both of which will reduce hearing loss (the latter via
prevention of tuberculous meningitis causing hearing loss and a reduction in use of streptomycin, and ototoxic antibiotic, as second line treatment of TB. A rubella vaccine is usually used now as part of the MMR vaccine against measles, mumps, and rubella, all of which cause hearing loss, rubella as an often devastating congenital infection. It is important to note that rubella vaccination should not be introduced in a country until the coverage rate for vaccines such as measles has reached 80% to produce “herd immunity”. If rubella vaccine is commenced before this coverage is reached it may have the paradoxical effect of more women reaching child bearing age who are susceptible to rubella infection (by reducing opportunities for natural protection through infection in early childhood) and hence lead to an increase in incidence of congenital rubella syndrome. In developed countries women of child-bearing age are tested for rubella susceptibility and immunised provided they are not pregnant. Because rubella vaccine is a live vaccine there is a slight risk of teratogenicity to the foetus, so pregnant women should be vaccinated immediately after birth.

Other infections which cause hearing loss and for which research is seeking vaccines include Cytomegalovirus and HIV.

3.1.2 Secondary Prevention

Screening

Universal neonatal hearing screening programmes are expensive if fully implemented, and even in developed countries there were assessments of the cost-effectiveness and cost-benefits. The expense has precluded introduction of UNHS in most developing countries. Most developed countries and a few developing countries have implemented UNHS. Targeted neonatal screening is more common in developing countries.

Most developed countries and a few developing countries have implemented UNHS. Targeted neonatal screening is more common in developing countries. In low- and middle-income countries, due to the difficult access to health care facilities, and it is not always possible to implement such screening. Child delivery often takes place at home and health care facilities are sometimes at several hours of walking away. School screening is common in developed countries but much less common in developing countries. Screening campaigns for adults and elderly are however lacking in most countries even in developed countries and should be implemented.

3.1.3 Tertiary prevention

Raising awareness of users of ototoxic medications

Very few people, including few health care professionals, know that medications such as non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or naproxen, antibiotics such as gentamicin, and streptomycin, anti-malarial drugs such as quinine, chemotherapy agent cisplatin and some diuretic drugs and certain industrial chemicals can cause transient or permanent hearing loss. In a study published by the American Journal of Medicine researchers found that regular users of NSAIDs who were 50 or younger were 61 per cent more likely to develop hearing loss than those who were not regular users.24

Prevention involves ongoing awareness raising through information and campaigns amongst the general public, people who are hard of hearing, health care professionals, and
legislators. This should be associated with an enforceable pharmaceutical licensing, distribution and clinical testing programme.

Genetic counselling

Other approaches to prevention include genetic counselling for some inherited causes of hearing loss, improved primary ear and hearing care including more trained personnel, better ante-natal and peri-natal care, nutritional supplementation in areas where critical nutrients are lacking (e.g. iodine), more widespread availability of affordable hearing aids and services to fit and follow up (this can be classed as tertiary prevention or rehabilitation).

Raising awareness of decision makers

Although hearing loss is considered to be the most prevalent chronic impairment worldwide, awareness of the problem amongst decision makers is rare because data from well-conducted, population-based epidemiological surveys are scarce, especially from developing countries. Monitoring the incidence and prevalence of hearing loss in the entire population ranging from infants to elderly would help implement appropriate measures for prevention and allocate fundings for research towards better treatment and rehabilitation.

3.2 Therapies

Hearing loss is not yet curable but research into auditory hair cell and nerve regeneration has made considerable progress. Hearing aids such as cochlear implants and hearing aids and other amplification systems, especially in schools, can help a person to recover partly his/her hearing and communication skills.

Audiologic rehabilitation is essential to provide appropriate training on how to best use these devices and improve hearing capacity.

Audiologic Rehabilitation

Audiologic rehabilitation is the process of providing training and treatment to improve hearing for those who are hearing impaired. Hearing rehabilitation services focus on adjusting to hearing loss, making the best use of hearing aids, exploring assistive devices, managing conversations and other hearing strategies, and taking charge of communication.

With infants and children, audiologic rehabilitation focuses on restoring a skill that is lost. In very young children, a skill such as talking or understanding speech may not be there in the first place and needs to be taught. The services provided will depend on each child’s individual needs and are based on the following factors: age of the child, age of onset of the hearing loss, age when hearing loss was discovered, degree of hearing loss, type of hearing loss, age of child when hearing aids were first used, commitment and capability of the parents or guardians. Early detection of hearing loss and early use of hearing aids or cochlear implants are critical for the development of speech, language, and communication skills in children with hearing loss. In fact, infants identified with a hearing loss before the onset of the critical period of language development around six months of age who received a hearing aid or cochlear implant and habilitation services have been shown years later to have language skills similar to those of children of the same age who have normal hearing.2,25
cost of cochlear implants is high ($40,000 in the United States) but are ranked as among the most cost effective procedures in the USA. (http://www.asha.org/about/news/tipsheets/cochlear_facts.htm) and also in other developed countries. In developing countries the cost is prohibitive for the majority of individuals with severe or profound hearing loss, and for their state health care providers. There is little data on this at present from developing countries at present. However it appears that such financial resources used in a national programme would alleviate a far larger proportion of the burden of hearing loss if allocated to strengthening of ear and hearing care services at primary and secondary levels and provision of affordable hearing aids and services, than if used for cochlear implant programmes. More research is needed on this issue.

4. What is known of the Availability, Feasibility and Sustainability of the Control Strategy?

4.1 The European Burden of Hearing Loss and cost

According to the international scientific report “Evaluation of the Social and Economic Costs of Hearing Impairment” by Shield (2006) untreated hearing loss costs Europe 213 billion euros per year.31 Figures of a similar order of magnitude have been estimated in the USA and Australia.32 33

“In the EU alone, more than 55 million people are hearing impaired, and the costs in the EU of unaided hearing impairment of all grades are estimated to 168 billion Euros per year.34 Based on population statistics, here are some examples of the estimated cost of untreated adult hearing loss per country:

- Germany €30 200 000 000
- France €22 400 000 000
- United Kingdom €22 000 000 000
- Italy €21 300 000 000
- Spain €16 300 000 000
- Poland €14 000 000 000
- The Netherlands €6 000 000 000

The calculations are made in accordance with the European Commission standard, setting a statistical value for ‘one quality life year’ at 44 000 euros, and the commonly used Health Utility Index, rating different types and degrees of diseases and sufferings/conditions in relation to a healthy person.

According to the report, a mild hearing loss costs society 2 200 euros per individual each year, a moderate hearing loss costs 6 600 euros annually per person, while a severe or profound hearing loss costs 11 000 euros per person per year. These figures do not include lost income and lost tax revenues due to unemployment or early retirement because of hearing loss.”35

These figures do not include the societal costs of unemployment or early retirement caused by hearing loss. Compared to many other diseases, hearing loss more often involves the social welfare system rather than the medical care system. Therefore, medical costs, e.g. hearing aids, only account for a small percentage of the real general cost.
4.2 Feasibility and Control Strategy

Hearing devices are a viable option for hearing impaired persons to live a better quality of life but still with reduced auditory capacity. Hearing devices such as hearing assistive technologies or cochlear implants remain very expensive and many health care systems do not reimburse the cost of such devices.\textsuperscript{50} For most low- and middle-income countries, hearing aids and devices are just not affordable. Studies based on hearing aids production indicate that, relative to need, few hearing aids are sold in developing countries. There is likely a large unmet need for innovative interventions including affordable hearing aids and possibly cochlear implants in low- and middle-income countries.\textsuperscript{50, 52} The global partnership WWHearing (Website for WWHearing: www.wwhearing.org) was set up to address the need to provide affordable, good quality hearing aids and services on a large scale in low- and middle-income countries, through its collaboration agreement with WHO.\textsuperscript{39} They do not currently advocate cochlear implants in developing countries, believing that the resources needed would be more effectively utilized on provision of hearing aids and thereby help much larger numbers of people with moderate or severe hearing loss.

Prevalence of disabling hearing loss for the entire population increases as the out of pocket expenditure ratio (against private expenditure on health) increases for some regions such as: high Income, sub-Saharan Africa, Latin America and Caribbean region, and South Asia region as shown in Figure 6.21.6.

Despite their intensive attempts, Stevens et al. were unable to address hearing aid use in developing countries. They stated in their discussion \textquotedblleft We did not have sufficient data to estimate hearing aid use in developing countries, but suspect that coverage is small to negligible: one study in Brazil did not identify anyone who used a hearing aid, and combining our data with data on hearing aid production indicates that, relative to need, few hearing aids are sold in developing countries. A primary obstacle to hearing aid provision in developing countries is their cost. There is likely a large unmet need for innovative interventions including low-cost hearing aids in developing countries.\textquotedblright Since the burden of hearing loss is much greater in developing countries, this is where the focus of action should be, from a public health point of view.
5. Why does the Disease Burden Persist?

5.1 Lack of awareness of the problem

Although hearing loss is the most important cause of disability worldwide, there is a lack of awareness of the problem in all sectors of the population including health care professionals as well as a lack of health educational programmes for prevention and detection (in addition to the lack of investment by most developing countries in programmes, infrastructure and trained personnel). Because hearing loss is an invisible disability, and most people and governments are not aware of the large size of the problem, children with hearing loss are not discovered and may be mistaken to have intellectual disabilities in school. In adults, hearing loss more often evokes irritation than sympathy. In health care, there is a lack of national programmes to address hearing loss, especially in developing countries where the burden and need is greatest, and a lack of investment in training, equipment, career structures and infrastructure.
5.2 Poor Diagnosis

Diagnosis for hearing loss is often neglected. In most high income countries, only newborns infants and school children are screened systematically, but not young adults and elderly. In high income countries, people with moderate hearing loss delay diagnosis because they are afraid to be stigmatized.

In low- and middle-income countries, screening of newborns and children is sparse and adults are not diagnosed for hearing impairment due to difficulty of access to medical facilities, and lack of trained personnel and equipment. Moreover, cochlear implants remain too expensive and not affordable. Studies based on hearing aid production indicates that, relative to need, few hearing aids are sold in developing countries. There is likely a large unmet need for innovative interventions including affordable hearing aids in low and middle income countries.37 38

5.3 A lack of epidemiological data

There is a lack of epidemiological data worldwide, especially from population-based, random sample surveys using standardised methods in developing countries. Only a few countries, even in Europe, have implemented programmes of detection to cover the entire population. Hearing loss remains poorly reported and many countries and surveys use different classification systems, making it difficult to compare data between countries. There is a need for standardized procedures when collecting and reporting epidemiological data on hearing loss, such as the WHO Ear and Hearing Disorders Survey Protocol.

5.4 Poor living conditions and lack of vaccination coverage

In developing countries, disease burden of hearing loss persists because of the poor health care systems, especially at the primary level of health care, absence or lack of vaccination coverage for children and mothers, poor personal hygiene factors and poor living conditions as well as cultural issues such as consanguineous marriage that favors the transmission of genetically inherited forms of hearing impairment. It is estimated that 50% of these hearing losses could be prevented by primary, secondary and tertiary means, and the lack of programmes and poor availability and cost of health care in these developing nations often makes preventive interventions unavailable and treatment expensive.1 Cochlear implants remain too expensive and are not affordable.39

5.5 Underuse of hearing devices

Hearing aids can be used effectively for patients with moderate to severe hearing loss, however, only one out of five people who could benefit from a hearing aid actually wears one.39 In high income countries, because of stigmatization and as hearing loss is negatively perceived, the usage of these devices is low and only occurs when a person realizes that he/she needs help from a professional or when their hearing is very poor. Major barriers to improve hearing in older adults include lack of recognition of hearing loss, perception that hearing loss is a normal part of aging or is not amenable to treatment, and patient non-adherence with hearing aids because of stigma, cost, inconvenience, disappointing initial results, or other factors.22, 28, 33 40 41
While the development of the cochlear implant has been remarkable, the prognosis for those individuals receiving an implant is still variable and, even with the best outcomes, normal hearing is not restored. Therefore patients with severe hearing loss would welcome alternative strategies, and in particular, medical treatments for hearing rehabilitation.

This may not apply to persons with profound or complete hearing loss, some of whom regard themselves as a distinct cultural and linguistic group with their own language (sign language) and rights similar to other minorities.42

5.6 Exposure to noise

Urbanisation and modern living life style has generated a noisier environment. Loud concerts, use of headphones, road traffic, are all likely to contribute to the loss of audition in many young adults.

Exposure to excessive noise is the major avoidable cause of permanent hearing impairment worldwide according the World Health Organization (WHO).2 Occupational noise and urban, environmental noise are increasing risk factors for hearing impairment worldwide, including in developing countries.

WHO recommends that countries should implement National Programmes for the Prevention of noise-induced hearing loss, integrated with Primary Health Care, and including elements on health promotion, and measures to reduce noise sources and introduce properly enforced legislation and effective hearing conservation.2, 41

5.7 Aging of the population

Aging leads to deterioration of hearing function in the majority of elderly persons and is one of the major key factor for hearing loss. As the world population ages people affected by hearing loss are expected to rise significantly. According to the World Health Organization “In 2010, an estimated 524 million people were aged 65 or older, 8% of the world’s population. By 2050, this number is expected to nearly triple to about 1.5 billion, representing 16% of the world population. Although more developed countries have the oldest population profiles, the vast majority of older people, and the most rapidly aging of the world’s populations, are in less developed countries. Between 2010 and 2050 the number of older people in less developed countries is projected to increase more than 250 per cent, compared with a 71 per cent increase in developed countries.” (From the WHO Global Health and Aging Report 2012.)

5.8 Gaps of research into pharmacological interventions

As a result of a lack of awareness of decision makers, very limited research funding has been allocated towards search for pharmaceutical compounds. The search for pharmaceutical agents to prevent or treat hearing loss has been for many years under-investigated. New research and clinical trials towards a possible treatment have started to emerge in the past few years.
6. Past/Current Research into Pharmaceutical Interventions for this Condition

Based on the successful results from animal studies, several clinical trials have been launched to investigate the effects of a wide variety of compounds in preventing hearing loss in humans. Most of these studies are focused on patients exposed to ototoxic medications such as cisplatin or aminoglycoside therapies or exposed to high level of noise. The different strategies such as the use of antioxidants, anti-inflammatory agents, anti-apoptotic factors as well as RNA silencing or use of stem cells to restore hair cell function within the cochlea are described below.43

Ototoxicity is an alteration caused by medications that compromises the auditory and vestibular functions. Cisplatin is a potent agent used for the treatment of cancer in both adults and children although it has several side effects. Current opinion is that cisplatin ototoxicity occurs due to alterations in the antioxidant system of the outer hair cells (OHC) of the cochlea. The distortion-product otoacoustic emissions (DPOAE) has been showed to be a sensitive test for diagnosis of OHC injury and has been used for monitoring treatment with ototoxic drugs.

6.1 Antioxidants and ROS scavengers

6.1.1 Sodium thiosulfate (STS)

Sodium thiosulfate is an inactive ingredient contained in sulfacetamide ophthalmic solution which is used routinely as an otic solution delivered to the middle ear space. Sodium thiosulfate is a free–radical-scavenging thiol agent.44

In vitro, STS acts in several ways: it directly inactivates cisplatin by the covalent binding of cisplatin to its thiol moiety to form an inactive complex, it scavenges cisplatin-related reactive oxygen species, and it may concentrate in the perilymph or endolymph, further inactivating cisplatin in the inner ear.45

A large Clinical Study with 250 participants led by the German GPOH, the Japanese Study Group for Pediatric Liver Tumors, and several USA centers, began the first large randomized trial of STS (SIOPEL 6) in 2007 to reduce ototoxicity in children with hepatoblastoma.26 In this trial, sodium thiosulfate is given intravenously and there are concerns that it could potentially affect the antitumorigenic effect of cisplatin by interacting in the blood and inactivating it.

In a parallel study, the Children’s Oncology Group launched a randomized phase III clinical trial NCT00716976 to evaluate the efficacy of STS for preventing cisplatin-related hearing loss in newly diagnosed children with hepatoblastoma, germ cell tumors, medulloblastoma, and osteosarcoma.46 47

The primary objective of clinical trial NCT00716976 “Sodium Thiosulfate in Preventing Hearing Loss in Young Patients Receiving Cisplatin for Newly Diagnosed Germ Cell Tumor, Hepatoblastoma, Medulloblastoma, Neuroblastoma, Osteosarcoma, or Other Malignancy” is to “compare the efficacy of sodium thiosulfate versus observation in preventing hearing loss in young patients receiving cisplatin
for the treatment of newly diagnosed germ cell tumor, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or other malignancy.”

Two clinical trials are currently in phase III and are recruiting participants.

The primary outcome of clinical trial NCT01369641 “The Effect of sodium thiosulfate (STS) Eardrops on Hearing Loss in Patients Who Receive Cisplatin Therapy” is “to assess the efficacy of intratympanic sodium thiosulfate (STS) on reducing the degree or incidence of hearing loss in patients receiving systemic cisplatin therapy using puretone and speech audiometry, and distortion product otoacoustic emissions (DPOAE). Hearing will be assessed prior to any initiation of cisplatin therapy, again at three weeks, six weeks, 12 weeks, and every six months thereafter for up to one year.” The trial is currently recruiting patients and final data collection date for primary outcome measure is expected for 2015.

The hypothesis of this study is that local administration of sodium thiosulfate (STS) will result in improved hearing compared to ears not receiving the study drug in patients receiving systemic cisplatin therapy.

Clinical trial NCT00652132 “Cisplatin With or Without Sodium Thiosulfate (STS) in Treating Young Patients With Stage I, Stage II, or Stage III Childhood Liver Cancer”, was sponsored by Children’s Cancer and Leukaemia Group. This randomized phase III trial is studying how well sodium thiosulfate (STS) works to decrease hearing loss caused by cisplatin in treating young patients with stage I, stage II, or stage III childhood liver cancer as well as carefully monitor any potential impact of STS on response to cisplatin and survival.

Results are expected in the following years. In this trial, sodium thiosulfate is given intravenously and there are concerns that it could potentially affect the antitumorigenic effect of cisplatin by interacting in the blood and inactivating it. New ways of injections of STS in the inner ear will certainly help circumvent this potential effect. Cisplatin is an important anticancer drug in children, potentially limited by its ototoxic effect which is particularly serious in children. Thus research on minimising or eliminating this side effect would be important for the children’s oncology field although this would not make a large reduction to the overall burden of hearing loss. However research in this may have spin-off in protecting against other causes of ototoxicity. This would increase its prioritization from a public health point of view.

6.1.2 Alpha Lipoic Acid

Alpha lipoic acid is a fatty acid found naturally inside every cell. As an antioxidant it protects against free-radical damage, supports nerve system function, and plays an essential role in generating mitochondria in the hair cells of the inner ear. Animal models have shown that alpha lipoic acid protected tested animals from age, noise and cisplatin induced ototoxicity.48 49 50

Phase II and III clinical trials (NCT00477607) Alpha-Lipoic Acid in Preventing Hearing Loss in Cancer Patients Undergoing Treatment with Cisplatin were completed in 2011.

In this trial “patients received oral alpha-lipoic acid supplement or placebo once a day beginning one week before the start of cisplatin treatment and continuing for up to one month after the completion of
cisplatin. During cisplatin treatment, patients discontinue supplement one day prior to the cisplatin treatment and resume daily supplements two days post treatment.” Results have not been posted yet.

6.1.3 N-acetylcysteine

Animal studies have shown that N-acetylcysteine can protect the inner ear against damage.\textsuperscript{38} It is not known whether the drug has similar effects in humans. This compound is currently being tested in several clinical trials.

The clinical trial (NCT00552786) \textit{Antioxidation Medication for Noise-induced Hearing Loss}, sponsored by the National Taiwan University Hospital, showed that N-acetylcysteine prevented temporary daily threshold shifts at high noise frequencies but did not seem to affect the temporary threshold shift at low frequencies.\textsuperscript{43}

The clinical trial (NCT01271088) \textit{Protective Effect of N-acetylcysteine Against From Ototoxicity}, sponsored by TC Erciyes University, has been completed and no results have been posted so far.\textsuperscript{43}

The clinical trial (NCT01131468) on \textit{Prevention of Drug Induced Ototoxicity in Peritoneal Dialysis Patients by N-acetylcysteine} has been completed in 2010 but no results have been posted so far.\textsuperscript{43}

The clinical trial (NCT00525551) on the \textit{Efficacy of N-acetylcysteine in Patients Undergoing Surgery for Otosclerosis}, sponsored by Karolinska Institutet and AstraZeneca, is currently recruiting participants. This study will assess the efficacy of N-acetylcysteine in patients undergoing surgery for otosclerosis.\textsuperscript{43}

6.1.4 Ginkgo Biloba

Ginkgo biloba is a potent antioxidant and ROS scavenger that has been shown to be an effective otoprotectant in sudden hearing loss and cisplatin ototoxicity in animal models.\textsuperscript{51}

A clinical trial (NCT01139281) on “The Protective Effect of Ginkgo Biloba Extract (GBE761) on Cisplatin-induced Ototoxicity in Humans” has been completed. Side effects have been reported such as bleeding, gastrointestinal disturbances, headaches, dizziness, and allergic skin reactions. Results concerning the protective effect of ginkgo biloba extract (GBE761) have not been posted so far.\textsuperscript{52}

6.1.5 Dietary supplements: Vitamins and minerals

Antioxidant therapy has been shown to be effective in animal studies. Vitamins that act as ROS scavengers (such as vitamins A, C, and E) act in synergy with minerals like magnesium (Mg) to effectively prevent noise-induced damage to the inner ear.\textsuperscript{53}

Results from Phase II Clinical trial (NCT00808470) “Micronutrients to Prevent Noise-induced Hearing Loss”, sponsored by University of Brasilia, are expected. Pharmaceutical interventions against noise-induced hearing loss would be a public health priority since this is a widespread cause which can be prevented by primary prevention but has as yet no therapeutic interventions that can prevent or treat it.
6.2. Anti-inflammatory agents

6.2.1 Salicylate/Aspirin

Aspirin has been shown to be otoprotective in both cisplatin as well as noise induced ototoxicity in animal experiments. The permanent threshold shift (PTS) in mice pretreated with salicylic acid just before the noise exposure was significantly smaller than that in mice exposed to the same noise without salicylic acid. The PTS in the latter was not significantly different from that in mice who received the drug just after the noise. Thus treatment with salicylates, just before noise exposure, may protect the ear from a noise-induced hearing loss.

Clinical trial: “Use of Aspirin to alleviate aminoglycoside ototoxicity : A prospective, randomized, double-blind placebo-controlled clinical trial of aspirin administration to patients receiving gentamicin” showed a slight protective effect of aspirin versus placebo on incidence of hearing loss. Side effects such as gastric symptoms occurred more frequently in the aspirin-treated group, and three patients had to be discontinued from the study because of gastric bleeding.

Results from another clinical trial NCT00578760 “Does Aspirin Have a Protective Role Against Chemotherapeutically Induced Ototoxicity?”, sponsored by the University Health Network in Toronto are also expected.

6.2.2 Steroids

Sudden hearing loss can be treated with the use of corticosteroids although there are few clinical trials and none that clearly demonstrate their effectiveness. However almost all physicians use them since there are few other options for treatment for idiopathic sudden hearing loss in which there is any evidence of effectiveness. Steroids, provided they are not contraindicated, are usually given as an oral course for 10-14 days and the dose then tapered. The problems of oral steroids that may occur such as of weight gain, insomnia, and an increase in blood sugar are unlikely to be difficult to manage if the treatment is not prolonged further and the correct dosage used. Audiologists have found that these side effects can be avoided when steroids are injected into the middle ear. Recent guidelines state that the intratympanic route should be used if systemic steroids are contraindicated or the side effects thought to be difficult to manage. However there are also risks with this procedure. Studies from animals experiments showed that corticosteroids can attenuate the cisplatin and aminoglycoside induced generation of ROS in the cochlea, and thus prevent hearing loss.

Use of steroids for treating hearing loss is a very active field of investigation at present.

A Cochrane Review on the use of steroids for treating hearing loss showed that “corticosteroids significantly reduced hearing loss and neurological sequelae, but did not reduce overall mortality. Data support the use of corticosteroids in patients with bacterial meningitis in high-income countries. We found no beneficial effect in low-income countries.” But an unproven effectiveness, or lack thereof, of steroids in the treatment of idiopathic sudden sensorineural hearing loss as well as “no evidence of benefit from treatment of OME with topical intranasal steroids, alone or in combination with an antibiotic, either at short or longer-term follow up.”
See Cochrane summary table in Annex 6.21.3. Other specific therapies are needed, such as adequate-doses of antibiotics for meningococcal meningitis which is epidemic in Africa and also quite common elsewhere.

Several clinical trials are currently recruiting participants:

**Clinical trial NCT01186185 “Fludrocortisone for Sudden Hearing Loss”, sponsored by Oregon Health and Science University.**

**Brief summary:** The standard of care treatment of sudden hearing loss uses a type of steroid called glucocorticoid. Examples of glucocorticoids are prednisone, methylprednisolone and dexamethasone. Not everybody recovers hearing with glucocorticoid treatment. Fludrocortisone is a different type of steroid called mineralocorticoid. Unlike glucocorticoids, which work by reducing inflammation, mineralocorticoids work by changing salt and fluid balance. In animal studies, fludrocortisone is at least as effective as glucocorticoid in preserving hearing. Fludrocortisone is not approved for the treatment of sudden hearing loss. The purpose of this study is to test whether fludrocortisone can treat sudden hearing loss.

**Clinical trial NCT00802529 “Transtympanic Gentamicin versus Steroids in Refractory Meniere’s Disease”, sponsored by Imperial College London.**

The purpose of this trial is to compare transtympanic steroids against the standard treatment (transtympanic gentamicin) in refractory unilateral Meniere disease.

**Clinical trial NCT01412177 “OTO-104 for the Treatment of Meniere’s Disease”, sponsored by Otonomy, Inc.**

The purpose of this study is to evaluate the effectiveness of OTO-104 for the treatment of Meniere disease.

### 6.2.3 TNF-α inhibitors

Pro-inflammatory cytokines like TNF-α, IL-6, IL-1β have been shown to be released by the organ of Corti on cisplatin exposure, aging and sudden sensorineural hearing loss (SSHL). Acute noise-induced inner ear hearing loss is characterized by microcirculatory disturbance in the stria vascularis. In addition to the immunomodulatory effect, inhibition of TNF-α activity might prevent vasoconstriction of the spiral modiolar artery by inactivation of sphingokinase-1 in the S1P/S1P2 signaling system in vascular smooth muscle cells as well as reduce downregulation of nitric oxide-mediated vasodilation. Therefore, early treatment with TNF-α-inhibitors might prevent hearing impairment by restoring cochlear blood flow. Studies showed that the use of TNF-α neutralizing antibody infliximab or etanercept either by intraperitoneal or subcutaneous route of administration provided complete protection from cisplatin ototoxicity. TNF-α antibody Enbrel® (Amgen and Pfizer Inc) is already FDA and EMA approved for autoimmune disorders including rheumatoid arthritis.

**Clinical trial NCT01526174 “Intratympanic Injection for Autoimmune Inner Ear Disease (AIED)”, sponsored by Janssen Services, LLC and House Research Institute, is currently recruiting participants.** AIED is a rare disease with a prevalence of less than 1/1000 of the population.
Summary: The investigators plan to conduct an open-label intratympanic injection proof-of-concept trial of golimumab, a TNF-alpha inhibitor, assessing for hearing loss progression in patients with autoimmune inner ear disease (AIED). This specific aim will be achieved using a two-arm approach. First, the investigators propose to dose three individual subjects with a single intratympanic injection of golimumab and follow each for 30 days, closely examining them for adverse events. If there are no serious adverse events, with FDA approval, the investigators propose to dose 14 subjects, each with four intratympanic injections of golimumab. Results are expected for August 2014.

6.3 Anti-apoptotic agents

High level of noise exposure as well as ototoxic medications have been shown to induce the stress leading to death apoptotic pathways of the outer hair cells of the inner ear. Inhibitors of signaling molecules involved in the apoptotic pathway such as mitogen-activated protein kinase (MAPK)/c-Jun-N terminal kinase (JNK) by transtympanic injections have been successful in conservation of hearing in animals. Clinical trials in humans have been performed to evaluate the potentiality of these inhibitors,60 61 62 63 64

Results of the study *Intratympanic treatment of acute acoustic trauma with a cell-permeable JNK ligand: a prospective randomized phase I/II* showed that AM-111 is therapeutically effective in noise induced hearing loss.42 A larger study with more participants is required to test the efficacy of AM-111 in noise induced hearing loss. However, because of the high incidence of side effects, this drug may not prove tolerable in patients with noise trauma.65

Summary: In hearing loss induced by cisplatin and aminoglycosides therapies exist which appear to be effective in humans. More research is needed to identify which patients benefit most and which are the most effective therapies. This is particularly important for patients treated for multidrug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) in which hearing loss is common.

6.4 New Promising drug candidates from animal studies

6.4.1 RNA interference

Both microRNA (miRNA) and short interfering RNA (siRNA) are promising tools for gene delivery within the cochlea. The anatomical isolation of the cochlea reduces the risk of degradation of siRNA and miRNA by contact with blood and degrading enzymes. Recent progress in optimization of delivery techniques within the cochlear render cochlear injection possible. Gene transfer therapy offers the possibility of arresting, reversing and even curing hearing loss/deafness from some causes. Research currently in noise-induced and ototoxic hearing loss. Ultimately the target would be in persons with inherited forms of hearing loss.66

This is major cause, and recognised as one of the three commonest causes of hearing loss by WHO, the other two being presbyacusis and otitis media.

Studies have at present been performed on animal models only and results are promising. Silencing of genes such as transient receptor potential vanilloid 1 (TRPV1), NOX3, cochlear specific NADPH oxidase enzyme and the signal transducers and activators of transcription 1
(STAT1) by transtympanic injection of siRNA showed protective effects from cisplatin ototoxicity.\textsuperscript{68, 69, 70} siRNA and miRNA present exciting possibilities for the prevention of hearing loss and otoprotection as they are gene specific and thus are not likely to compromise the chemotherapeutic activity of cisplatin.

\section*{6.4.2 Nanotechnology for drug administration to the cochlea}

Lipid nanocapsules are potential vectors for drug delivery into the spiral ganglion cells, nerve fibers, hair cells, and spiral ligament. Tested in animal models, they have shown to distribute throughout the inner ear without any signs of inflammation.\textsuperscript{68}

\section*{6.4.3 D-methionine}

D-methionine, a sulfur-containing amino acid was shown to effectively reduce cisplatin ototoxicity, noise induced hearing loss and increase the levels of antioxidant enzymes in animal models. Concern remains whether systemic administration of D-methionine would potentially inhibit the anti-tumor efficacy of cisplatin.\textsuperscript{69, 70, 71}

The phase III clinical trial NCT01345474 “D-methionine to reduce Noise-Induced Hearing Loss (NIHL)”, sponsored by the Department of Defense and Southern Illinois University, is currently recruiting participants.

“This goal of the study is to develop a safe, oral pharmacological agent to augment physical hearing protectors for noise exposures that exceed the protective capabilities of ear plugs and/or muffs. The study population is a cohort of Drill Sergeant (DS) instructor trainees during and 22 days after their 11 day weapons training. The primary objective of this study is to determine the efficacy of D-Met in preventing NIHL or reducing tinnitus secondary to a minimum of 500 rounds of M-16 weapons training occurring over an 11 day period.” Results are expected in 2017.

\section*{6.4.4 Resveratrol}

Resveratrol is the active polyphenol found in the skin of red grapes and is thus abundant in red wine. Resveratrol ingestion for three weeks prior to noise exposure and continued post noise exposure period of four more weeks showed significant preservation of hearing in rats.\textsuperscript{72}

\section*{6.4.5 Neurotrophic factors}

T-817MA (1-[3-[2-(1-benzothiophen-5-yl) ethoxy] propyl]-3-azetidinol maleate) protected the cochlea functionally and morphologically during noise induced hearing loss in guinea pigs.\textsuperscript{73}

\section*{6.4.6 Caspase Inhibitors}

The caspase family of cysteine proteases plays a key role in apoptosis. When administered by intracochlear perfusion inhibitors of caspases 3 and caspases 9 showed significant protection
from cisplatin ototoxicity in guinea pigs. A number of interesting chemicals are being investigated and are receiving more attention because of the huge problem of hearing loss. However it is difficult to recommend any for further research funding until further results are known.

6.4.7 Stem cell transplantation

One very exciting and promising field of research for restoring hearing function is the use of stem cells. The recent emergence of stem cell technology has the potential to open new approaches for hair cell and auditory nerve regeneration.

In contrast with mammals, birds and all other vertebrates have been shown to add and/or regenerate hair cells and auditory function throughout their lives. These regenerated hair cells arise from a population of stem/progenitor cells that reside within the sensory epithelia. Over the past two decades, research has been undertaken that led to better understanding of the genes and cellular interactions that regulate different aspects of inner ear morphogenesis and hair cell regeneration in model systems such as chicken and zebrafish.

The stem cells can be obtained from many different adult stem cell types, such as fibroblasts, which offer several advantages as they can be obtained from any patient and transplanted back to the same patients without immunological reaction or ethical concern. Exciting new research has shown that mouse embryonic stem and induced pluripotent stem cells could be converted into otic progenitor cells. After several treatment, these cells could aggregate into epithelial clusters and following mechanical stimulation, bundle-bearing cells in these clusters generated currents resembling transduction currents from immature hair cells. Even though the use of stem cells to repair cochlear injury is relatively new they appear to be a very promising possibility for the treatment of hearing loss induced by noise, ageing or ototoxic drugs. These three causes comprise a major part of the burden of hearing loss, so if this approach were successful could have a large public health effect of hearing impairment. Further research should be supported.

Clinical trials based on the use of stem cells for the treatment of hearing loss are expected to be launched in the future.

6.4.8 Targeted Neural Stimulation

Stanford researchers are studying ways to bypass the hair cells and directly stimulate auditory nerve cells by using focused laser energy to restore hearing. According to the researchers “Using laser light to precisely target a single auditory nerve cell may have the potential to restore hearing and speech discrimination or a wide range of frequencies. The technology could be integrated into a hearing aid that could be positioned outside of the cochlea, eliminating the risk of additional hearing loss or meningitis.”

This approach sounds far-fetched at present but if it could work would eliminate many of the problems associated with cochlear implants, such as invasiveness of the procedure and the potential complications, as mentioned. This technology research should be watched but not yet supported until some preliminary results are available. The Stanford group conducting
this research, are conducting other ground-breaking research on Gene therapy, stem cell therapy and molecular therapy. 80 81

7. What is the Current “Pipeline” of Products that Are to Be Used for this Particular Condition?

At present very few medicines are being used to treat hearing loss. Steroids and antioxidants can be prescribed to palliate sudden sensory hearing loss (as discussed previously). Apart from this particular case, no medicines are currently available at present to treat loss of hearing. New agents that could potentially restore hearing capacity after cellular damage or prevent hearing loss are currently in development. Some products can be used to prevent predictable hearing loss.

Several devices such as hearing aids, cochlear implants, middle ear implant can be used to amplify sounds or help people hear better. Alternatively, when none of these devices can be used, sign language and speech reading remain an alternative to help people to communicate and lead a life as normal as possible.

In public health terms, the greatest burden of hearing loss is in less developed countries (80% of disabling hearing loss is in LMIC, two thirds in developing countries). The majority of these countries lack even basic programmes against hearing loss and the personnel and infrastructure to prevent hearing loss or provide rehabilitation with affordable hearing aids and services. The knowledge and technology is available now, what is lacking is the awareness, political will leading to training for personnel, infrastructure and equipment to provide them effectively. This should include strengthening ear and hearing care at the primary level of health care, especially targeting acute and chronic otitis media, the largest cause of mild & moderate hearing loss in children in developing countries. This would make the largest difference to the problem and implementation could start immediately. In addition, the EC could support promising cutting edge research such as use of anti-oxidants and other drugs and their delivery to the cochlea, gene therapy and stem cell research.

7.1 Extended Wear Hearing Aids

These aids are devices that are nonsurgically placed in the ear canal by an audiologist. These are expensive and special training is needed to fit them. They are worn up to several months at a time without removal. The devices are made of soft material designed to fit the curves of the ear. They are worn continuously and then replaced with a new device. They are very useful for active individuals because their design protects against moisture and earwax, and they can be worn while exercising, showering, etc.

The majority of hearing aids sold today are canal hearing aids and in-the-ear hearing aids. The majority of hearing aids are sold today in high income countries despite the majority of the burden being in low- and middle-income countries. Fewer than one in 40 of the people in the developing world who need a hearing aid actually have one. There is a massive unmet need in LMICs. BTE hearing aids would be suitable for use in these countries (less expensive, easier to fit and follow-up, possible problem with stigma). The behind-the-ear (BTE) hearing
aid is the most commonly recommended aid for infants and young children (see below for explanation); however, many adults now wear the open fit style of BTE.

There are also special hearing aids built to handle very specific types of hearing loss. For example, a bone conduction aid uses a headband and a bone vibrator for individuals who have no ear canal or outer ear. These devices bypass the outer and middle ear and directly stimulate the cochlea. A relatively new innovation is the osseo-integrated hearing aid (bone anchored), which is implanted in the skull. This device has three parts: a titanium implant, an external abutment, and a detachable sound processor.

7.2 Cochlear Implants

A cochlear implant is a device that provides direct electrical stimulation to the auditory nerve in the inner ear. Children and adults with a severe to profound hearing loss who cannot be helped with hearing aids may be helped with cochlear implants. This type of hearing loss is sensorineural, which means there is damage to the hair cells in the cochlea. Because of this damage, sound cannot reach the auditory nerve. With a cochlear implant, the damaged hair cells are bypassed, and the auditory nerve is stimulated directly.

The benefits from a cochlear implant depend on many factors, such as the age of the patient, whether the hearing loss was present before or after the patient developed language skills and the motivation of the patient.

Cochlear implants have external (outside) parts and internal (surgically implanted) parts that work together to allow the user to perceive sound.

The external parts include a microphone, a speech processor, and a transmitter. The microphone picks up sounds and sends them to the speech processor. The speech processor is a computer that analyzes and digitizes the sound signals and sends them to a transmitter worn on the head just behind the ear. The transmitter sends the coded signals to an implanted receiver just under the skin.

The internal (implanted) parts include a receiver and electrodes. The receiver is just under the skin behind the ear. The receiver takes the coded electrical signals from the transmitter and delivers them to the array of electrodes that have been surgically inserted in the cochlea. The electrodes stimulate the fibers of the auditory nerve, and sound sensations are perceived.

Both children and adults receive extensive rehabilitation services from audiologists, speech-language pathologists, teachers, and counsellors as they learn to listen, improve speech, use speechreading, and handle communication. They are taught how to use the implant and how to respond to the sounds they are receiving. For those who have heard before, sounds through the cochlear implant may seem unnatural at first. Those who have never heard before must be taught what the sounds are.

In developing countries the cost [of cochlear implants] is prohibitive for the majority of individuals with severe or profound hearing loss, and for their state health care providers. There is little data on this at present from developing countries at present. However it appears that such financial resources used in a national programme would alleviate a far
larger proportion of the burden of hearing loss if allocated to strengthening of ear and hearing care services at primary and secondary levels and provision of affordable hearing aids and services, than if used for cochlear implant programmes. More research is needed on this issue. Some centres are trying to develop an “affordable cochlear implant” but the cost is still far too high for most people in developing countries.

7.3 Middle Ear Implants

These hearing systems are implanted in the space behind the eardrum that mechanically vibrate the middle ear structures. This device has two parts: an external portion and an implanted portion. There are also hearing aids called CROS (contralateral routing of signal) aids that route sounds coming to one ear over to the other ear. These devices are for use by individuals who have no hearing in one ear. In special cases, hearing aids can be built into glasses for individuals who need that type of fitting. Given the many innovations, there are hearing aids available that can accommodate virtually any kind of hearing loss, except when it is very severe or profound or the wearer is unable to tolerate or manage a hearing aid.62

7.4 Sign Language

When the infant or young child is totally deaf and there are no alternative for the use of hearing assistive technology or cochlear implants, sign language and speechreading can be taught. Speechreading training provides formal instruction in how speech sounds are made, which sounds look alike on the lips. Learning which words have the same mouth movement but very different meaning can be incredibly useful in increasing understanding of conversations. People can also gain a great deal of helpful information from following other visual clues like facial expression, gestures, body movement, and body language. Sign language and speechreading will allow the child and future adult to communicate, have an education and lead a well-adjusted life.

8. What is the Current Status of Institutions and Human Resources Available to Address the ear disease and hearing impairment and disability?

Numerous hearing loss & deaf associations and organisations in Europe, the USA and across the world work to inform patients, provide counselling, support people affected by hearing loss. Research has been performed up to now only in academic settings.

8.1 Public Fundings

8.1.1 European Sources of Funding

Member states in the European Union are implementing The Directive on Environmental Noise in order to protect the European citizens against noise encroaching on their homes.

The Directive on Environmental Noise, passed by the European Parliament in June 2002 obliges the member states to map out noise patterns in heavily populated areas. These
measures are intended to protect the European citizens against noise surrounding their homes. Authorities must educate the population about noise and develop action plans to lower noise pollution from auto-traffic, trains, airplanes and industry.83

The Institute of Health and Consumer Protection, one of the seven scientific institutes of the European Commission’s Joint Research Centre (JRC), is providing technical support for the implementation of these directives. Its activities focuses on the development and harmonization of noise assessment methods, based on state-of-the-art scientific and technical know-how, in collaboration with experts nominated by the EU Member States, the European Environmental Agency (EEA), the European Aviation Safety Agency, and the World Health Organization in Europe. This process, which is known as CNOSSOS-EU, is coordinated by the JRC-IHCP. In March 2011, a joint WHO-JRC “Report: Burden of disease from environmental noise. Quantification of healthy life years lost in Europe”, reviewed the evidence of health effects consequent to noise exposure and estimated the burden of disease in western European countries, providing guidance on how best to quantify risks from environmental noise. In September 2012, a JRC Reference Report "Common Noise Assessment Methods in Europe (CNOSSOS-EU)" described the common framework required for the implementation of the 'Environmental Noise' directive.84

8.1.2 Initiatives from the World Health Organization (WHO)

In 1997, the Programme for the Prevention of Deafness and Hearing Impairment of the World Health Organization, organised a meeting of experts from developed and developing countries in order, not only to assess research needs, but also to seek methods for prevention. Occupational setting as well as environmental and leisure settings are recognised as sources of excessive noise and significant risk for hearing loss.

Experts have stressed on the need for the development or improvement of prevention initiatives, for an increase in the awareness of risk from noise, improvement of the training of health personnel, and gathering of epidemiological data.85

Other sources of funding include bilateral aid from various governments, the work and support of various NGOs, notably CBM which is the largest funder of programmes for hearing loss in the developing world and various foundations that have funded hearing loss research and programmes.

8.2 Private Fundings

At present, very few companies are starting to develop potential pharmacological treatments for hearing loss.

In June 2011, Sanofi (EURONEXT: SAN and NYSE: SNY) announced a two-year research collaboration with the biopharmaceutical company Audion Therapeutics (Audion) to develop potential treatments for hearing loss through the optimization of small molecules by using a regenerative medicine approach.

“This collaborative research will utilize technology developed at the Massachusetts Eye and Ear Infirmary in the Eaton-Peabody Laboratory, one of the world’s largest basic research facilities dedicated to the study of hearing and deafness, by investigator and Audion co-founder Dr Albert Edge, who has strong expertise in stem cells and inner ear biology. Audion licensed Dr Edge’s
9. Gaps between current research and potential research issues which could make a difference

Recent studies have demonstrated the efficacy of a wide variety of protective agents against hearing loss and cochlear damage from noise and ototoxic injury from aminoglycosides and cisplatin. Most of these investigations were carried out in vitro or in rodent models. Several clinical trials have been initiated to study the effects of these agents in patients.

The key findings in research done in this field to date are that a wide variety of potential protective agents have been reported against noise and ototoxic drugs in animal models such as rat, guinea pig, gerbil, or mouse. There have been reports that a wide range of drugs appear to protect against hearing loss from ototoxic insults from cisplatin, aminoglycoside antibiotics and noise. However, most experimental studies have demonstrated only partial protection. Positive results from ongoing trials combined with additional laboratory tests should accelerate the time from the bench to clinical treatment.

There are challenges in delivery of protective agents to the cochlea. Some drugs or genes have been delivered by intracochlear perfusion, which is too invasive for application to patients. Very few investigations have used the oral route of administration. Very little information on side effects has been reported, including the potential for interference with desired therapeutic effects of chemotherapy or antimicrobial therapy. Delivery should be noninvasive or only minimally invasive. Oral delivery would be ideal if the protective agent has the desired pharmacokinetic characteristics, however, intravenous or subcutaneous injection would also be acceptable.

The discovery of new compounds can be facilitated by testing potential agents for efficacy, and toxicity using a systematic approach with high throughput screening e.g., the zebrafish model or mammalian in vitro models (organotypic organ culture, hair cell precursor cultures, such as the UB-OC-1 or HEI-OC1 cell lines). This would allow the screening of a wide range of compounds that could be followed by in vivo testing in mammalian animal models to provide proof of concept for efficacy, mechanisms of action and potential side effects. Ultimately clinical trials will be needed.

The field appears to be moving toward alternative technologies or approaches including use of stem cells, gene therapy or RNA silencing using non-viral delivery methods.

Novel developments of drug delivery in the future could provide exciting possibilities to treat hearing loss. The ability to deliver a variety of protective agents by trans-tympanic injection is of great interest as it avoid systemic toxicity and interference with the pharmacokinetics and pharmacodynamics of the aminoglycoside antibiotics or cisplatin.
The field of treatment of hearing loss using medicines is just starting to emerge and offers a wide range of possibilities of intervention. It is hoped that in the following years new compounds will be available to prevent or treat hearing loss.

10. Conclusion

Hearing loss is a major cause of human disability in Europe and in the world. As previously stated 360 million persons have disabling hearing loss in the world in 2012. With the ageing of the world population hearing loss is expected to increase substantially in the future.

Large epidemiological surveys as well as use of standardization methods of evaluation and reporting would certainly help gain awareness of the prevalence and impact of hearing loss in societies.

Rapid advances in bioscience and technology make it realistic to envision a pharmacological treatment for hearing loss of different causes.

There has been exciting research performed towards a possible treatment for hearing loss ranging from the search for new pharmacological compounds, gene therapy, RNA silencing, stem cells, and discovery of new delivery routes of administration.

If at present most of these research have been done in academic settings it is likely that the pharmaceutical industry will also start soon innovative projects towards a pharmacological treatment of hearing loss and that public-private partnerships (PPP) will arise in a relatively short time. As the prevalence of hearing impairment in the world is very high this opens huge potential markets for pharmacological interventions. Consortiums of top-level European research and industrial partners will need to act in this direction and contribute to strengthen the EU’s leadership on research into treatment and pharmacological prevention of hearing loss.

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## Annex 6.21.1: Countries and territories in analysis regions.

<table>
<thead>
<tr>
<th>Subregion</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>East Asia region</strong></td>
<td>China, Hong Kong SAR (China), Macau SAR (China), Democratic People's Republic of Korea, Taiwan</td>
</tr>
<tr>
<td><strong>Southeast Asia</strong></td>
<td>Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Maldives, Myanmar, Philippines, Sri Lanka, Thailand, Timor-Leste, Viet Nam</td>
</tr>
<tr>
<td><strong>Oceania</strong></td>
<td>Cook Islands, Fiji, French Polynesia, Kiribati, Marshall Islands, Micronesia (Federated States of), Nauru, Palau, Papua New Guinea, Samoa, Solomon Islands, Tonga, Vanuatu, Tuvalu, Nieuw</td>
</tr>
<tr>
<td><strong>South Asia region</strong></td>
<td>Afghanistan, Bangladesh, Bhutan, India, Nepal, Pakistan</td>
</tr>
<tr>
<td><strong>Central Asia</strong></td>
<td>Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, Uzbekistan</td>
</tr>
<tr>
<td><strong>Central Europe</strong></td>
<td>Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia, Macedonia (Former Yugoslav Republic of)</td>
</tr>
<tr>
<td><strong>Eastern Europe</strong></td>
<td>Belarus, Estonia, Latvia, Lithuania, Moldova, Russian Federation, Ukraine</td>
</tr>
<tr>
<td><strong>North Africa and Middle East</strong></td>
<td>Algeria, Bahrain, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Occupied Palestinian Territory, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, Turkey, United Arab Emirates, Yemen</td>
</tr>
<tr>
<td><strong>Sub-Saharan Africa region</strong></td>
<td>Angola, Central African Republic, Congo, Democratic Republic of the Congo, Equatorial Guinea, Gabon</td>
</tr>
<tr>
<td><strong>East Africa</strong></td>
<td>Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mauritius, Mozambique, Rwanda, Seychelles, Somalia, Sudan, Uganda, United Republic of Tanzania, Zambia</td>
</tr>
<tr>
<td><strong>Southern Africa</strong></td>
<td>Botswana, Lesotho, Namibia, South Africa, Swaziland, Zimbabwe</td>
</tr>
<tr>
<td><strong>West Africa</strong></td>
<td>Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Côte d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone, São Tomé and Príncipe, Togo</td>
</tr>
<tr>
<td><strong>Latin America and Caribbean region</strong></td>
<td>Bolivia, Ecuador, Peru</td>
</tr>
<tr>
<td><strong>Central Latin America</strong></td>
<td>Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Venezuela (Bolivarian Republic of)</td>
</tr>
<tr>
<td><strong>Southern Latin America</strong></td>
<td>Argentina, Chile, Uruguay</td>
</tr>
<tr>
<td><strong>Tropical Latin America</strong></td>
<td>Brazil, Paraguay</td>
</tr>
<tr>
<td><strong>Caribbean</strong></td>
<td>Antigua and Barbuda, Bahamas, Barbados, Belize, Bermuda, British Virgin Islands, Cuba, Dominica, Dominican Republic, Grenada, Guyana, Haiti, Jamaica, Netherlands Antilles, Puerto Rico, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago</td>
</tr>
<tr>
<td><strong>Asia-Pacific, high-income</strong></td>
<td>Brunei Darussalam, Japan, Republic of Korea, Singapore</td>
</tr>
<tr>
<td><strong>Australasia</strong></td>
<td>Australia, New Zealand</td>
</tr>
<tr>
<td><strong>North America, high-income</strong></td>
<td>Canada, United States of America</td>
</tr>
<tr>
<td><strong>Western Europe</strong></td>
<td>Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Greenland, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Netherlands, San Marino, Monaco, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom</td>
</tr>
</tbody>
</table>
Annex 6.21.2: DALYs caused by hearing loss, by age group, regions and sex*

Data from the Global Burden of Disease 2010, Lancet Dec 2012.


*Created by Faraz Chavoushi, Department of Essential Medicines, World Health Organization, Geneva
Update on 2004 Background Paper, BP 6.21 Hearing Loss

**DALY rates caused by hearing loss, by age group and region**

- **Central Europe**
- **Eastern Europe**

**Absolute DALYs caused by hearing loss by region and sex**

- **Female**
- **Male**

**DALY rates caused by hearing loss by sex and region**

- **Global**
- **Central Europe**
- **Eastern Europe**
- **Western Europe**
- **Female**
- **Male**
# Update on 2004 Background Paper, BP 6.21 Hearing Loss

## Annex 6.21.3: Cochrane study summary on medical interventions

<table>
<thead>
<tr>
<th>Study population</th>
<th>Number of patients</th>
<th>Interventions compared</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus</strong></td>
<td>Any adult with acute onset sensorineural hearing loss and/or tinnitus of any duration.</td>
<td>392 participants 7 trials</td>
<td>Trials using hyperbaric oxygen administered in a compression chamber above 1.2 ATA and for treatment times between 30 and 120 minutes on at least one occasion were eligible. The comparator group was somewhat diverse. We accepted any standard treatment regimen designed to maximise hearing loss recovery or reduction in tinnitus, or where the comparator was designed to improve quality of life for appropriate patients. Subgroup analysis was considered to evaluate the impact of different comparator strategies.</td>
<td>1.53 recovery of hearing as measured by audiometry. Outcome 1 Greater than 50% return of hearing.</td>
</tr>
<tr>
<td><strong>Virals for idiopathic sudden sensorineural hearing loss</strong></td>
<td>Patients of any age with sudden sensorineural hearing loss (ISSHL), defined as follows. A history of a sudden decrease in hearing within three days. A sensorineural hearing loss of at least 30 dB for three subsequent 1-octave steps in frequency, unilateral or bilateral, demonstrable on a standard pure-tone audiogram at the time of entry into the trial. No other neurological signs except for the eighth cranial nerve defect. Commencement of treatment within 14 days of the onset of the hearing loss.</td>
<td>257 participants 4 trials</td>
<td>Antivirals (oral or intravenous). Examples include acyclovir and valacyclovir, given at any dose for any duration. Comparisons were: antiviral versus placebo; antiviral versus no treatment; (antiviral + other treatment) versus (placebo + same other treatment); and (antiviral + other treatment) versus (same other treatment).</td>
<td>There is currently no evidence to support the use of antiviral drugs in the treatment of ISSHL. The four trials included in this review were, however, small and with a low risk of bias. Further randomised controlled trials with larger patient populations, using standardised inclusion criteria, antiviral regimes and outcome measures, are needed in order for adequate meta-analysis to be performed to reach definitive conclusions.</td>
</tr>
</tbody>
</table>
### Steroids for idiopathic sudden sensorineural hearing loss

<table>
<thead>
<tr>
<th>Study population</th>
<th>Number of patients</th>
<th>Interventions compared</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients of any age with ISSHL and treated with steroids were included. These patients had to fit the entry criteria as below. Idiopathic sudden sensorineural hearing loss (ISSHL) was defined as: a history of a sudden decrease in hearing; a sensorineural hearing loss demonstrable on a pure tone audiogram at the time of entry into the trial (as it was anticipated that limited data would be available, a criterion for sensorineural hearing loss was not predefined); no other neurological signs except the eighth cranial nerve defect; commencement of treatment within 14 days of the onset of hearing loss.</td>
<td>164 participants 2 trials</td>
<td>Trials using hyperbaric oxygen administered in a compression chamber above 1.2 ATA and for treatment times between 30 and 120 minutes on at least one occasion were eligible. The comparator group was somewhat diverse. We accepted any standard treatment regimen designed to maximise hearing loss recovery or reduction in tinnitus, or where the comparator was designed to improve quality of life for appropriate patients. Subgroup analysis was considered to evaluate the impact of different comparator strategies.</td>
<td>1.10 Effects of oral steroid versus oral placebo immediate post-treatment, Outcome 1 Hearing recovery; average speech frequencies (500, 1000, 2000 Hz), no conclusions can be drawn about the effectiveness, or lack thereof, of steroids in the treatment of idiopathic sudden sensorineural hearing loss.</td>
<td></td>
</tr>
</tbody>
</table>

### Corticosteroids for acute bacterial meningitis

<table>
<thead>
<tr>
<th>Study population</th>
<th>Number of patients</th>
<th>Interventions compared</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants of any age and in any clinical condition.</td>
<td>4041 participants 24 trials</td>
<td>Participants with community-acquired bacterial meningitis treated with antibacterial agents and randomized to adjuvant corticosteroid therapy of any type.</td>
<td>0.76 Adults, Outcome 2 Any hearing loss.</td>
<td>Corticosteroids significantly reduced hearing loss and neurological sequelae, but did not reduce overall mortality. Patients with bacterial meningitis in high-income countries.</td>
</tr>
</tbody>
</table>

### Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children

<table>
<thead>
<tr>
<th>Study population</th>
<th>Number of patients</th>
<th>Interventions compared</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>The focus was on studies of children up to the age of 12 years, and we report when older subjects were included. The age of the patients is pertinent in respect of both the natural history of the disease process and the measurable outcomes (see below).</td>
<td>945 participants 12 trials</td>
<td>Systemic or topical intranasal steroids compared with control (placebo or non-intervention control). We included additional treatments such as antibiotics so long as they were identical in the treatment and in the control groups. We grouped studies according to the comparisons made: (1) oral steroid versus control; (2) oral steroid plus additional treatment versus control plus identical additional treatment; (3) topical intranasal steroid versus control; and (4) topical intranasal steroid plus additional treatment versus control plus identical additional treatment.</td>
<td>Oral steroids versus control, Outcome 1 Hearing loss at six weeks (hearing not improved by at least 10 dB in either ear), 0 No evidence of longer-term benefit and no evidence that they relieve symptoms of hearing loss.</td>
<td></td>
</tr>
</tbody>
</table>
## Update on 2004 Background Paper, BP 6.21 Hearing Loss

<table>
<thead>
<tr>
<th>Study population</th>
<th>Number of patients</th>
<th>Interventions compared</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children</strong></td>
<td>Children aged 1 to 12 years with unilateral or bilateral otitis media with effusion.</td>
<td>Treatment in the form of grommet insertion in the tympanic membrane could be unilateral (randomisation by ears) with no surgery or myringotomy in the other ear as control, or bilateral (randomisation by children) with no surgery or myringotomy alone in the control group.</td>
<td>Hearing levels by child, Outcome 2 By child hearing levels at 12 months follow up. -0.41</td>
<td>No effect was found on other child outcomes but data on these were sparse.</td>
</tr>
<tr>
<td><strong>Medical interventions for the prevention of platinum-induced hearing loss in children with cancer</strong></td>
<td>Children (aged 0 to 18 years at diagnosis) with any type of childhood malignancy.</td>
<td>total number of patients 149 two RCTs and one CCT Platinum-based therapy together with a protective medical intervention versus platinum-based therapy with placebo, no additional treatment or another protective medical intervention.</td>
<td>1.04 Amifostine versus no otoprotective intervention, Outcome 2 Ototoxicity according to NCI CTC v2 criteria with intravenous platinum (combined asymptomatic and symptomatic disease).</td>
<td>Since pooling of results was not possible and all studies had serious methodological limitations, no definitive conclusions can be made.</td>
</tr>
</tbody>
</table>
Update on 2004 Background Paper

Background Paper 6.22
Pneumonia

By Nga Tong, BA, MPH

May 2013
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## Abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTI</td>
<td>Acute Respiratory Tract Infection</td>
</tr>
<tr>
<td>ALRTI</td>
<td>Acute Lower Respiratory Tract Infection</td>
</tr>
<tr>
<td>AMC</td>
<td>Advance Market Commitments for Vaccines</td>
</tr>
<tr>
<td>CAP</td>
<td>Community-Acquired Pneumonia</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-adjusted life-year</td>
</tr>
<tr>
<td>DHS</td>
<td>Demographic and Health Surveys</td>
</tr>
<tr>
<td>ECDC</td>
<td>European Centre for Disease Prevention and Control</td>
</tr>
<tr>
<td>EEA</td>
<td>European Economic Area</td>
</tr>
<tr>
<td>EFTA</td>
<td>European Free Trade Association</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GAPP</td>
<td>Global Action Plan for Prevention and Control of Pneumonia</td>
</tr>
<tr>
<td>GAVI</td>
<td>Global Alliance for Vaccine Immunization</td>
</tr>
<tr>
<td>GBD</td>
<td>Global Burden of Disease</td>
</tr>
<tr>
<td>GSK</td>
<td>Glaxo-Smith Kline</td>
</tr>
<tr>
<td>Hib</td>
<td><em>Haemophilus influenza</em> type b</td>
</tr>
<tr>
<td>IMCI</td>
<td>Integrated Management for Childhood Illness</td>
</tr>
<tr>
<td>IPD</td>
<td>Invasive Pneumococcal Disease</td>
</tr>
<tr>
<td>LRRTI</td>
<td>Lower Respiratory Tract Infection</td>
</tr>
<tr>
<td>MDG</td>
<td>Millennium Development Goal</td>
</tr>
<tr>
<td>MICS</td>
<td>Multiple Indicator Cluster Surveys</td>
</tr>
<tr>
<td>PATH</td>
<td>Program for Appropriate Technology in Health</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PCV</td>
<td>Pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>PERCH</td>
<td>Pneumonia Etiology Research for Child Health</td>
</tr>
<tr>
<td>PPV</td>
<td>Pneumococcal Polysaccharide Vaccine</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory Syncytial Virus</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>VE</td>
<td>Vaccine efficacy</td>
</tr>
<tr>
<td>VT-IPD</td>
<td>Vaccine-Serotypes Invasive Pneumococcal Disease</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>YLD</td>
<td>Years Lost due to Disability</td>
</tr>
<tr>
<td>YLL</td>
<td>Years of Life Lost</td>
</tr>
</tbody>
</table>
Executive Summary

The 2004 Priority Medicines for Europe and the World Report had 17 chronic and acute priority diseases whose inclusion were based on data from the World Health Organization (WHO) Global Burden of Disease and Database. This updated 2013 Report revised its methods and found reason for the inclusion of five new priority diseases using both the WHO Global Burden of Disease Database 2008 and the Lancet Global Burden of Disease Study 2010. In addition to previous conditions on the list, the five new priority diseases or risk factors are: obesity, low back pain, neonatal conditions, pneumonia, and hearing loss. This background paper focuses on pneumonia in two high-risk populations: children under five and the elderly. Worldwide, children under five are primarily affected by this disease, followed by adults 65 years and older, together making up the majority of pneumonia deaths especially in Europe.

Poor maternal and child health remains a significant problem in developing countries. Although the under-five mortality rate has dropped 35% since 1990, with every developing region seeing a 30% reduction, progress at the global level to reduce under-five mortality is behind schedule for 2015. Pneumonia remains a major killer of children under five years of age, and the highest under-five mortality rates are in low- and middle-income countries (LMIC), namely in sub-Saharan Africa and in Southern Asia. Children in low-income countries are nearly 18 times more likely to die before the age of five than children in high-income countries due to pneumonia and other acute infections.

As a result, there is a considerable need for effective interventions in all parts of the world in order to bring down mortality and morbidity rates due to pneumonia. Reducing child mortality is one of the eight Millennium Development Goals (MDGs), and one way to reach this target is to reduce pneumonia-related mortality by providing effective treatment promptly. Effective interventions to reduce pneumonia deaths are available through vaccinations and antibiotics. However, access to and information on antibiotic use is limited. In addition, only one in five caregivers know to seek appropriate medical care immediately for children with signs of pneumonia. Currently, rapid diagnostic devices that can be used at point of care are not available.

Rapid diagnostics for distinguishing between viral and bacterial pneumonia is not yet well developed. Existing laboratory tests for certain biochemical markers (e.g. procalcitonin, C-reactive protein, white blood cells, etc) only detect the likelihood of bacterial pneumonia. In addition, clinical signs (e.g. fever, shortness of breath, wheezing, crepitation, etc) and radiographic tests (e.g. consolidation or infiltration in the lung) can confirm or disprove diagnosis of pneumonia. However, it is difficult to differentiate between viral and bacterial pneumonia in resource-poor settings lacking in technology and laboratory equipment. Attention should focus on continued updates on existing pneumococcal vaccines to help match the pattern of disease. More effective and rapid diagnostics would also help play a substantial role in detecting cases of pneumonia in order to treat patients at the earliest onset of the disease. Furthermore, scaling up treatment coverage at a relatively low cost would aid in the reduction of childhood pneumonia mortality. While there are current care management for pneumonia, including interventions involving integration of vaccines into national immunization programs, targeted antibiotic treatments for both severe and non-severe pneumonia, and more accurate and rapid diagnostics will help to reduce the global
mortality rates in children under five and the elderly. Preventing children from developing or dying from pneumonia is critical to reducing mortality and working towards achieving the MDG4 in reducing the under-five mortality rate by two thirds by 2015.
1. Introduction

1.1 Background

Pneumonia is the single leading cause of mortality in children under five and is a major cause of child mortality in every region of the world, with most deaths occurring in sub-Saharan Africa and South Asia. Pneumonia kills more children under five than AIDS, malaria, and measles combined, yet increased attention in recent years have been on the latter diseases.\(^3\)

Pneumonia is a form of acute respiratory tract infection (ARTI) that affects the lungs. When an individual has pneumonia, the alveoli in the lungs are filled with pus and fluid, which makes breathing painful and limits oxygen intake. Pneumonia has many possible causes, but the most common are bacteria and viruses. The most common pathogens are \textit{Streptococcus pneumoniae}, \textit{Haemophilus influenzae} type b (Hib), and respiratory syncytial virus (RSV). \textit{S. pneumoniae} is the most common cause of bacterial pneumonia in children under five years in the developing world.\(^4\) The second most common cause of bacterial pneumonia in children is Hib, followed by RSV - the most common cause of viral pneumonia in children under two years. The populations most at risk for pneumonia are children under five years, people aged 65 or over, and people with pre-existing health problems.

\textit{Streptococcus pneumoniae} frequently colonizes the upper respiratory tract. The human nasopharynx is the only natural reservoir for \textit{S. pneumoniae} and these bacteria along with viruses are commonly found in a child’s nose or throat; these pathogens are then aspirated into the lungs, causing disease. Pneumonia can be spread in a number of ways. The pathogen is transmitted through direct contact with respiratory secretions, colonizes the nasopharynx and may then cause blood-borne diseases.\(^5\) \textit{S. pneumoniae} can cause both non-invasive and invasive disease in all age groups, particularly in children younger than five years and adults 65 years or older.\(^5, 3\) In addition, people with certain medical conditions, such as chronic heart, lung, or liver diseases, or sickle cell anemia are also at increased risk for pneumococcal diseases. People living with HIV/AIDS or people who have had organ transplants and are taking medications that decrease their immunity to infection are also at high risk of getting this disease.\(^3\)

A healthy child has many natural defenses that protect its lungs from pneumonia. Undernourished children, especially those who are not exclusively breastfed or with inadequate zinc intake, are at a higher risk of developing pneumonia.\(^4\) Immunosuppression due to other coinfections are important risk factors in pneumonia-related mortality; infants, children, or the elderly suffering from illnesses, such as AIDS, measles, or malaria are also more likely to develop pneumonia. Additionally, environmental factors, such as crowded living conditions and exposure to indoor air pollution may contribute to increasing children’s susceptibility to pneumonia.

The Lancet Global Burden of Disease (GBD) Study 2010 has a category for lower respiratory tract infections (LRTI), which includes influenza, \textit{Streptococcus pneumoniae} (pneumococcal pneumonia), \textit{Haemophilus influenzae} type b (Hib), respiratory syncytial virus (RSV), and “other lower respiratory infections”. For the purposes of this report, pneumococcal
pneumonia, Hib, and RSV were chosen as the focus to assess the disease burden in further details.6

1.2 Size and nature of the disease burden

1.2.1 Europe

In Europe, mortality rates for pneumonia are substantially higher in children up to the age of 4 and in adults aged 75 and over than in most other age groups. Most strikingly, in Western Europe the highest mortality rates for pneumonia are in the elderly aged 80 and over (279 deaths per 100 000 people), while in Eastern Europe similar mortality rates for pneumonia exist in infants aged 0-6 days (278 deaths per 100 000). See Figure 6.22.2.

Very young children and the elderly are most at risk for invasive pneumococcal disease (IPD), which is a form of pneumonia where the bacterium S. pneumoniae enters the blood, cerebrospinal fluid, pleural fluid, joint fluid, or pericardial fluid and can lead to other complications and infections such as pneumococcal sepsis.7 In contrast, non-invasive pneumococcal disease, spread through aerosolization of bacteria from the nasopharynx to the alveoli—can cause otitis media, sinusitis, and bronchitis. Comparing the two, IPD is the leading cause of mortality and morbidity in children and adults compared to non-invasive pneumococcal disease.8 Although pneumococcal conjugate and Hib vaccines have been introduced into the childhood vaccination schedule in a number of European Union (EU), European Economic Area (EEA), and European Free Trade Association (EFTA) countries, the average number of confirmed cases for IPD in 2009 was 4.3 cases per 100 000 population (see Figure 6.22.1 below).8 In 2009, the European Center for Disease Prevention and Control (ECDC) detected 14 272 cases of confirmed IPD. In 2008 the number of confirmed cases of IPD has decreased since the previous year (14 759 cases in 2008); however, the 2009 total cases was still higher than the number of confirmed cases in 2006 (14 272 versus 13 235 cases, respectively).8 The rates for IPD cases in children 0-4 years and in adults 65 years and older are higher than most other age groups (see Figure 6.22.1).

Figure 6.22.1: Rates of reported cases of confirmed invasive pneumococcal disease, by age and gender, in EU and EEA/EFTA countries, 2009

Source: European Centre for Disease Prevention and Control 2011
Update on 2004 Background Paper, BP 6.22 Pneumonia

Data for combined non-invasive and invasive pneumonia mortality rates are listed in Figure 6.22.2 below; the graph shows that pneumonia mortality rates are highest among children under five and the elderly over 75 years of age with well over 300 deaths per 100,000 in the relative age categories for all of Central, Eastern, and Western Europe. Most notable are the high mortality rates due to pneumonia in Eastern Europe among children under five and in Western Europe among the elderly. For clarification, this report refers to *S. pneumoniae* (pneumococcal pneumonia), Hib, and RSV as the three major pathogens contributing to pneumonia incidence and mortality. Despite good access to antibiotics and immunization programs, pneumonia is still a substantial cause of illness and death in the EU and EEA/EFTA countries especially among the elderly.

**Figure 6.22.2: Death rates caused by pneumonia by European region and age group, 2010**

![Graph showing death rates caused by pneumonia by European region and age group, 2010](source)

Source: Institute of Health Metrics and Evaluation 2010

**Europe: Children Under Five**

According to the ECDC, rates of reported IPD cases for children under the age of five in Europe are lower than rates for people aged 65 and older (see Figure 6.22.1). Nonetheless, this number still constitutes a majority of reported cases. Central, Eastern, and Western regions of Europe show similar trends in mortality rates for each pneumonia-causing organism (*S. pneumoniae*, Hib, and RSV); Eastern Europe has the highest mortality rates for all three pneumococcal diseases, followed by Central Europe, then Western Europe (see...
Figure 6.22.2). Respiratory syncytial virus has the highest mortality rates in all three European regions among children under five, of about 105 deaths per 100,000—nearly double the highest RSV mortality rate for Central Europe of roughly 48 deaths per 100,000 (see Figure 6.22.3). Out of the three pneumonia-causing organisms, RSV mainly affects infants and children 0-364 days, but children 1-4 years show a higher mortality rate due to pneumococcal pneumonia than Hib or RSV. The disability-adjusted life-year (DALY) burden for children aged 0-364 days is highest compared to other age groups, with over 24,000 DALYs per 100,000 in Eastern Europe (see Figure 6.22.4). Therefore, pneumonia interventions would yield the highest health benefits and DALYs averted in children less than one year of age, especially in Eastern and Central Europe.

Figure 6.22.3: Under-five death rates by region in Europe and causes of pneumonia, 2010

Source: Institute of Health Metrics and Evaluation 2010

Europe: The Elderly

Another at-risk population is the elderly, who often suffer from flu-like symptoms caused by RSV and *S. pneumoniae*. Due to an increasing ageing population in developed countries, nursing homes are often overcrowded, which provides for opportunistic infections. Moreover, the incidence of infectious diseases, such as pneumonia is common in the elderly because of their impaired immunity. The rate of intermittent pneumonia among nursing
home residents is almost 14 times as high as that among elderly people living in the community.\textsuperscript{9}

In 2009 the ECDC showed that reported cases of IPD are the highest among people over the age of 65 (see Figure 6.22.1). Within the 65 and older age group, there is a gender discrepancy of more cases in males than females. Similarly, data from the Lancet Global Burden of Disease (GBD) Study 2010 also showed that people aged 80 and older have the highest mortality rates due to pneumonia (from \textit{S. pneumoniae}, Hib, and RSV) with 279 deaths per 100 000 in Western Europe, comparable to the 278 deaths per 100 000 for infants 0-6 days in Eastern Europe (see Figure 6.22.2). People 80 years and older in Central Europe have the third highest mortality rate among all age groups with 157 deaths per 100 000. However, the DALY burden for people 65 years and older is relatively low (355–1709 DALYs per 100 000) compared to the under-five age groups (399–23 972 DALYs per 100 000) (see Figure 6.22.4 below).

\textbf{Figure 6.22.4: DALY rates caused by pneumonia by European region and age group, 2010}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{DALY_rates.png}
\caption{DALY rates caused by pneumonia by European region and age group, 2010}
\end{figure}

Source: \textit{Institute of Health Metrics and Evaluation 2010}
1.2.2 Worldwide

Globally, the four major killers of children under five years old are pneumonia, diarrhoeal diseases, preterm birth complications, and birth asphyxia. Pneumonia remains the leading cause of mortality in children under five worldwide. Of the estimated 6.9 million child deaths each year, pneumonia accounts for anywhere from 1.3 to 1.6 million deaths a year in this age group, roughly 18% of deaths among children under age five (see Figure 6.22.5).

Figure 6.22.5: Global distribution of deaths among children under age five by cause, 2009

Note: Undernutrition contributes to more than a third of deaths among children age five. Values may not sum to 100% because of rounding.

The trend in global mortality due to pneumonia and pneumonia-related deaths has decreased between 1990 and 2010, along with deaths under five due to pneumonia (see Annex 6.22.1). However, mortality for children under five due to pneumonia constitutes over 20% of the total global mortality for pneumonia for 1990, 2005, and 2010 (33%, 23%, and 20%, respectively, see Annex 6.22.1). More than 99% of all pneumonia mortalities occur in low- and middle-income countries (LMIC). South Asia and sub-Saharan Africa bear the
burden of more than half of the total number of cases of suspected pneumonia among children under five worldwide (see Figure 6.22.6 below, also see Annex 6.22.2). Children in low-income countries are nearly 18 times more likely to die before the age of five than children in high-income countries, due mainly to pneumonia and other acute infections. In 2010, 70% of the world’s under-five mortalities occurred in only 15 countries, and about half in only five countries (India, Nigeria, Democratic Republic of Congo, Pakistan, and China). These numbers looked only at the three leading pneumonia-causing organisms: S. pneumoniae, Hib, and RSV. For both European Regions and the world, the disease burden for pneumonia (caused by pneumococcus, Hib, and RSV) is highest in children under one year of age. Roughly 434 779 pneumonia deaths occur in this age group and this is over 74% of pneumonia deaths in the under-five age group.

Figure 6.22.6: Under-five deaths due to pneumococcal pneumonia, Hib, and RSV by regions, 2010

Of the 7.6 million children who died in the first five years of life in 2010, 4.9 million (64%) died of infectious conditions. Of all infectious diseases, pneumonia, diarrhoea, and malaria were the leading causes of death in children under five worldwide. Pneumonia caused 1.4 million deaths (18.3%) of all mortalities in children under five, and 4% of that 18.3% of pneumonia mortalities are in the neonatal period. Overall, numbers in under five mortality for pneumonia is less in children aged 1-59 months than they are in neonates (for neonatal conditions, see Background Paper Chapter 6.23).

Globally, respiratory syncytial virus (RSV) causes 253 537 worldwide mortalities each year (see Annex 6.22.3) and it is the most common cause of serious lower respiratory tract infections in infants and young children aged 0-364 days worldwide (see Figure 6.22.7). While all children are at risk of RSV disease, the incidence of severe disease is highest in children with cardiopulmonary disease and those born prematurely. The highest mortality
rates due to RSV complications occur in all regions of sub-Saharan Africa and South Asia in infants aged 0-6 days. A substantial proportion of RSV-associated morbidity occurs in the first year of life, with incidence in infants that is two or three times greater than is reported for children younger than five years of age overall.\textsuperscript{14} Also important to consider is the etiologic diagnosis of pneumonia causing organisms where coinfections from both viruses and bacteria can make it difficult to distinguish which organism is the major contributor to the disease outcome. Viruses are thought to cause most of LRTIs, but identification of the viral pathogen is not always successful. In other cases, bacteria \textit{S. pneumoniae} are isolated in the sputum of 50\% of patients with bronchitis, but such colonization of the bacteria presents little clinical relevance.\textsuperscript{15} Therefore, reported pneumonia mortalities from a specific organism may have some uncertainty because no sensitivity and specific tests for the diagnosis of Hib, RSV, or pneumoccal pneumonia are available.\textsuperscript{16} Nonetheless, impact of pneumonia interventions looking at population costs and health effects of the intervention of different country profiles show low-cost outcomes between US$ 10 and US$ 60 per DALY averted for interventions in the WHO Africa D and E subregions, and in the WHO Eastern Mediterranean D subregion.\textsuperscript{17}

\textbf{Figure 6.22.7: Under five death rates by regions in sub-Saharan Africa and South Asia according to the causes of pneumonia, 2010}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{under_five_deaths_by_region.png}
\caption{Under five death rates by regions in sub-Saharan Africa and South Asia according to the causes of pneumonia, 2010}
\end{figure}

Source: Institute of Health Metrics and Evaluation 2010
2. Control Strategy

Pneumonia is caused by a combination of a variety of factors, including pathogens, the environment, health systems, and health-seeking behaviours. Therefore, no single intervention can effectively prevent, treat, or control pneumonia. As such, a confluence of key interventions to control pneumonia would include immunization against specific pathogens, early diagnosis and treatment of the disease, and improvements in nutrition and environmental living conditions (e.g., safe drinking water, sanitation, hygiene, low household air pollution). Children under five, especially infants aged 0-5 months, not exclusively breastfed are 15 times more likely to die due to pneumonia than children who are exclusively breastfed\(^4\) (see Figure 6.22.8); interventions for increased breastfeeding practices will help decrease childhood mortality due to pneumonia as well as diarrhoea (also see Background Paper Chapter 6.20 on diarrhoeal disease). The potential for saving lives by scaling up the proper interventions is large. Modeled estimates suggest that by 2015 child mortality, due to pneumonia, could fall 30% across the 75 countries with the highest mortality burden if national coverage of key pneumonia interventions were raised to the level in the richest 20% of households in each country.\(^4\)

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.22.8.png}
\caption{Relative risk among young infants who are not/partially breastfed compared to those exclusively breastfed for pneumonia and diarrhoea incidence and mortality}
\end{figure}

Source: UNICEF. *Pneumonia and diarrhoea: Tackling the deadliest diseases for the world’s poorest children*, 2012
2.1 Care-seeking behavior

The Multiple Indicator Cluster Surveys (MICS) and Demographic Household Survey (DHS) provide information on caregivers’ knowledge of symptoms of pneumonia and on the extent to which caregivers seek appropriate provider for their children with suspected pneumonia. According to these two surveys from 1998 to 2004, the majority of caregivers did not recognize the common symptoms of pneumonia and only 54% of children under five in the developing world were taken to an appropriate provider. However, recent data from MICS and DHS between 2000 to 2010 showed that care-seeking for children with symptoms of pneumonia has increased slightly in developing countries, from 54% in 2000 to 60% in 2010 (see Figure 6.22.9).

Figure 6.22.9: Every region has shown progress in appropriate care seeking for suspected childhood pneumonia over the past decade.

![Graph showing care-seeking progress](image)

Source: UNICEF. Pneumonia and diarrhoea: Tackling the deadliest diseases for the world’s poorest children. 2012

In addition, feeding infants only breast milk in the first six months of life is a key protective intervention highlighted in the Global Action Plan for Prevention and Control of Pneumonia (GAPP) report. Exclusive breastfeeding has multiple positive effects such as nutritional benefits and allows the mother to pass on key components of her immune system to her child to strengthen the infant’s immunity, thereby protecting infants from pneumonia, diarrhoea, and other infections (see Figure 6.22.8).
2.2 Diagnosis

Pneumonia can be diagnosed in a number of different ways. Healthcare providers can diagnose pneumonia by the symptoms, a physical examination, or by ordering diagnostics. Laboratory tests can include chest X-rays and cell cultures (followed by PCR antigen testing of blood or antigen testing of urine) to look for pathogenic bacteria in the infected part of the body. Usually there should be a combination of clinical, radiological, and laboratory findings to increase the likelihood of correct diagnosis. Chest X-rays and laboratory tests can help confirm the diagnosis of pneumonia by presence of specific findings, such as consolidation or infiltration in the lung, which still would need qualified assessment in conjuction with clinical picture. Localization of infiltrates is important for differential diagnosis (e.g. primary tuberculosis with other pathogens, and in the case of upper lob infiltrate, diffusive infiltration can be seen in pneumocystic pneumonia and sometimes in disease caused by virus or Chlamydia), but should not be used as a unique criteria. In the developing world, children with suspected pneumonia are diagnosed based on their clinical symptoms, given that access to laboratory technologies is often unavailable in resource-poor settings. Healthcare providers can diagnose many cases by using a stethoscope and/or observe a child’s respiratory rate and any breathing problems. Children and infants are presumed to have pneumonia if they exhibit a cough and fast or difficult breathing.3 The WHO and UNICEF Integrated Management of Childhood Illness (IMCI) guidelines help inform healthcare providers and personnel on standard clinical symptoms and effective treatment for pneumonia.3

Respiratory syncytial virus (RSV) is an important cause of viral pneumonia in children under five. However, differentiating between viral and bacterial pneumonia is difficult because X-ray detected lesions can look similar for various viruses and coinfections can occur between various pathogens.20 Studies looking at RSV incidence and mortality in developing countries identified RSV by enzyme-linked immunosorbent assay (ELISA) or immunofluorescence assays, which have 12% to 50% lower sensitivity than does polymerase chain reaction (PCR).21 The need for low-cost, key interventions like accurate and point-of-care diagnostic tools for pneumonia would significantly contribute to the prevention of childhood mortality related to pneumonia.

2.3 Antibiotic treatments

Around 85% to 90% of antibiotic consumption occurs in the community, with 80% of this consumption going towards treating respiratory tract infections.22 Once a child develops pneumonia, death is avoidable through cost-effective and life-saving treatment from antibiotics for bacterial pneumonia. When children suffering from pneumonia are treated promptly and effectively with antibiotics their chances of survival increases significantly. The most common antibiotics currently recommended for children younger than five years are cotrimoxazole and amoxicillin. Children aged 2-59 months with non-severe pneumonia can be treated with oral amoxicillin (40 mg/kg/dose) for three days and five days for severe pneumonia (see Table 6.22.10).23 For very severe pneumonia, parenteral ampicillin (or penicillin) and gentamicin are recommended as a first line treatment; ceftiraxone should be used as a second line treatment when the first line treatment fails.23
Table 6.22.10: Treatments for pneumonia and their dosage forms

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxycillin</td>
<td>250 mg, 500 mg</td>
<td>Tablets</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>500 mg, 1 g</td>
<td>Powder for injection</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>250 mg, 1 g</td>
<td>Powder for injection</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>20 mg/ml, 40 mg/ml</td>
<td>Injection</td>
</tr>
<tr>
<td>Procaine benzylpenicillin</td>
<td>1 g, 3 g</td>
<td>Powder for injection</td>
</tr>
<tr>
<td>Oxygen</td>
<td>-</td>
<td>Medicinal gas</td>
</tr>
</tbody>
</table>


While there is a variety of therapeutics for children under five with suspected pneumonia, healthcare providers must be able to identify pneumonia among children with different types of “wheezes” with or without lower chest indrawing, fast breathing, and fever. Accurately diagnosing the type of pneumonia (severe, non-severe, bacterial, viral) will help with rationalizing appropriate treatment while reducing risk for antimicrobial resistance from judicious use of antibiotics (see Background Paper Chapter 6.1 on antimicrobial resistance). Although preventive measures such as vaccination against common pathogens can help to reduce the overall number of pneumonia cases, these interventions will not eliminate pneumonia completely, thus the need for access to safe and effective antibiotic treatments will remain.

2.4 Vaccination

Vaccination is a safe, effective, and cost-effective tool for preventing pneumonia. There are vaccines against major infectious diseases that can cause pneumonia – the flu (influenza virus), measles, pertussis, Hib, and pneumococcus. The WHO recommends that all routine childhood immunization programs include vaccines that protect against these diseases. New vaccines against Hib and pneumococcus are available; many low-income countries have already introduced the Hib vaccine, and pneumococcal conjugate vaccines (PCVs) are increasingly becoming available in developing countries as well. The 7- and 13-valent conjugate vaccines (PCV7, PCV13) have demonstrated effectiveness in reducing incidence and severity of pneumonia and other lower respiratory infections in children. Immunizations help reduce childhood pneumonia in two ways. First, vaccinations help prevent children from developing infections that directly cause pneumonia, such as Hib and S. pneumoniae. Second, immunizations may prevent infections that can lead to pneumonia as a complication, such as influenza, measles, and pertussis. Pneumococcal conjugate vaccines are highly effective in preventing pneumococcal disease. Currently, there are three vaccines on the children’s routine immunization schedule that have the potential to significantly reduce childhood mortality from and related to pneumonia: measles, Hib, and pneumococcal conjugate vaccines. In 2007, the WHO recommended introducing pneumococcal conjugate vaccine (PCV) into all national immunization programs, particularly in countries with high mortality. Since that time, progress has been made in introducing PCV globally with increasing usage in low-income countries.
2.4.1 Hib vaccine

*Haemophilus influenza* type b (Hib) is the second leading cause of bacterial pneumonia in children, but it is preventable with the highly effective Hib vaccine. The Hib vaccine has been shown to have protective efficacy greater than 90% against both laboratory-confirmed invasive meningitis and bacteraemic and non-invasive pneumonia.\(^2\), \(^25\), \(^26\) By the end of the 1990s, two-thirds of high-income countries had added Hib vaccine to their immunization schedule, but lower-income countries were slower to implement routine vaccination into their national programmes.\(^27\) In 2006, the WHO recommended the introduction of the Hib vaccine into all national routine immunization programmes. By 2010, 169 countries (88% of all WHO Member States) have adopted this plan.\(^7\) Since then the gap in vaccination introduction between low- and high-income countries has significantly decreased (Figure 6.22.11).\(^4\) Hib conjugate vaccines are some of the safest and efficacious (over 90% efficacious against invasive Hib disease) vaccines available.\(^28\), \(^25\), \(^26\) High coverage of Hib vaccine immunization in children under five could reduce childhood pneumonia and decrease incidence of severe pneumonia.

Figure 6.22.11: Closing the ‘rich-poor’ gap in the introduction of Hib vaccine in recent years

![Graph showing the introduction of Hib vaccine in different income groups over time](image)

Source: UNICEF. *Pneumonia and diarrhoea: Tackling the deadliest diseases for the world’s poorest children*, 2012
2.4.2 Pneumococcal vaccines

The two vaccines that protect against pneumococcal disease are the 23-valent polysaccharide vaccine (PPV23) and the 13-valent protein-conjugated polysaccharide vaccine (PCV13), which replaced the 7-valent conjugate vaccine (PCV7) in 2010 in the United States. The polysaccharide vaccine (PPV) is T cell-independent and does not produce an anamnestic reaction; this means it does not enhance the reaction of the body’s immunologic memory and immunity may not be long-lasting. Therefore, PPV is not effective in children younger than two years old, but it is approved for individuals aged two and older at risk for developing pneumonia and the vaccine is deemed more appropriate for adults (mostly those aged 50 years and older). On the other hand, conjugate vaccines (PCV) elicits a T cell-dependent response and produce an anamnestic reaction that makes the vaccine more effective in infants and children younger than two years of age. There are three PCVs available globally:

- **PCV7** (the 7-valent CRM197 conjugated vaccine)
- **PCV10** (has the same serotypes as PCV7 plus serotypes 1, 5, and 7F, but different carrier proteins: protein D, diphtheria toxoid and tetanus toxoid)
- **PCV13** (has the same serotypes as PCV7 plus serotypes 1, 3, 5, 6A, 7F, and 19A each conjugated to CRM197)

As the first licensed conjugate vaccine, PCV7 demonstrated effectiveness against invasive (meningitis, bacteraemia, and bacteraemic pneumonia) and non-invasive (pneumonia and otitis media) pneumococcal disease. The subsequent vaccines, PCV10 and PCV13, were licensed against invasive disease based on demonstrating in clinical trials comparable immunogenicity to the PCV7. PCV7 and PCV10 are indicated for use in children from six weeks to five years old. PCV13 is available to children six weeks to 17 years old and for adults 50 years and older. The PCV7 was first introduced in the United States in 2000, followed by many other countries in the subsequent years, both in industrialized countries and in the developing world. This conjugate vaccine protected against seven serotypes of the bacterium responsible for 65% to 80% of cases of severe pneumonia in young children living in industrialized countries. By 2008, the 7-valent pneumococcal conjugate vaccine (PCV7) was used in more than 60 countries. By 2010, PCVs had been introduced into the national immunization program of 55 countries. However, this 7-valent vaccine did not contain all the other important serotypes that are more prevalent in developing countries. Most countries in the European Union have recommended national vaccination with PCV in children.

Newer pneumococcal vaccines with more serotypes (PCV10, PCV13) are currently on the market and have been prequalified by the WHO for use in developing countries, which will provide increased coverage of the serotypes most commonly found in those areas (Table 6.22.12). The WHO recommends that use of PCV in routine childhood immunization programs in all countries and particularly in countries where all-cause mortality among children under five is greater than 50 per 1000 live births, or where there are more than 50,000 children dying annually in countries with a high prevalence of HIV infection.
### Table 6.22.12: Current pneumococcal conjugate vaccines

<table>
<thead>
<tr>
<th>Pneumococcal vaccine</th>
<th>Serotypes included</th>
<th>Conjugate protein</th>
<th>Trade name (manufacturer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV7</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F</td>
<td>Mutant diptheria toxoid (CRM 197 protein)</td>
<td>Prev(e)nar ® (Pfizer)</td>
</tr>
<tr>
<td>PCV10</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F</td>
<td>Protein D from non-typeable <em>Haemophilus influenzae</em>, tetanus toxoid and diphtheria toxoid</td>
<td>Synflorix ® (GlaxoSmithKline)</td>
</tr>
<tr>
<td>PCV13</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6A, 19A</td>
<td>CRM 197 protein</td>
<td>Prev(e)nar-13 ® (Pfizer)</td>
</tr>
</tbody>
</table>

Source: *Measuring impact of Streptococcus pneumonia and Haemophilus influenza type b conjugate vaccination. WHO Department of Immunization, Vaccines and Biologicals, 2012.*

### 3. Why Does the Disease Burden Persist?

Children of low socioeconomic class or caste (social stratification in India), minority ethnic groups, or living in isolated geographic areas suffer more from inequity than their counterparts. These children are at a disadvantage in access to appropriate and adequate health services. The extent to which caregivers are aware of the basic symptoms for pneumonia and seek appropriate care for their children with is often low. A child’s condition may worsen if he or she is not brought into be seen by a health care worker and given treatment immediately, and the chances of dying from pneumonia or co-infections increase. As a result, less than 50% of the children from families of the poorest quintile receive the necessary care for pneumonia compared to the richest quintile whose coverage in care seeking for pneumonia is well over 60%.

Also important to note is that antibiotic treatments are usually empirical, as in most cases of bacterial pneumonia, where isolation of the organism is an exception rather than the rule. Health-care providers prescribing or care givers administering oral antibiotics to children with suspected pneumonia without ascertaining the actual pathogenic cause of pneumonia are taking the risk of treating an organism that may or may not respond to antibiotics.

Furthermore, lack of rapid diagnostic testing plays a major role in the continual presence of pneumococcal disease incidence in developing countries. Community health care workers in less developed countries rely on 1) observation of clinical symptoms of pneumonia to determine the severity of the illness, and 2) empirical antibiotic treatments. This form of care management may not always result in accurate diagnosis of pneumococcal diseases as other coinfections can occur. Chest indrawing, wheezing and/or a temperature greater than 39 degrees Celsius are indications of pneumonia. However, the presence of either or both can be misleading to caregivers (and untrained health care workers) in assessing whether the condition is bacterial or viral. More often than not, antibiotic treatments are prescribed for cases of suspected pneumonia. The use of antibiotics to treat pneumonia is ineffective when the child has viral pneumonia, which can be difficult to determine without proper diagnostics or health care provider knowledge of clinical symptoms.
Globally, respiratory syncytial virus (RSV) is the most common cause of childhood acute lower respiratory tract infections (ALRTI) and a major cause of admission to hospitals as a result of severe ALRTI. Unlike pneumococcal pneumonia or Hib, there is no current effective vaccine for the prevention of RSV. While there is immunoprophylaxis with monoclonal antibodies therapy for RSV the high cost of treatment is not affordable in developing countries.14

In developing countries with weak health systems and lack of laboratory diagnostic tools, the management of childhood illnesses is presumptive and symptom-based and health-care providers rely on the WHO/UNICEF Integrated Management of Childhood Illnesses (IMCI) algorithm. In these guidelines, pneumonia includes history of a fever, cough, or difficulty in breathing in the presence of increased respiratory rate according to age-related symptoms (e.g. fever and coughing, etc) that may also indicate malaria. Children who are brought into these health centers with malaria, with overlapping pneumonia symptoms, are given both antimalarials and antibiotics.31 This dual treatment results in unnecessary overprescription of either or both medicines, which in turn could lead to antimicrobial resistance down the road (see Background paper 6.1 on antibacterial drug resistance).

4. Lessons From Research Into Pharmaceutical Interventions For Pneumonia

4.1 Antibiotics

4.1.1 Treatment for children

There are multiple antibiotics indicated and effective in the treatment of pneumonia. Administration of the most appropriate antibiotic as a first-line medicine may improve the outcome of pneumonia. In order to effectively treat the disease while minimizing antimicrobial resistance and virulence, it is important to know which antibiotics work best for children depending on the severity of the illness. The four types of antibiotics suggested for treatment of pneumonia are cotrimoxazole, amoxycillin, cephalosporins, and macrolides. Current recommendations to treat non-severe pneumonia in children includes oral amoxycillin and for very severe pneumonia ampicillin and gentamicin.23 The WHO recommends amoxicillin provided twice daily for three days (in settings with low HIV prevalence) or five days (in settings with high HIV prevalence) as the most effective antibiotic treatment for childhood pneumonia.4
Update on 2004 Background Paper, BP 6.22 Pneumonia

Figure 6.22.13a: Comparative effectiveness of antibiotics on clinical cures for community-acquired pneumonia in children under 18 years of age

![Comparative effectiveness of antibiotics on clinical cures for community-acquired pneumonia in children under 18 years of age](image)

Results from various randomized controlled studies from the Cochrane Database of Systematic Reviews (see Figure 6.22.13a above, and respective studies indicated in brackets e.g. [1]) show a multitude of available treatments for pneumonia in children. Only three of the 17 antibiotic comparisons proved to be statistically significant difference in its outcome to clinically cure community-acquired pneumonia (CAP) in children; cefpodoxime was more effective than amoxicillin [3] and amoxicillin was more effective than chloramphenicol [4]. The comparison between co-amoxiclavulanic acid and amoxicillin [13] was also statistically different in its outcome; however, the confidence interval range was very large and the sample size of 100 children was small, which cannot be generalizable data for the population of children under five. The rest of the comparisons showed no statistically significant differences in favoring one treatment over the other. The implications for practice based on these studies is that for the treatment of ambulatory patients with CAP, amoxicillin is an alternative to co-trimoxazole [14] with little difference in outcome of clinical cure of CAP of one treatment over the other (OR=1.12, CI 0.61-2.03). There are no apparent differences between azithromycin and erythromycin [6], azithromycin and co-amoxiclavulanic acid [7], or cefpodoxime and co-amoxiclavulanic acid [9]. Co-amoxiclavulanic acid and cefpodoxime may be alternative second-line drugs. For children hospitalized with severe and very severe CAP, penicillin/ampicillin plus gentamycin is superior to chloramphenicol (see Annex 6.22.4 [3]). The head-to-head comparisons of the different antibiotics in these studies indicate that the list of macrolides, cephalosporins, and penicillins are all efficacious in treating severe and non-severe bacterial pneumonia, while some are more favorable than others.
While there are many antimicrobials available for the management of non-severe and severe community-acquired pneumonia (CAP), there is also a need for more studies and higher quality trials with large numbers of patients, for example, to compare amoxycillin with co-amoxyclylvanic acid, macrolides with amoxycillin and amoxycillin with oral cephalosporins. Data from these studies comparing the different types of antibiotics were mainly from least-developed countries and included children with varying severity of illness and geographic locations. Therefore, attempts to isolate specific etiological agents of pneumonia in order to targetly treat the pathogen may not be as cost-effective as empirical treatment. Results from these studies may be more applicable to the management of pneumonia in developing countries, but the comparisons can also help guide antibiotic therapy in industrialized countries.

Furthermore, there is a need for reformulation of existing, recommended antibiotic treatments for children. The WHO ‘Priority life-saving medicines for women and children 2012’ listed two recommended dosages of gentamicin: 40 mg/ml and 20 mg/ml. The 40mg/ml is an adult formulation, adaptable to older children but unsuitable for neonates, and the 20 mg/ml formulation is ideal for neonates and children. However, 20 mg/ml of gentamicin is not currently manufactured; as a result, dilutions of the 40 mg/ml formulation will need to be made until that time when the 20 mg/ml formulation is available. Lastly, the worldwide estimate is that 30% of isolates from those with pneumonia are resistant to macrolides, including erythromycin, azithromycin, and clarithromycin. Similarly, 30% of S. pneumoniae is now multidrug resistant. The continual rise in antibiotic resistance is a major public health concern that requires keen observation of respiratory illness in children to assess proper treatment options.

4.1.2 Treatment for the elderly

Studies on comparative effectiveness of antibiotics in community-acquired pneumonia (CAP) in adults reviewed by the Cochrane Database of Systematic Reviews indicated that S. pneumoniae was the main causative organism, showing 56% of positive cultures. In each of the comparisons across antibiotic groups, a macrolide and a quinolone were compared. Overall, success rates (based on clinical, bacteriological, or radiological examination) were very high, ranging from 87% to 96% (see Figure 6.22.13b below). However, individual study results did not reveal significant differences in efficacy between various antibiotics and antibiotic groups. Given the limited studies reviewed, it is not possible to make strong evidence-based recommendations for the choice of antibiotics to be used for the treatment of CAP in ambulatory adult patients.
Figure 6.22.13b: Comparative effectiveness of antibiotics on success rates for CAP in adults aged 65 years and older

**Comparative effectiveness of antibiotics on success rates for community acquired pneumonia in adult patients**

<table>
<thead>
<tr>
<th>Antibiotic Comparison</th>
<th>Outcome (R: Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin vs. clarithromycin [1]</td>
<td>0.59</td>
</tr>
<tr>
<td>Azithromycin microspheres vs. levofloxacin [2]</td>
<td>2.27</td>
</tr>
<tr>
<td>Azithromycin microspheres vs. clarithromycin [3]</td>
<td>0.98</td>
</tr>
<tr>
<td>Telithromycin vs. clarithromycin [4]</td>
<td>0.85</td>
</tr>
<tr>
<td>Telithromycin vs. levofloxacin [5]</td>
<td></td>
</tr>
</tbody>
</table>

Outcome: Success rates defined as cure or improvement in clinical, bacteriological, or radiological, as assessed at a predefined follow-up visit.

2. D’Ignazio 2005, 363 patients
3. Brielh 2005, 431 patients
5. Kohne 2003, 123 patients

### 4.2 Vaccines

#### 4.2.1 Prevention for children

*Streptococcus pneumoniae* is a transformable bacterial pathogen that has been showing rapid evolution in response to antibiotic therapies. Since the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in 2000 for immunization in children, the incidence of invasive pneumococcal disease (IPD) has declined in both children and adult population. This reduction is driven by the decrease in incidence of IPD caused by vaccine-serotypes (VT-IPD) targeted by the PCV7. Randomized controlled trials conducted in Africa, the USA, the Philippines, and Finland on PCV effectiveness in children provided evidence that the conjugate vaccine was able to prevent pneumococcal infections. In these studies, the tested conjugate vaccines included 7-, 9-, and 11-valent serotypes and not the 10- or 13-valent serotypes. In a study in Gambia conducted by Cutts et. al in 2005, PCV9 (9-valent CRM197 conjugated vaccine) had a vaccine efficacy of 35% in preventing radiological (X-ray) pneumonia caused by *S. pneumoniae* (see Figure 6.22.14 below) and mortality was reduced by 16%.
Children in developing countries may develop pneumococcal diseases caused by a broader range of serotypes of the pneumococcal bacteria than children in industrialized countries. A review of studies done on pneumococcal conjugate vaccines looked at 9-valent PCV and 11-valent PCV (neither of these PCVs have been registered) in Africa and the Philippines to determine the vaccines' efficacy on IPD among children under two years of age. What the studies showed was that PCV9 and PCV11 were effective in preventing X-ray defined pneumonia in children under two, with a pooled vaccine efficacy of 27% (see Figure 6.22.14). For children in industrialized countries, PCV7, PCV10, and PCV13 are readily available and part of the national immunization programs; however, the WHO is now recommending using higher valent conjugate vaccines (higher than PCV7) to cover more serotypes in developing countries.

Pneumococcal conjugate vaccine impact assessment from the WHO and the GAVI Alliance deemed PCV7, PCV10, and PCV13 appropriate for introduction into immunization programs in countries around the world. Serotypes not covered by the existing 7-, 10-, and 13-valent pneumococcal conjugate vaccines may still contribute to pneumonia incidence in children; such a situation requires surveillance for evolving pneumococcal isolates and attention to research newer vaccine serotypes.
4.2.2 Prevention for the elderly

Unlike the conjugate type vaccine recommended for children, the 23-valent pneumococcal polysaccharide vaccine (PPV23) has been utilized internationally in high- and low-income countries to varying extents, but mainly limited to older adults and adults with risk factors for IPD.\textsuperscript{37} Meta-analysis provides evidence supporting the recommendation for PPV to prevent IPD in adults. Figure 6.22.15 shows a selective number of trials designed for adults 65 years and older. Of the seven trials conducted, three showed that the PPV was efficacious in preventing pneumococcal infections in the elderly. Vaccine efficacy (VE) among the three statistically significant trials ranged from 45\% to 70\% efficacy; however, the upper limit of the vaccine’s efficacy is still lower than the desired 80\% to 90\% protection. The available evidence does not demonstrate that PPVs prevent all causes of pneumonia or mortality in adults. The studies that were not randomized-controlled studies may be more susceptible to confounding with smoking status and influenza vaccination status.\textsuperscript{37} Moreover, these results were based on limited studies looking at a specific population group (the elderly) that are often excluded from drug clinical trials (see Chapter 7.3 on Priority Medicines for the Elderly). However, another study done by Maruyuma et al. looking at PPV in nursing home showed that the vaccine prevented pneumococcal pneumonia in nursing home residents. Although the vaccination rate in nursing homes is only 5\%, the possibility of a protective effect for residents is attainable through increased coverage.\textsuperscript{37}

In late 2011, a supplement was issued to the U.S. Food and Drug Administration (FDA) license for expanded use of PCV13 in adults. Thus, the 13-valent conjugate vaccine (PCV13) is now registered to use in adults 50 years and older and not just in children aged 2-59 months as before.\textsuperscript{38} While PCV13 has demonstrated equal or greater immunogenicity than PPV23, an immune response comparable with the establishment of immune memory could only be shown for the PCV13.

In addition to PPV23 and now PCV13 as the recommended vaccines in adults, newer PCVs have been shown to reduce the number of healthy carriers of the pathogen in a community, which is known as “herd immunity” where unvaccinated people are protected from the pathogen. An example of this herd immunity took place in the United States where one year after the introduction of PCVs, the incidence of IPD fell by 69\% among vaccinated children under two years. Incidence of IPD also declined by 32\% in adults aged 20-39 and by 18\% in people 65 years and older, none of whom were vaccinated.\textsuperscript{5}
Figure 6.22.15: Efficacy of PPV in preventing pneumococcal infections in the elderly aged 65 years and older

4.3 Diagnostics

It is important to determine the cause of community acquired pneumonia (CAP) (e.g. bacterial, viral, fungal, or mixed) because of differences in treatment approaches. In children under five, the bacterium *S. pneumoniae*, which is a bacterium, is the most common cause of pneumonia, another cause of the disease is RSV. Although symptoms may differ, they often overlap, which can make it difficult to identify the organism by symptoms alone.

In resource-rich settings where inpatient care can be monitored, health-care providers can request laboratory tests such as bacteriological and/or PCR tests of blood, induced sputum, urine, or chest X-rays. However, health facilities (i.e. hospitals where patients can have co-infections, present diagnostic difficulties in that sputum or blood tests) often detect bacteria or other organisms, but such agents do not necessarily indicate pneumonia. Finding bacteria or viruses in sputum or nasopharyngeal swab does not confirm their etiological potential in causing pneumonia. Polymerase chain reaction (PCR) and latex agglutination are two methods that would ensure a high degree of specificity and sensitivity using DNA sequencing and organism-specific antibodies-antigen for detection. Current tests for identifying the respiratory syncytial virus include (but are not limited to) six different laboratory diagnostic methods (see Table 6.22.16). Most of these tests require utilization of health facilities and serves patients who are admitted to hospitals. Ultimately, the cost of these diagnostic tools present a barrier in resource-poor settings and health care workers must rely on observations of symptoms based clinical IMCI guidelines.
The Pneumonia Etiology Research for Child Health (PERCH) study has looked at diagnosing the microbiological etiology of pneumonia using various specimens to formulate a rational approach to the appropriate types of specimens collected. Of the eight possible specimens (lung aspirates, lower respiratory tract secretions, pleural fluid, upper respiratory tract, blood, urine, postmortem lung tissues, and exhaled breath), lung aspirates and pleural effusion provided high specificity.

Even though there are a variety of preventive medicines and treatments available in the form of pneumococcal vaccines and different types of antibiotics, some children are not benefiting from these interventions because the pneumonia-causing organism may be viral rather than bacterial. There are currently no available rapid point-of-care diagnostics to differentiate between bacterial and viral pneumonia; this is a key gap in monitoring the spread of both bacteria and viruses contributing to pneumococcal disease and in providing proper treatment.

5. Current “Pipeline” of Products That Are to Be Used For Pneumonia

There are several protein vaccine studies currently underway. One such progress in pneumococcal disease research is undertaken by PATH and Intercell AG to launch the first-in-human clinical trial for a “common protein” pneumococcal vaccine candidate. Phase I clinical trials, currently taking place in Germany, will test the safety and immunogenicity of IC47 recombinant subunit vaccine consisting of three conserved surface proteins from the pneumococcus bacteria. Vaccines containing proteins common to all pneumococcus serotypes are promising because they could provide broad protection to children worldwide. Another study looking at innovative protein-plus-conjugate vaccines that could lead to broad coverage across numerous pneumococcal serotypes is currently in Phase II in Gambia with collaborators such as GSK, PATH, the Medical Research Council in Gambia, and the London School of Hygiene and Tropical Medicine.

The Pneumococcal vaccines Accelerated Development and Introduction Plan (PneumoADIP) is another collaborating centre currently conducting various research and surveillance
studies looking at novel diagnostic tools for pneumonia. There is the Binax study that evaluates the utility of Binax Now®, which is an antigen test for *S. pneumoniae* as an adjunct to culture for the diagnosis of pneumococcal meningitis in a variety of settings.

In addition to radiography and laboratory culture specimen testing, more accurate, robust, and straightforward techniques to count the breathing rate of sick children can help improve specificity for pneumonia. One such example is pulse oximetry, which is a non-invasive method allowing the monitoring of the oxygen saturation of a patient’s hemoglobin.⁴,¹⁰ The pulse oximeter sensor is placed on a thin part of the body, usually a fingertip or earlobe, or in the case of an infant, across the foot. The device monitors blood oxygen saturation levels and pulse rate. In emergency situations, the simplicity of this medical device can help to detect the severity of a child’s respiratory condition in order to determine the severity of wheezing in suspected pneumonia. Although the utility of pulse oximetry may not be for diagnosing pneumonia, it can help to monitor a patient’s intake of oxygen that may be indicative of severe pneumonia. This has the potential to improve the diagnosis and appropriate treatment of pneumonia.

Clinical trials looking at RSV prevention in children included studies for humanized monoclonal antibody produced by recombinant DNA technology, such as Motavizumab (MEDI-524), MEDI-534, and palivizumab (see Table 6.22.17). These biologics have been investigated by MedImmune, Abbott Laboratories, and other major pharmaceuticals as prophylaxis for the prevention of RSV infection in high-risk infants in hopes of decreasing the need for hospitalization. There has been a study looking at a live, attenuated RSV vaccine candidate, called MEDI-559, which completed in August 2012. These studies have been completed (from 2008 to the latest in 2012), but no study results have been published as to date.²¹

**Table 6.22.17: Clinical trials on pneumonia in children and the elderly as of 2013**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Topic</th>
<th>Group</th>
<th>No. of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em></td>
<td>Safety and immunogenicity of pneumoccal vaccines.</td>
<td>Elderly</td>
<td>19</td>
</tr>
<tr>
<td>RSV</td>
<td>Evaluation of prophylaxis treatments and vaccines: MEDI-524, MEDI-534, palivizumab, MEDI-559.</td>
<td>Children</td>
<td>74</td>
</tr>
</tbody>
</table>

Source: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
5.1 Research and development funding

Funding for research, prevention, and treatment for pneumonia is by a few large organizations: the Bill and Melinda Gates Foundation for investing in the creation and delivery of diagnostics and treatment for pneumonia; Program for Appropriate Technology in Health (PATH) for the research and development of new serotypes in pneumococcal conjugate vaccines; GAVI Alliance for the introduction of new vaccines into developing nations’ immunization programs; and AMC for Vaccines for the procurement of pneumococcal vaccines (see Table 6.22.18 below).

Table 6.22.18: Funding from donors for prevention, treatment, and/or research for pneumonia in 2011

<table>
<thead>
<tr>
<th>Funder</th>
<th>Intervention</th>
<th>Funding amount US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gates Foundation</td>
<td>Grants for Global Health program area in pneumonia</td>
<td>88.9 million</td>
</tr>
<tr>
<td>GAVI Alliance</td>
<td>To UNICEF for purchase of pneumococcal vaccines</td>
<td>380.7 million</td>
</tr>
<tr>
<td>PATH</td>
<td>Research for development of new pneumococcal vaccines</td>
<td>96.5 million</td>
</tr>
<tr>
<td>AMC for Vaccines</td>
<td>Procurement of pneumococcal vaccines from manufacturers</td>
<td>270.0 million</td>
</tr>
<tr>
<td></td>
<td>Purchase of pneumococcal vaccines (Funds for GAVI to fund UNICEF’s purchase)</td>
<td>168.6 million</td>
</tr>
</tbody>
</table>


According to the Global Action Plan for Prevention and Control of Pneumonia (GAPP), commodities like medicines, injection materials, and diagnostics for pneumonia management account for only 0.4% of total costs of 68 countries that makes up about 98% of global pneumonia mortalities in children under five. Bacterial pneumonia is considered a ‘second tier’ disease in the realm of global investment into research and development (R&D) compared to the ‘top tier’ diseases like HIV/AIDS, malaria, and tuberculosis. Nonetheless, bacterial pneumonia has seen an increase in funding (up US$ 10.7 million) from 2010 to 2011. The total funding for neglected disease R&D in 2011 was US$ 3.045 million, of which bacterial pneumonia received about 13.1% of global neglected disease R&D funding.

The Advance Market Commitments for Vaccines (AMC) scheme ensures that partners like GAVI Alliance, contracts with major manufacturers like Pfizer and Glaxo-Smith Kline to allocate AMC funds in the procurement of pneumococcal vaccines at a set amount of supply of doses and price over an agreed upon period of time. Both suppliers have agreed to supply 18 million doses annually from 2014 for a period of 10 years up to a maximum of 180 million doses, with each dose priced at US$ 3.50, and an increase of supply should there be a demand. The price of US$ 3.50 is specifically priced for developing countries while the
currently existing pneumococcal vaccine is more than US$ 70 per dose in industrialized countries.27

Globally, funding for pneumonia research and development, specifically for bacterial *S. pneumoniae* is approximately US$ 200 million. Over 90% of this amount went towards vaccines research and development while diagnostics only received 5% of the total funding (see Table 6.22.19). Finally, there have been three projects commissioned by the European Commission, under the Seventh Framework Programme (FP7), towards methods for identification of various organisms contributing to pneumonia (see Table 6.22.20).44 The aims of these projects are to gain understanding of the host-pathogen interaction and to fill the gap between genomic data and development of novel vaccines and diagnostic tools.

Table 6.22.19: Funding for pneumonia R&D (thousand US$), by pathogen, 2008-2011

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vaccines</th>
<th>Diagnostics</th>
<th>Unpsecified</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial pneumonia (Str. pneumoniae)</td>
<td>185 715 751</td>
<td>10 116 222</td>
<td>4 180 877</td>
<td>200 011 851</td>
</tr>
</tbody>
</table>

Source: G-FINDER Global Funding of Innovation for Neglected Diseases. 2008-2011 funding data has been adjusted for inflation and is reported in 2007 US dollars (US$).

http://g-finderpolicycures.org/gfinder_report/search.jsp

Table 6.22.20: European Commission projects for vaccines and diagnostic research and development

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Project Title</th>
<th>Start Date</th>
<th>EC contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>MICROBEARRAY</td>
<td>Genome scale analysis of the immune response against pathogenic micro-organisms leading to diagnostic and vaccine candidates and development of an integrated micro array platform for clinical use.</td>
<td>21 June 2004</td>
<td>€1 401 002</td>
</tr>
<tr>
<td>OMMVAC</td>
<td>Novel prevention and treatment possibilities for otitis media through the comprehensive identification of antigenic proteins.</td>
<td>1 October 2006</td>
<td>€2 320 000</td>
</tr>
<tr>
<td>SAVINMUCOPATH</td>
<td>Novel therapeutic and prophylactic strategies to control mucosal infections by South American bacterial strains.</td>
<td>1 October 2006</td>
<td>€1 699 908</td>
</tr>
</tbody>
</table>

6. Opportunities for Research and Challenges

To date, only live attenuated vaccine candidates have been tested in young infants—the group most at risk for severe RSV disease. A recombinant RSV vaccine with multiple mutations can be well tolerated and can likely be protective in this age group. Clinical testing of the vaccine candidates was conducted by a consortium of investigators as part of a cooperative agreement between industry (Wyeth Vaccines Research) and the United States government laboratories (National Institute of Allergy and Infectious Diseases and the National Institute of Health). New approaches to the genetic manipulation of vaccine candidates can now be considered, including the use of gene rearrangement or genetic recombination of several candidate viral genes.

Academic researchers have been hesitant to pursue RSV vaccine development and testing. Respiratory syncytial virus vaccine development by manufacturers has been affected by the financial risk involved, the high level of investment required, and the low return the investment provides. Therefore, clinical development of RSV vaccine candidates remains extremely limited.

Rapid diagnostic tests (RDTs) currently exist for malaria, which allow for a definitive diagnosis to be made even in health settings lacking any laboratory facility. While RDTs help to differentiate between malaria and pneumonia, it does not differentiate between viral and bacterial infections in the case of pneumonia. The availability of a RDT for malaria to target the use of artemisinin based combination therapy (ACT) should also call for a RDT for pneumonia to target the use of antibiotics.

The Advanced Market Commitment (AMC) has ensured the rollout of the pneumococcal vaccine in 2006 with US$ 1.5 billion funding from Italy, Norway, the United Kingdom, Canada, Russia, and the Bill & Melinda Gates Foundation. The commitment established a set price for any vaccine, guaranteeing a future market for vaccine producers and lowering the risk of product development. For developing countries, AMC allows organizations like GAVI Alliance to subsidize the price of vaccines, with each dose priced at US$ 3.50 (subsidy can lower price to US$ 0.15 per dose). This effective approach to ensuring an advanced market commitment for conjugate vaccines could be tried for a product other than a vaccine; a promising area would be towards the development for rapid point-of-care diagnostic test to differentiate between viral and bacterial pneumonia. A possible challenge for such an invention would be an issue of effective usage of the technology. For example, results from malaria studies conducted in Tanzania showed that although point-of-care tests for malaria are more accurate than diagnosis using microscopy, clinicians often ignored both negative results and those patients were still being treated with antimalarial drugs.

Pneumonia often coincides with other infections, especially in preterm infants as well as in the elderly. If pneumonia is combined with hypoxaemia, as happens in 13% of cases, children are five time more likely to die than those with only pneumonia. Oxygen concentration should therefore be monitored and oxygen therapy should be made available. In addition to radiography and laboratory culture specimen testing, pulse oximetry can help improve specificity for pneumonia.

Even with the availability of novel pneumococcal vaccines, the decision to introduce at the country level is only the first step; storage, transport, education efforts, and health care
worker training must also be strong enough to successfully manage the increased human resource and infrastructure burdens of new vaccine introduction. Without sufficient and operational system capacity, health systems face a hurdle in supporting the introduction of PCVs into countries’ national immunization programs.

7. Pharmaceutical Gaps

Despite existing Hib and pneumococcal conjugate vaccines, disparities in access to these vaccines exist within countries, which reduce vaccines’ impact as cost-effective interventions against childhood pneumonia and impede efforts to close the ‘rich-poor’ gap in vaccine introduction. The ‘rich-poor’ gap still exists in national vaccination programs among countries with varying income levels (see Figure 6.22.21). Introducing a vaccine into the national program does not necessarily translate to equitable and high coverage even within countries, which further reduces the impact of vaccines. While there are currently three types of pneumococcal vaccines for children under five, none of the PCVs are available in a combined form with other vaccines within the same routine immunization schedule. The multiple shots vaccination to a child under five or to a toddler within multiple visits may create additional discomfort; this could create potential problems where mothers are less likely to get their child vaccinated due to skepticism of vaccine effectiveness and side effects.

Figure 6.22.21 Progress in introducing PCV globally, particularly in the poorest countries, but a ‘rich-poor’ gap remains

Source: UNICEF. Pneumonia and diarrhoea: Tackling the deadliest diseases for the world’s poorest children, 2012
Furthermore, new pneumococcal serotypes are continuously shifting. There is the possibility that serotypes not covered by PCV7, PCV10, or PCV13 could be replaced by new serotypes not in current vaccines, as already observed in some countries in the EU.\(^8\) Therefore, there is a need for constant monitoring of possible serotype replacement to guide research and development for next generation vaccines. Such research and development requires constant funding throughout multiple clinical trials in order to get the vaccine on the market and implemented into national immunization programs. There is a need for additional conjugate vaccines, as well as vaccines made of protein antigens that are conserved across pneumococcal serotypes so that an immune response can be generated against all pneumococcal pathogens regardless of their serotype. Research is needed towards the discovery of a pneumococcal vaccine which is immunogenic in all young children as well as the elderly. An ideal vaccine would also protect against pneumococci regardless of their capsular types. Another pneumonia-causing organism is the respiratory syncytial virus (RSV), which is the leading cause of bronchiolitis and pneumonia in infants and the elderly worldwide. Despite that, there is no licensed RSV vaccine and only limited therapeutics exist.

Further pharmaceutical gaps lie in the need for rapid diagnostic tools for pneumonia. While X-rays and cultures laboratory tests can confirm the presence of the organism, those diagnostic tools can be costly and time consuming, especially in lower-income and least-developed countries. These tests may have low specificity. Moreover, cases of suspected pneumonia cannot be categorized as a bacterial infection or a viral infection without performing the necessary lab cultures. The burden of lower respiratory tract infections caused by \textit{S. pneumoniae}, Hib, or RSV is difficult to determine because current techniques to establish bacterial etiology lack sensitivity and specificity. Therefore, there is a need for rapid diagnostic tools to differentiate between a viral or bacterial infection. A quick and accurate point of care tool could aid health-care providers in providing children with proper treatment in a timely manner and help decide whether or not antibiotics are needed. More precise diagnosis would also help reduce antimicrobial resistance through rational and judicial use of antibiotics in treating pneumonia.

Despite good access to antibiotics, \textit{S. pneumoniae} is still a major cause of illness and mortality in EU and EEA/EFTA countries.\(^8\) The implication of this is associated with the increasing trend in antimicrobial resistance (AMR); thus, development of new antibiotics is imperative to addressing AMR and the decrease in effective antibiotics for pneumonia (See Background Paper Chapter 6.1 on antimicrobial resistance). The goal to reduce incidence and increase prevention lies with access to affordable vaccines and treatments. Meanwhile, there is also a need to balance access and affordability with research and development of new vaccines and antibiotics in order to stay on track with the disease’s evolving pathogenic strains and increased susceptibility to drug resistance.

### 7.1 Research priorities

#### University and research institutions

- Institutions in high-income countries should support the collaboration of public-private partnerships to share knowledge and skills and enable development of low-cost technologies benefiting the health of specific, at-risk population groups.
- More research should be done on the elderly population and PPV/PCV efficacy trials involving large number of participants from this age group.
Ministries of health

- Methods to implement or strengthen monitoring and evaluation of interventions.
- Evaluation of approaches to implementation or strengthening of immunization programmes in countries to ensure all child and elderly patients are vaccinated with the WHO recommendations for vaccinations and integrate the latest pneumococcal conjugate vaccine in all national immunization programme schedule.
- Develop robust effective prompt methods to strengthen regulation in pricing, sustainable procurement, and quality of pneumococcal vaccines and antibiotic supplies.
- Research into barriers affecting PPV vaccination in the elderly in nursing homes (see Chapter 7.3 on Priority Medicines for the Elderly).

Health care pharmaceutical technology companies and small and medium enterprises

- Develop low-cost pneumococcal vaccines with room for more production should there be an increase in market demand.
- Conduct more research into vaccine development to discover new targets for 1) novel serotypes in pneumococcal vaccines, and 2) antiviral drugs for viral pneumonia like RSV.
- Research and develop a high specificity rapid diagnostic test at point-of-care for bacterial versus viral pneumonia organisms.
- Reformulation of currently recommended antibiotics for treatment of pneumonia for better metabolic uptake in children and dosage of injectable products for neonates.

8. Conclusion

Over one million children will die before their fifth birthday, nearly all of which are preventable. The attainment of the Millenium Development Goal 4 (MDG4) is possible only if life-saving newborn and child health interventions for pneumonia are rapidly scaled up in high-burden regions and countries, as well as in special population groups in the next few years. Prevention by means of vaccination would be most crucial for reducing pneumonia mortality in children under five, while effective (uptake of) antibiotic therapy for the elderly would serve to decrease mortality due to pneumonia in Europe. Community-based management of severe disease could be an important complementary strategy to reduce pneumonia mortality in children under five as well as in the elderly. Pneumonia has a great burden of morbidity and mortality in developing countries, which results in economic and social pressures on families and the country as a whole. Therefore, pneumonia prevention is not only about saving the lives of children, but it is also about preventing illness, hospitalization, and related economic costs. An integrated care management system has proven to be effective in reducing pneumonia mortality by 17% with the available vaccines against Hib and S. pneumoniae; in addition to breastfeeding promotion and zinc supplementation, overall childhood mortality could be further reduced.17
The high global burden of pneumonia warrants further investigation in technology innovation in the field of rapid diagnostic tests and in novel vaccines for viral pneumonia. Improved rapid diagnostics at point-of-care along with effective antibiotic treatments would aid in the reduction of pneumonia mortality, while wide-scale implementation of pneumococcal vaccines would help prevent incidences of pneumonia worldwide. Moving forward, research institutions, pharmaceuticals, and small and medium enterprises must work alongside government and funders to create initiatives for the development of novel medical devices and biologics. The constant and unpredictable nature of pneumococcal pathogens can outpace technological and drug development, thus it is crucial for researchers and innovators to continue to make progress in research and development of pharmaceuticals and non-pharmaceuticals interventions.

References


Recommendations for management of common childhood conditions: Newborn conditions, dysentery, pneumonia, oxygen use and delivery, common causes of fever, severe acute malnutrition and supportive care. WHO, 2012.


Annexes


Annex 6.22.3: Mortality for all ages due to pneumococcal disease by European regions and the world, 2010.

Annex 6.22.4: Comparative effectiveness of antibiotics on community acquired pneumonia death in children under 18 years of age

Annex 6.22.5: Pneumococcal conjugate vaccine in preventing vaccine-serotypes invasive pneumococcal disease in children <24 months

Annex 6.22.6: Pneumococcal conjugate vaccine in preventing all-serotypes invasive pneumococcal disease in children <24 months

Annex 6.22.7: Pneumococcal conjugate vaccine in preventing clinical pneumonia in children <24 months

Annex 6.22.8: Comparative effectiveness of antibiotics on community-acquired pneumonia deaths in children under 18 years of age

Annex 6.22.9: Global mortality for all causes of death and pneumonia by age groups, 2010.

Annex 6.22.10: Death rates caused by pneumonia in the world by age group, 2010

Annex 6.22.11: DALY rates caused by pneumonia in the world by age group, 2010

Annex 6.22.12: Global mortality rates by age group and gender for pneumococcal pneumonia, 2010

Annex 6.22.13: Death rates caused by pneumonia by gender, age group, and region, 2010

Annex 6.22.14: Death rates caused by pneumonia by gender, age group, and European region, 2010

Annex 6.22.15: DALY rates caused by pneumonia by gender, age group, and region, 2010

Annex 6.22.16: DALY rates caused by pneumonia by gender, age group, and European region, 2010

Annex 6.22.17: Death rates by pneumococcal pneumonia, Hib, and RSV, and region, 2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Global mortality for all causes of death</th>
<th>Global mortality due to pneumonia</th>
<th>Deaths under five for all causes</th>
<th>Deaths under five due to pneumonia</th>
<th>Percentage total pneumonia deaths for children under five of the total global mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>93 022 392</td>
<td>4 000 312</td>
<td>11 559 494</td>
<td>1 348 153</td>
<td>33.7</td>
</tr>
<tr>
<td>2005</td>
<td>103 326 074</td>
<td>3 057 075</td>
<td>7 842 254</td>
<td>705 716</td>
<td>23.1</td>
</tr>
<tr>
<td>2010</td>
<td>105 539 348</td>
<td>2 921 420</td>
<td>6 841 199</td>
<td>585 125</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Source: Institute of Health Metrics and Evaluation (IHME).


<table>
<thead>
<tr>
<th>Region</th>
<th>Under five deaths due to pneumonia</th>
<th>Percentage total pneumonia deaths for children under five of the total global mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>585 125</td>
<td>-</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>252 970</td>
<td>43.2</td>
</tr>
<tr>
<td>South Asia</td>
<td>220 287</td>
<td>37.6</td>
</tr>
<tr>
<td>Europe</td>
<td>3 154</td>
<td>0.5</td>
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</table>

Source: Institute of Health Metrics and Evaluation (IHME).
Annex 6.22.3: Mortality for all ages due to pneumococcal disease by European regions and the world, 2010.

<table>
<thead>
<tr>
<th>Region</th>
<th>Disease</th>
<th>Moralties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>Pneumococcal pneumonia</td>
<td>827 316</td>
</tr>
<tr>
<td></td>
<td>Hib</td>
<td>379 857</td>
</tr>
<tr>
<td></td>
<td>RSV</td>
<td>253 537</td>
</tr>
<tr>
<td>Central Europe</td>
<td>Pneumococcal pneumonia</td>
<td>10 659</td>
</tr>
<tr>
<td></td>
<td>Hib</td>
<td>3 153</td>
</tr>
<tr>
<td></td>
<td>RSV</td>
<td>647</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>Pneumococcal pneumonia</td>
<td>13 755</td>
</tr>
<tr>
<td></td>
<td>Hib</td>
<td>6 454</td>
</tr>
<tr>
<td></td>
<td>RSV</td>
<td>969</td>
</tr>
<tr>
<td>Western Europe</td>
<td>Pneumococcal pneumonia</td>
<td>66 741</td>
</tr>
<tr>
<td></td>
<td>Hib</td>
<td>9,442</td>
</tr>
<tr>
<td></td>
<td>RSV</td>
<td>1,584</td>
</tr>
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</table>

Source: Institute of Health Metrics and Evaluation (IHME).
Annex 6.22.4: Comparative effectiveness of antibiotics on community acquired pneumonia death in children under 18 years of age
Annex 6.22.5: Pneumococcal conjugate vaccine in preventing vaccine-serotypes invasive pneumococcal disease in children <24 months

![Graph showing the comparison of vaccine efficacy in preventing invasive pneumococcal disease in children <24 months.](chart)

Legend:
- PCV-7 vs. Control
- PCV-7 vs. PCV-13
- Polio-7 vs. Control
- Polio-7 vs. Polio-13
- PCV-11 vs. Control
- PCV-11 vs. PCV-13
- PCV-11 vs. MenB vaccine
- PCV-11 vs. MenB + PCV-13

Outcome: Vaccine-serotypes invasive pneumococcal disease (VT-IPD).
Risk Ratio: Relative Risk less than 1 favors the intervention (less VT-IPD).

<table>
<thead>
<tr>
<th>Risk Ratio</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>[1] Broch 2000</td>
</tr>
<tr>
<td>0.17</td>
<td>[3] Escola 2003</td>
</tr>
<tr>
<td>0.17</td>
<td>[4] Huguen 2003</td>
</tr>
<tr>
<td>0.17</td>
<td>[5] Debber 2003</td>
</tr>
<tr>
<td>0.24</td>
<td>[6] Cutts 2006</td>
</tr>
<tr>
<td>0.20</td>
<td>[7] Lucero 2009</td>
</tr>
</tbody>
</table>

PCV-7 serotypes include 1, 4, 6A, 9V, 14, 18C, 19F, 23F.
PCV-13 serotypes include 1, 3, 5, 6A, 7F, 10A, 11A, 12F, 15B, 19A, 20A, 22F, 33F, 49, 51H.

Annex 6.22.6: Pneumococcal conjugate vaccine in preventing all-serotypes invasive pneumococcal disease in children <24 months

Pneumococcal Conjugate Vaccine in preventing all-serotypes invasive pneumococcal disease in children <24 months

- POV-7 vs. Control (meningococci type C CRM-197 conjugate vaccine)
- POV-7 vs. Control (Haemophilus influenzae type b vaccine)
- POV-7 vs. Control (Neisseria meningitidis group C vaccine)
- POV-9 vs. Placebo
- POV-11 vs. Placebo

Relative Risk

- Outcome: all-serotypes invasive pneumococcal disease
- Risk Ratio: Relative Risk less than 1 favors the intervention (less all-serotypes IPD)
- All serotypes include: 1, 3, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F.

References:
[8] Lucero 2009

6.22-45
Annex 6.22.7: Pneumococcal conjugate vaccine in preventing clinical pneumonia in children <24 months

Outcome: Clinical pneumonia
Risk Ratio or Relative Risk less than 1 favors the intervention (less X-ray defined pneumonia)
Clinical pneumonia: an infection that can occur in a child's lung
Annex 6.22.8: Comparative effectiveness of antibiotics on community-acquired pneumonia deaths in children under 18 years of age
Annex 6.22.9: Global mortality for all causes of death and pneumonia by age groups, 2010.

<table>
<thead>
<tr>
<th></th>
<th>All age groups</th>
<th>Under 5</th>
<th>5-9 years</th>
<th>Adolescents (10-19)</th>
<th>Adults (20-64)</th>
<th>65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes of mortality</td>
<td>52 769 679</td>
<td>13 682 307</td>
<td>453 051</td>
<td>1 075 214</td>
<td>17 750 910</td>
<td>26 649 295</td>
</tr>
<tr>
<td>Mortalities due to pneumonia</td>
<td>2 921 422</td>
<td>585 125</td>
<td>14 423</td>
<td>17 240</td>
<td>237 276</td>
<td>606 646</td>
</tr>
</tbody>
</table>

Source: Institute of Health Metrics and Evaluation (IHME).

Annex 6.22.10: Death rates caused by pneumonia in the world by age group, 2010

Source: Institute of Health Metrics and Evaluation 2010
Annex 6.22.11: DALY rates caused by pneumonia in the world by age group, 2010

Source: Institute of Health Metrics and Evaluation (IHME).
Annex 6.22.12: Global mortality rates by age group and gender for pneumococcal pneumonia, 2010

Source: Institute of Health Metrics and Evaluation 2010
Annex 6.22.13: Death rates caused by pneumonia by gender, age group, and region, 2010

Source: Institute of Health Metrics and Evaluation 2010
Annex 6.22.14: Death rates caused by pneumonia by gender, age group, and European region, 2010

Source: Institute of Health Metrics and Evaluation 2010
Annex 6.22.15: DALY rates caused by pneumonia by gender, age group, and region, 2010

Source: Institute of Health Metrics and Evaluation 2010
Annex 6.22.16: DALY rates caused by pneumonia by gender, age group, and European region, 2010

Source: Institute of Health Metrics and Evaluation 2010
Annex 6.22.17: Death rates by pneumococcal pneumonia, Hib, and RSV, and region, 2010

Source: Institute of Health Metrics and Evaluation 2010
Background Paper 6.23
Neonatal Conditions

By Clara Setiawan, MPH, BSc
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### Glossary

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<th>Terms and acronyms</th>
<th>Definitions</th>
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</thead>
<tbody>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>COX</td>
<td>Cyclo-oxygenase</td>
</tr>
<tr>
<td>DALYs</td>
<td>Disability-adjusted life years</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin</td>
</tr>
<tr>
<td>LOC</td>
<td>Lab-on-a-chip</td>
</tr>
<tr>
<td>MDG</td>
<td>Millennium Development Goal</td>
</tr>
<tr>
<td>MNCH</td>
<td>Maternal, newborn, and child health</td>
</tr>
<tr>
<td>NMR</td>
<td>Neonatal mortality rate (per 1 000 livebirths)</td>
</tr>
<tr>
<td>PA</td>
<td>Progestational agents</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>pPROM</td>
<td>Premature rupture of membranes</td>
</tr>
<tr>
<td>RDS</td>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually transmitted infection</td>
</tr>
<tr>
<td>Tx</td>
<td>Treatment</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>YLD</td>
<td>Years lived with disability</td>
</tr>
<tr>
<td>YLL</td>
<td>Years of life lost</td>
</tr>
</tbody>
</table>
Executive Summary

The neonatal period is only the first 28 days of life and yet accounts for 40% of all deaths in children under-five. Globally, neonatal conditions accounted for 3,072,000 deaths in 2010 alone. Although the number of neonatal deaths has decreased since 1990, all regions have seen slower reductions in neonatal mortality compared to under-five mortality resulting in an increased share of neonatal deaths among total under-five deaths. In order to achieve the Millennium Development Goal 4 in reducing the under-five mortality rate by two-thirds by 2015, neonatal conditions need to be addressed immediately.

Among many neonatal conditions; 1) premature birth, 2) neonatal infections, and 3) birth asphyxia, were identified as major contributors to the global burden of disease. Due to the complex etiology of these conditions, preventive methods, diagnostic tools, and treatments remain limited. Many of the current preventive approaches focus on maternal health prior to the newborn’s arrival such as maternal immunization and ensuring a healthy pregnancy. Several treatments exist for neonatal conditions that may reduce the risk of maternal and neonatal mortality. However, these treatments are still not ideal in formulation, packaging, and/or accessibility. For example, several tocolytics are available to inhibit preterm labor, but are often accompanied by adverse side effects to both the mother and newborn. The current formulation and packaging for the recommended antibiotics to treat neonatal sepsis are not readily available and require properly trained care providers to administer them. Surfactant preparations are effective in treatment of newborns with respiratory distress syndrome, but are expensive to produce and are limited. Furthermore, lack of rapid diagnostics often leads to non-judicial use of antibiotics that may contribute to the rising concern for antimicrobial resistance. These are only several challenges that currently exist in addressing neonatal conditions.

Despite the large global burden from neonatal conditions, investment in research funding for neonatal survival is extremely low. It is estimated that only around US$ 20 million per year is invested into research for neonatal survival. A recent global analysis suggests that newborn survival will remain vulnerable on the global agenda without adequate funding and without high-level engagement of policy-makers. For this reason it becomes imperative that more funding and long-term support from the European Commission be allocated towards research and development addressing neonatal conditions.
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). The topic and background paper on neonatal conditions was not included in the 2004 report.

As a result of the 2008 updated Global Burden of Disease list released by the WHO and the 2010 Global Burden of Disease study published by the Lancet, neonatal conditions are now included in this report. Related to the rising need for attention to neonatal conditions, other important reports such as *Born Too Soon: The Global Action Report on Preterm Birth* was published in 2012 in support of the Global Strategy for Women’s and Children’s Health and the efforts of the Every Woman Every Child campaign, led by the UN Secretary-General, Ban Ki-moon.

In this paper, you will find the background on neonatal conditions including its disease burden, both globally and in Europe; the current control strategies via vaccinations, preventative approaches, and treatments; current research and development activities including the lessons learned from past research and the current pipeline. Most importantly, this paper will expose the pharmaceutical gaps that needs to be addressed and highlight opportunistic areas for research and development. This background paper will serve as the basis for the chapter to be found in the updated 2013 Priority Medicines report.

1.1 Background

Neonatal conditions are defined as conditions occurring during the first month after birth (0-28 days). Among many neonatal conditions; 1) premature birth, 2) neonatal infections, and 3) birth asphyxia, were identified as major contributors to the global burden of disease and will be the conditions focused on in this chapter.
Premature Birth

Premature birth is defined by the WHO as all births before 37 completed weeks of gestation or fewer than 259 days since the first day of a woman’s last menstrual period. Causes of premature births are typically classified into two subtypes: 1) spontaneous preterm birth (spontaneous onset of labor or following pre-labor premature rupture of membranes (pPROM)) and 2) provider-initiated preterm birth (induction of labor or elective caesarian birth for maternal or fetal indications or other non-medical reasons). Risk factors for spontaneous preterm birth have been identified such as age, multiple pregnancy, infection, maternal medical conditions and psychological health, nutritional, lifestyle, and genetic factors.

Complications of premature birth are the single largest contributor to neonatal mortality. In addition to mortality outcomes, the implications of being born too soon extend beyond the neonatal period. Preterm babies lack the necessary physical development which often requires special care and they face greater risks of serious health problems in the future. Survivors of premature birth may suffer lifelong effects such as impaired neurodevelopmental functioning, higher risk of non-communicable disease, and physical impairments in visual, hearing, lung function, and cardiovascular function.
1.1.2 Neonatal Infections

The term “neonatal infections” in this background paper includes all infections except for diarrhoeal diseases and neonatal tetanus. Among the infections, sepsis and pneumonia account for the majority of the burden. Neonatal pneumonia will be discussed in detail in Background Paper 6.22, while neonatal sepsis will be the focus of neonatal infections in this chapter.

Neonatal sepsis is a blood infection that can be caused by a number of different bacteria, including *Escherichia coli* (E. coli), *Listeria*, and certain strains of *Streptococcus*. *Streptococcus agalactiae* (Group B *Streptococcus*, GBS) is the most common cause of neonatal sepsis in many countries, though lower rates are reported from many low-income countries particularly in South Asia.

Early-onset neonatal sepsis is seen within the first seven days of life and most often appears within 24 hours of birth where the baby is infected from the mother before or during the delivery. Preterm delivery, rupture of membranes longer than 24 hours before birth, infection of the placental tissue and amniotic fluid (chorioamnionitis), and group B *Streptococcus* infection during pregnancy increases an infant’s risk of early-onset sepsis. Late-onset neonatal sepsis occurs after day eight of life and is acquired after delivery. Having a catheter in a blood vessel and/or staying in the hospital for an extended period of time increases an infant’s risk of sepsis after delivery.

The chances of survival are reduced for newborns with a serious infection regardless of whether they are hospitalized or in the community. Therefore, the complications of neonatal sepsis may be death or lifelong disability. Identifying and diagnosing neonatal sepsis is difficult because sick newborns often present with non-specific signs and symptoms that vary from changes in body temperature, breathing problems, diarrhea, low blood sugar, reduced movements and sucking, seizures, slow heart rate, swollen belly area, vomiting, and jaundice.

1.1.3 Birth Asphyxia

One of the most common birth complications is RDS where babies struggle to breathe because their immature lungs do not produce enough surfactant, a protein that keeps small air sacs in the lungs from collapsing. Birth asphyxia, defined as the failure to establish breathing or perfusion at birth, accounts for an estimated 900 000 deaths per year. Complications of low oxygen intake include damage to the brain tissues that can cause seizures and other neurological problems. The clinical presentation is not specific to birth asphyxia and the preferred term is “neonatal encephalopathy”, where the precise cause is not implied. Possible antecedents for neonatal encephalopathy include infection, cerebral infarction, intracranial haemorrhage, congenital brain malformations, inborn errors of metabolism, and genetic syndromes. However, the most likely antecedent is hypoxia-ischaemia (19 to 52%) that arise from birth asphyxia. Neonatal encephalopathy is clinically assessed into three Sarnat staging where stage 1 may likely have unaffected outcome, stage 2 where 25% develop cerebral palsy, and stage 3 often results in disability or death.
1.2 Neonatal Conditions: Burden of Disease

The neonatal period is only 28 days and yet accounts for 40% of all deaths in children younger than five years.\(^4\) The average daily mortality rate during the neonatal period is almost 30-times higher than during the post-natal period.\(^6\) Furthermore, there is still variation within the neonatal period such that mortality is very high in the first 24 hours after birth (25 to 45% of all neonatal deaths) while three quarters of neonatal deaths happen in the first week after birth.\(^6,12\)

Neonatal conditions exert a heavy burden on families, society, and the health system. With the most potential for years lived with disability (YLD) and years of life lost (YLL), neonatal conditions are significant DALYs contributors.

1.3 Global Burden of Disease

Over past decades, neonatal mortality along with under-five mortality has been slowly decreasing. Globally, the number of neonatal deaths has decreased from 4,362,000 in 1990 to 2,955,000 in 2011.\(^{13}\) However, all regions have seen slower reductions in neonatal mortality compared to under-five mortality resulting in an increased share of neonatal deaths among the under-five deaths. Neonatal deaths accounted for 36% of the under-five deaths in 1990 and rose to 40% in 2010.\(^4\) This trend is expected to continue.\(^{13}\)

The Millennium Development Goal (MDG) 4 calls for a reduction in the under-five mortality rate by two-thirds between 1990 and 2015.\(^3\) Even with the visible progress, the rate of decline is insufficient to reach the set targets, particularly in sub-Saharan Africa and South Asia.\(^3\) Child survival programs have primarily focused on causes of death after the neonatal period such as pneumonia, diarrhea, malaria, and vaccine-preventable diseases.\(^{14}\) The lack of attention to neonatal conditions such as preterm birth, neonatal sepsis, and birth asphyxia, has resulted in it accounting for an increasing proportion of under-five deaths.\(^{15}\) Unless actions are taken to reduce neonatal deaths, neonatal conditions will remain a barrier to progress on MDG 4.

An estimated 15 million babies in the world were born preterm in 2010, of which over one million children die each year due to complications of preterm birth.\(^3\) For the newborns that survive this often means a lifetime of significant disability.\(^1\) There is a dramatic survival gap for premature babies depending on where they are born. A 10:90 survival gap exists where over 90% of preterm babies born in low-income countries die within the first few days of life while less than 10% of babies of this gestation die in high-income settings.\(^3\) Furthermore, over 60% of preterm births occur in Africa and South Asia and of the 11 countries with preterm birth rates of over 15%, all but two are in sub-Saharan Africa (Table 6.23.1).\(^3\) The proportion of deaths due to prematurity drops with increasing neonatal mortality rate (NMR); however, this pattern is due to the large number of deaths from infection in high NMR settings.\(^{12}\)
Female neonates have a well-described biological survival advantage in the neonatal period. This pattern is reflected in the mortality trends for preterm deaths, particularly in neonates aged 0-6 days (Figure 6.23.2). Not surprisingly, the NMR (neonatal mortality rate) for neonates aged 0-6 days is consistently higher compared to neonates aged 7-27 days. There has been progress in reducing the global deaths from complications of preterm birth from a million since 1990, particularly in neonates aged 0-6 days, but much progress still needs to be made.

Table 6.23.1. Neonatal deaths by region, 2011

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of neonatal deaths (thousands)</th>
<th>Neonatal deaths as a share of under-five deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed regions</td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>Developing regions</td>
<td>2 902</td>
<td>43</td>
</tr>
<tr>
<td>Northern Africa</td>
<td>40</td>
<td>47</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>1 122</td>
<td>33</td>
</tr>
<tr>
<td>Latin America &amp; the Caribbean</td>
<td>107</td>
<td>53</td>
</tr>
<tr>
<td>Caucasus &amp; Central Asia</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>Eastern Asia</td>
<td>151</td>
<td>57</td>
</tr>
<tr>
<td>Southern Asia</td>
<td>1 216</td>
<td>52</td>
</tr>
<tr>
<td>South-Eastern Asia</td>
<td>155</td>
<td>50</td>
</tr>
<tr>
<td>Western Asia</td>
<td>77</td>
<td>49</td>
</tr>
<tr>
<td>Oceania</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>World</td>
<td>2 955</td>
<td>43</td>
</tr>
</tbody>
</table>


Figure 6.23.2. Global neonatal mortality rates from complications of preterm birth

Source: Adapted from Global Burden of Disease Study 2010 Results by Cause and Region 1990-2010
More than one-third of the estimated four million neonatal deaths each year are caused by severe infections, and a quarter, an equivalent of one million neonatal deaths, are due to neonatal sepsis and pneumonia alone. The risk of dying due to severe infection in high mortality countries (NMR >45) is roughly 11-fold the risk in low-mortality countries (NMR <15). The under-recognition of neonatal sepsis, delay in care seeking by the family, and lack of access to appropriate services means that not much progress has been made since 1990.

Figure 6.23.3. Global neonatal mortality rates from neonatal sepsis

![Image of neonatal sepsis mortality rate graph]

Source: Adapted from Global Burden of Disease Study 2010 Results by Cause and Region 1990-2010

Neonatal deaths from birth asphyxia are the fifth most common cause of under-five child deaths after pneumonia, diarrhea, preterm birth complications, and neonatal infections. The Global Burden of Disease 2004 report allocated 42 million DALYs to birth asphyxia, which is twice the number of DALYs allocated to diabetes and around 75% of the DALYs allocated to HIV/AIDS. The risk of dying due to birth asphyxia is roughly eight-fold for babies in countries with very high NMRs, even though the proportion of neonatal deaths is fairly constant across mortality levels.

Consistent with the other neonatal conditions, NMR are much higher in boys than in girls (Figure 6.23.4). This gender gap is more prominent in neonates aged 0-6 days compared to neonates aged 7-27 days. Not surprisingly, the overall NMR for neonates aged 0-6 is consistently higher compared to neonates aged 7-27 days. There has been progress in reducing the global DALY from complications of preterm birth from a million since 1990, particularly in neonates aged 0-6 days, but much progress still needs to be made.
1.4 EU/EEA Burden of Disease

The number of neonatal deaths in the EU has decreased from 169,999 in 1990 to 70,000 in 2011. However, there are large disparities even within the region where the highest national mortality rate is estimated to be 40 times the lowest. Eastern Europe consistently has higher mortality and DALYs in comparison to Western and Central Europe across all three neonatal conditions, particularly neonatal sepsis and neonatal encephalopathy (Figure 6.23.5-7). The greatest progress from 1990 to 2010 was seen in neonates aged 0-6 days compared to neonates aged 7-27 days across the neonatal conditions. However, the number of deaths and DALYs in neonates aged 0-7 days were much higher when compared to neonates aged 7-27 days. The gender survival gap is still consistent with the European data which show that girls have a survival advantage compared to boys.
1.4.1 Preterm birth

In a systematic review study, Europe was found to have the lowest rate of preterm birth (6.2% of all births) compared to all other regions. However, mortality rates vary even within the region. An estimated 4,506 deaths due to preterm birth complications occurred in Western Europe, 4,835 deaths in Eastern Europe, and 1,876 deaths in Central Europe in 2010.

Figure 6.23.5. Neonatal mortality rates from complications of preterm birth in Europe

Source: Adapted from Global Burden of Disease Study 2010 Results by Cause and Region 1990-2010
1.4.2 Sepsis

Most neonatal sepsis deaths are in Eastern Europe, both in neonates aged 0-6 days and neonates aged 7-27 days. With neonatal sepsis, the survival rate of girls is much higher than boys. The largest gender difference in survival rates is seen in neonatal sepsis compared to preterm birth and birth asphyxia. Mortality rates vary even within the region. An estimated 571 deaths due neonatal sepsis occurred in Western Europe, 1 417 deaths in Eastern Europe, and 208 deaths in Central Europe in 2010.16

Figure 6.23.6. Neonatal mortality rates from neonatal sepsis in Europe

![Neonatal Sepsis Mortality Rate - Europe](image)

Source: Adapted from Global Burden of Disease Study 2010 Results by Cause and Region 1990-201016
1.4.3 Encephalopathy

The DALY burden from neonatal encephalopathy is disproportionately heavy in Eastern Europe compared to Western and Central Europe such that despite having the largest progress in neonates aged 0-6 days, Eastern Europe still has the highest DALY burden with 325,898. Central Europe has the lowest DALY burden of 44,455, while Western Europe has a DALY burden of 153,542.

Figure 6.23.7. Neonatal mortality rates from neonatal encephalopathy as a result of birth asphyxia and birth trauma in Europe

Source: Adapted from Global Burden of Disease Study 2010 Results by Cause and Region 1990-2010
2. Control Strategy

2.1 Vaccination (Prevention)

Neonatal immunization has long been considered as a method for reducing neonatal infections. However, the response varies according to the antigen and maternal antibodies often interfere with a neonate’s response to the vaccine when administered under six months. Protein antigen vaccines given at birth show poor responses compared to the same antigen given at two months of age. Vaccines targeting *S. agalactiae* and *Streptococcus pneumonia* are shown to be ineffective when given in the neonatal period. However, herd immunity effects have been seen in infants too young to receive when the heptavalent pneumococcal conjugate vaccine (PCV7) was recommended for all children aged 2 to 23 months.

There are no available vaccines for premature birth, neonatal sepsis, or neonatal asphyxia for neonates, but some preventative recommendations include vaccinating the mother-to-be by promoting vaccination of all children and adolescents. Infections transmitted around the time of conception may result in preterm birth. Maternal immunization can provide neonates with the appropriate antibodies as soon as they are born. For example, studies of maternal immunization with *S. agalactiae* type III conjugate vaccine have demonstrated effective placental transfer and persistence of protective levels in two-month old infants.

Through a recent modeling study, maternal immunization with *S. agalactiae* vaccine would prevent 60-70% of neonatal *S. agalactiae* infections within the United States context alone. Encouraging results and promising safety profiles are also emerging from preliminary studies of maternal immunization with pneumococcal polysaccharide and conjugate vaccines. Furthermore, Novartis have recently completed a Phase II GBS vaccine which is being trialed in the second trimester to prevent neonatal infection.

The study is to evaluate the safety and immunogenicity of GBS vaccine at one dose in healthy non-pregnant women and eventually in three different doses in healthy pregnant women. However, barriers to maternal immunization still exists, including liability issues for vaccine manufacturers in developed countries, education of the public and health care providers regarding the benefits of maternal immunization and poor ascertainment of data from low-income countries.

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**Box 6.23.1: Maternal and Neonatal Tetanus elimination**

Maternal and neonatal tetanus deaths were among the most common lethal consequences of unclean deliveries and umbilical cord care practices. Mortality rates are extremely high once tetanus is diagnosed, especially when appropriate medical care is not available.

In 1988, WHO estimated that 787 000 newborns died of neonatal tetanus, roughly 6.7 deaths per 1 000 live births. Being a substantial public health problem, neonatal tetanus elimination was listed as one of the goals at the 1990 World Summit for Children and again at the 44th World Health Assembly in 1991. Through immunization of pregnant and child bearing age women and promotion of hygienic deliveries, WHO estimates that only 58 000 newborns died from neonatal tetanus in 2010 – a 93% reduction from the 1980s.

2.2 Other Preventative Approaches

2.2.1 Preterm birth

Alternative methods have been developed to help prevent preterm birth targeting from preconception to antenatal care. This includes a preconception care package that includes family planning (e.g. birth spacing and adolescent-friendly services), education and nutrition especially for girls of child bearing age, and STI prevention. An antenatal care package is recommended for all women that includes screening for and management of STIs, high blood pressure, and diabetes; behavior change for lifestyle risks; and targeted care of women at increased risk of preterm birth. Preconception care services for prevention of preterm birth recommended for all women include:

- **Prevent unintended pregnancies and promote optimal birth spacing** – Women who have very closely spaced pregnancies (within six months of a previous live birth or pregnancy) are at higher risk of a preterm or low-birthweight babies. Correct and consistent use of family planning and contraceptive methods (hormonal and barrier methods) leads to more women spacing their pregnancies 18 to 24 months apart, which is ideal. Breastfeeding is an underused method for preventing closely spaced pregnancies and should be promoted for 24 months. Twelve months of contraceptive use along with breastfeeding reduces the risk of mortality for the next newborn by 68.4%.

- **Optimize pre-pregnancy weight** – Women who are underweight before pregnancy (body mass index less than 18.5 kg/m²) and women who are overweight/obese (body mass index greater than 25 kg/m²) are at significantly greater risk of having premature, low birth weight newborns. Improving food security particularly in impoverished nations, and achieving a healthy maternal weight could reduce the rates of preterm birth.

- **Promote healthy nutrition including supplementation/fortification of essential foods with micronutrients** – Studies of the biological mechanisms leading to preterm birth suggest that more severe congenital disorders such as neural tube defects, might result in preterm delivery. Consuming multivitamins in the preconception period has been shown to help prevent neural tube and other birth defects. Iron and folic acid fortification of foods for mass consumption is considered an important strategy to increase micronutrient levels in that population.

- **Promote vaccination of children and adolescents** – Infections transmitted around the time of conception or during pregnancy may result in preterm birth. Many infections, such as rubella, could be prevented through routine childhood vaccinations.

In addition to the following care services, women with special risk factors that increase the risk for preterm birth should also be recommended:

- **Screen for, diagnose and manage mental health disorders and prevent intimate partner violence** – Maternal stressors including depression, socioeconomic hardship and intimate partner violence have been linked to preterm birth. Studies suggest that stress acts through inflammatory pathways involving maternal cortisol which causes premature birth. Furthermore, women with stressors have a greater likelihood to engage in risky behaviors such as smoking and alcohol use.

- **Prevent and treat sexually transmitted infections (STIs), including HIV/AIDS** – Reducing infectious diseases, particularly syphilis, can lower the rates of stillbirths...
and preterm birth.\textsuperscript{36} Behavioral, counseling, and mass treatment interventions with antibiotics have been shown to decrease the prevalence of STIs.\textsuperscript{37,38}

- **Promote cessation of tobacco use and restrict exposure to secondhand smoke** – Cigarette smoking roughly doubles the risk of preterm birth.\textsuperscript{39} Tobacco cessation interventions and preconception counseling involving the husbands or partners can increase the number of women who quit smoking and reduce the exposure to secondhand-smoke.\textsuperscript{40}

As of February 2011, Makena\textsuperscript{®} (17-alpha-hydroxyprogesterone caproate or 17P) was approved by the US FDA as a pharmaceutical drug for the reduction of the risk of certain preterm births in women who have had at least one prior preterm birth.\textsuperscript{41} Weekly injections of 17P resulted in significant reduction in the risk of delivery at less than 37 weeks of gestation (RR=0.66, 95\% CI: 0.45 to 0.81), delivery at less than 35 weeks of gestation (RR=0.67, 95\% CI:0.48 to 0.93), and delivery at less than 32 weeks of gestation (RR=0.58, 95\%CI:0.37 to 0.91).\textsuperscript{42} So far, this is the only pharmaceutical drug available in preventing preterm birth and has only been approved in the United States.

### 2.2.2 Sepsis

Although there is no way to prevent all types of sepsis, the transmission of Group B streptococcal (GBS) bacteria from mother to child could be prevented.\textsuperscript{43} If a woman tests positive for GBS, she can receive intravenous antibiotics during labor, optimally at least four hours before delivery.\textsuperscript{43}

In addition to maternal treatments, prophylactic approaches have also been considered. Any women with a fever during labor, pPROM, or if they had other children with sepsis or other diseases triggered by GBS are recommended to receive intravenous antibiotics during labor to lower the risk of transmission to the child.\textsuperscript{22} Intrapartum antibiotic prophylaxis has been highly effective in reducing both early-onset neonatal bacterial and maternal sepsis in developing countries.\textsuperscript{44} For example, chemoprophylaxis has halved the incidence of early-onset neonatal S. agalactiae sepsis from 1.7 per 1 000 live births in 1993 to 0.6 per 1 000 in 1998 in the United States.\textsuperscript{45}

In addition, hand washing and ensuring that those who come in contact with the newborn are not sick and have been fully vaccinated can also prevent infection in both home and health facility settings.\textsuperscript{19} Although, both important, there is stronger evidence for hand washing by health care providers after delivery for reducing neonatal sepsis and infection rates in hospitals compared to hand washing in mothers of their own infants.\textsuperscript{46,47} There is emerging evidence that neonatal skin antisepsis preparations, such as sunflower seed oil and chlorhexidine, provides cheap, safe, and effective protection against nosocomial infections in hospitalized preterm neonates in studies in South Asia.\textsuperscript{8,48,49}

Lastly, neonatal nutrition can be a protective factor in neonatal infections. Breast milk contains secretory IgA, lysozymes, white blood cells, and lactoferrin and has been shown to promote the growth of healthy *Lactobacilli* and reduce the growth of *E. coli* and other Gram-negative pathogenic bacteria.\textsuperscript{19} Early initiation and exclusive breastfeeding is associated with significant reductions in diarrhea and acute respiratory infections in neonates while other observational studies have demonstrated impact on infection specific mortality rates during the neonatal period.\textsuperscript{50,51,52} Trials of parenteral vitamin A supplementation have also shown
significant reductions in respiratory disease in low birth-weight infants and reductions in neonatal mortality.53,54

2.3 Diagnostic Testing

2.3.1 Sepsis

Neonatal clinical sepsis syndrome identification is difficult since the symptoms are often very similar to other life-threatening diseases such as necrotizing enterocolitis, perinatal asphyxia, and hyaline membrane disease.55,56 Seven danger signs have been identified to be used to diagnose infants with very severe disease including neonatal sepsis (Table 6.23.2) and have now been incorporated into the new neonatal WHO Integrated Management of Childhood Illness guidelines.56 These signs provide high sensitivity and moderate specificity for detecting serious illness.

Table 6.23.2. Clinical symptoms and signs of severe neonatal illness including sepsis

<table>
<thead>
<tr>
<th>Clinical symptoms and signs of severe neonatal illness including sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of difficulty feeding</td>
</tr>
<tr>
<td>History of convulsion</td>
</tr>
<tr>
<td>Movement only when stimulated</td>
</tr>
<tr>
<td>Respiratory rate ≥60 breaths per minute</td>
</tr>
<tr>
<td>Severe chest indrawing</td>
</tr>
<tr>
<td>Axillary temperature ≥37.5˚C</td>
</tr>
<tr>
<td>Axillary temperature &lt;35.5˚C</td>
</tr>
</tbody>
</table>

Source: Adapted from Clinical signs that predict severe illness in children under age two months56

Laboratory tests can help diagnose neonatal sepsis and identify the specific bacteria causing the infection. Blood tests may include blood culture, C-reactive, protein, and complete blood count.7 If necessary, a lumbar puncture will be done to examine the cerebrospinal fluid for bacteria.7 If the baby has a cough or issues breathing, a chest x-ray will be taken and urine culture tests can be done if the baby is older than several days.7 However, identification of pathogenic organisms remain difficult because bacterial load in neonates may be low due to mothers receiving antepartum or intrapartum antibiotics and also because only small amounts of blood can often be taken from newborns.7 Contamination rates may also be high due to difficulties of performing sterile venipuncture in small babies.8

Conventional assays are being replaced by newer “real-time” systems that are faster and associated with lower contamination rates because amplification and detection occur simultaneously in a closed system.58 The real-time polymerase chain reaction (PCR) produces quantitative results within 30 minutes and calculates bacterial load by using a single primer to detect the universal bacterial genome (16S RNA or 23S RNA).59 Broad-range real-time PCR can distinguish bacterial septicaemic disease from other causes of neonatal illness with similar symptoms such as asphyxia or premature complications.59 Alternatively, multiplex PCR amplifies different targets, but is focused only on specific pathogens.60 However, real time PCR requires the specimen to be collected with a sterile venipuncture which may be difficult in neonates. Typically, the specimen is collected via capillary heel prick due to its
ease, but also has the highest potential for contamination by skin flora. Furthermore, real-
time PCR technologies are expensive and can only be used by highly trained staff.

Antigen detection techniques allow for rapid detection and identification without culturing. The most commonly used commercially available test is the latex agglutination assay which is dependent on specific agglutination by bacterial cell wall antigens of antibody-coated latex particles. However, these tests are reliable in detecting limited organisms such as S. agalactiae and are associated with high false positive and negative rates.

Despite diagnostic advances, none of these diagnostic tests are ideal with results of blood culture being delayed up to 48 hours. Since the condition of a neonate with true sepsis can deteriorate quickly, broad-spectrum antibiotic therapy are often prescribed even before the test results are available. This often results in unnecessary antibiotic use, which may contribute to the emergence of antibiotic resistance.

2.4 Treatment

2.4.1 Preterm birth

In women with preterm labor, tocolytics are drugs used to suppress uterine contractions and are often given to delay birth by inhibiting uterine contractions. Several tocolytics are available that work to inhibit preterm labor via different mechanisms including oxytocin antagonists, betamimetics, calcium channel blockers, and magnesium sulphate. The provision of tocolytics has been shown effective in suppressing labor to allow enough time for antenatal corticosteroid treatment for fetal lung maturation prior to delivery and/or to transfer mother and baby to a higher-level facility where appropriate care may be available. Although betamimetics have been shown to delay delivery, its effects on neonatal outcomes and fetal maternal side effects have not been shown to improve perinatal outcome and have high frequency of unpleasant and sometimes fatal maternal side effects. Any use of strategies to prolong labor must be evaluated against the potential risk of prolonged exposure of mother and fetus to sub-optimal conditions that may result in harm. According to Cochrane systematic reviews, there are several pharmaceutical interventions which are effective in delaying delivery by at least two days after the initiation of preterm labor (Figure 6.23.8). Trans-abdominal amnioinfusion reduces the risk of delivery within seven days of treatment compared with the control group in women with pPROM (Relative risk (RR) = 0.18, 95% confidence interval (CI): 0.05 to 0.7). The most common drugs used to stop preterm labor are betamimetics such as ritodrine and terbutaline, as well as magnesium sulphate. However, another Cochrane Review showed that calcium channel blockers, such as nifedipine and nicardipine, may be more effective in delaying delivery within seven days of treatment compared with other more commonly used betamimetics (RR=0.76, 95% CI: 0.6 to 0.97). Lastly, any tocolytic administration seem to reduce births within 48 hours of treatment compared to no treatment at all (RR=0.55, 95% CI: 0.32 to 0.95). All these pharmaceutical interventions seem to be effective in delaying delivery long enough to allow for a 48-hour corticosteroid treatment for fetal maturation, hopefully, reducing the morbidity and mortality associated with prematurity. A recent systematic review and network meta-analysis conducted by Haas et al. showed that prostaglandin inhibitors (OR=5.39, 95% CI: 2.14 to 12.34) followed by magnesium sulfate (OR=2.76, 95% CI: 1.58 to 4.94), calcium channel blockers (OR=2.71, 95% CI: 1.17 to 5.91), beta mimetics (OR=2.41, 95% CI: 1.27 to 4.55), and
oxytocin receptor blocker (OR=2.02, 95% CI: 1.10 to 3.80) delayed delivery best by 48 hours when compared with placebo.  

Figure 6.23.8. Pharmaceutical interventions for delaying delivery by at least two days.

In contrast to interventions given after the initiation of preterm labor, several pharmaceutical interventions exist in preventing delivery prior to 37 weeks of gestation (Figure 6.23.9). The treatment methods vary depending on the potential risk of preterm birth. A Cochrane Review of antibiotic treatment for bacterial vaginosis before 20 weeks of gestation suggest reductions in the risk of preterm birth (OR=0.72, 95% CI: 0.55 to 0.95). However, there is little evidence that treating all pregnant women with bacterial vaginosis, including those beyond 20 weeks of gestation, is effective in preventing preterm birth. Vaginal antibiotic treatments, oral antibiotic treatments, and clindamycin (oral or vaginal) treatments did not show significant reduction in the risk of preterm birth compared to no treatment (OR=0.88, 95% CI: 0.64 to 1.21; OR=0.9, 95% CI: 0.75 to 1.08; OR=0.8, 95% CI: 0.6 to 1.05; respectively).

Another Cochrane Review of prophylactic antibiotic treatment during the second or third trimester of pregnancy reduced the risk of preterm delivery compared to the placebo group (RR=0.64, 95% CI: 0.47 to 0.88). However, there was substantial bias in the review’s results, warranting further research. Furthermore, a Cochrane Review compared non-selective cyclooxygenase (COX) inhibitors, such as indomethacin, with either placebo and other tocolytics. The results suggest reduced risk of preterm labor using COX inhibitor compared to both placebo and other tocolytics (RR=0.21, 95% CI: 0.07 to 0.62; RR=0.53, 95% CI: 0.31 to 0.94; respectively). It should be noted, however, that trial size was small and that the results, as well as the potential adverse effects of COX inhibition could not be adequately assessed. For some women, an episode of preterm labor settles and does not result in immediate
birth. Maintenance therapy with oxytocin receptor antagonist such as atosiban may have the potential to prevent premature birth. However, Cochrane Reviews of this treatment compared to placebo or no treatment did not provide enough evidence that maintenance treatment reduced the risk of preterm birth (RR=0.89, 95% CI:0.71 to 1.12). Lastly, a double-blind, placebo-controlled trial showed that treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (RR=0.66, 95% CI: 0.54 to 0.81).

Figure 6.23.9. Pharmaceutical intervention for preventing preterm birth defined as 37 weeks of gestation.

Currently, there are three key interventions that can be delivered during the pregnancy period with evidence of improving health outcomes in a premature baby: antenatal corticosteroids, antibiotics for pPROM, and magnesium sulphate (Table 6.23.3).
Antenatal corticosteroids can be administered to women at high risk of preterm birth as early as 23 weeks and can significantly reduce the premature baby’s risk of death, respiratory distress, and developmental problems. The WHO lists antenatal corticosteroids (betamethasone and dexamethasone) as a priority intervention for the prevention of respiratory distress syndrome (RDS) in premature babies and considers antenatal corticosteroids as a priority medicine for reducing mortality among premature babies. It should be noted that at the time of publication, dexamethasone was listed for treating allergies only. Despite the evidence of effectiveness, antenatal corticosteroid use remains low. In 2000, it was estimated that in the 42 countries with 90% of the world’s childhood deaths, only 5% of appropriate candidates received the intervention. This is a clear indication of missed opportunities for improving the survival chances of premature babies.

Premature rupture of the membranes is strongly associated with infection of the amniotic membranes contributing to preterm birth and other poor fetal outcomes such as cerebral palsy and chronic lung disease. Antibiotic treatment for pPROM has been shown to suppress labor for up to 48 hours as well as reduce neonatal infections and abnormal cerebral ultrasound scans prior to hospital discharge. However, due to increasing concern around bacterial resistance and the risk of maternal anaphylaxis with antibiotic use, its risks and benefits should be assessed to ensure judicious use of antibiotics.

Magnesium sulphate administration to women at risk of preterm birth reduces the risk of neurological disorders in their infants such as cerebral palsy and improve long-term neonatal health outcomes. It is a safe and relatively inexpensive drug. However, magnesium sulphate has a narrow safe dosage range and require close monitoring during treatment. Further studies are needed to investigate the maternal side effects (e.g. flushing, sweating, nausea, vomiting, headaches, and a rapid heartbeat).
**Table 6.23.3. Common medicines for preterm labor**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Possible maternal side effects</th>
<th>Possible side effects in baby</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone</td>
<td>• Fluid build-up in the body&lt;br&gt;• Rising blood pressure&lt;br&gt;• Increased risk of infection&lt;br&gt;• Problems with wound healing</td>
<td>• Increased risk of infection</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>• Fluid build-up in the body&lt;br&gt;• Rising blood pressure&lt;br&gt;• Increased risk of infection&lt;br&gt;Problems with wound healing</td>
<td>• Increased risk of infection</td>
</tr>
<tr>
<td>Calcium channel blockers (nifedipine)</td>
<td>• Redness of the skin&lt;br&gt;• Headache&lt;br&gt;• Dizziness or feeling faint&lt;br&gt;• Nausea&lt;br&gt;• Low blood pressure&lt;br&gt;• Constipation or diarrhea</td>
<td>No known side effects</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs (indomethacin)</td>
<td>• Dizziness&lt;br&gt;• Nausea or throwing up&lt;br&gt;• Heartburn&lt;br&gt;• Vaginal bleeding&lt;br&gt;• Swollen stomach lining</td>
<td>• Oligohydramnios&lt;br&gt;• Ductus arteriosis&lt;br&gt;• Rising blood pressure in the lungs&lt;br&gt;• Kidney problems&lt;br&gt;• Bleeding within the brain or heart&lt;br&gt;• Jaundice&lt;br&gt;• Necrotizing enterocolitis</td>
</tr>
<tr>
<td>Tocolytic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>• Fast or irregular heartbeat&lt;br&gt;• Fluid in the lungs&lt;br&gt;• Low blood pressure&lt;br&gt;• High blood sugar&lt;br&gt;• Low blood potassium&lt;br&gt;• Trouble breathing&lt;br&gt;• Chest pain&lt;br&gt;• Shaking or feeling nervous&lt;br&gt;• Seizure&lt;br&gt;• Nausea or throwing up&lt;br&gt;• Headache&lt;br&gt;• Dizziness&lt;br&gt;• Fever&lt;br&gt;• Diarrhea</td>
<td>• Fast heartbeat</td>
</tr>
</tbody>
</table>

Source: Adapted from March of Dimes, Preterm labor
2.4.2 Sepsis

Antibiotics are used to prevent life-threatening complications from infections for both the mother and the baby. Since early-onset neonatal sepsis is caused by infection from the mother before or during the delivery, antenatal and intrapartum interventions targeting the mother is common to reduce the risk of neonatal sepsis (Figure 6.23.10). Prelabour rupture of the membranes increases the risk of infection for the woman and her baby.76 A Cochrane Review of amnioinfusion treatment for pPROM showed reduction in neonatal sepsis compared to no treatment in other women with pPROM (RR=0.26, 95% CI:0.11 to 0.61).64 Antibiotic treatment is accepted as the standard of care, but routine use of prophylactic antibiotics for women at the time of pPROM raises concern due to the increasing problems with bacterial resistance and the risk of maternal anaphylaxis with antibiotic use.76 It should be noted that reviews of prophylactic antibiotic use compared to placebo or no treatment was associated with a reduction in neonatal sepsis, but the results did not reach statistically significance (RR=0.14, 95% CI:0.02 to 1.13).77 Antenatal corticosteroid treatment for accelerating fetal lung maturation for women at risk of preterm birth has been shown to reduce birth complications including the risk of neonatal sepsis (RR=0.56, 95% CI:0.38 to 0.85).78 Intraamniotic infection is also associated with neonatal sepsis and studies have been conducted to examine the effectiveness of different antibiotic regimens to treat this infection. Intrapartum antibiotic treatment was associated with a reduction in neonatal sepsis compared to antibiotic treatment given immediately postpartum, but the results did not reach statistical significance (RR=0.08, 95% CI:0.0 to 1.44).78

One intervention focused on the neonate exists in preventing neonatal infection in preterm and/or low birth weight infants (Figure 6.23.10). Preterm infants are deficient in immunoglobulin (IgG); therefore, prophylactic administration of intravenous immunoglobulin may have the potential of preventing infections.79 According to a Cochrane systematic review, the use of prophylactic intravenous immunoglobulin was statistically significant for reducing sepsis (RR=0.85, 95% CI:0.74 to 0.98).79
Several pharmaceutical interventions exist to treat neonatal sepsis once it develops. Prompt antibiotic treatment is necessary as newborn babies have an immature immune system and conditions can deteriorate quickly once sepsis is diagnosed. Cochrane Reviews were gathered to assess the effectiveness of antibiotic regimens for treatment of neonatal sepsis and the results are limited (Figure 6.23.11). Two small studies compared monotherapy (ticarcillin or clavulanate) with combination therapy (piperacillin and gentamicin) and showed no significant difference in mortality outcomes from neonatal sepsis (RR=0.75, 95% CI:0.19 to 2.9). Another review assessed the effectiveness of beta-lactam therapy compared with combination of beta-lactam plus aminoglycoside treatment and found that there was no significant difference in mortality outcome between these two therapies (RR=0.17, 95% CI:0.01 to 3.23).
Currently, parenteral (intravenous or intramuscular) regimens of a combination of penicillin/ampicillin and gentamicin or third-generation cephalosporins (e.g. ceftriaxone or cefotaxime) for 10 to 14 days is recommended by national paediatric associations and the WHO (Table 6.23.4). These antibiotics are shown to be safe and retain efficacy when administered at extended intervals. These treatments are effective against *Streptococcus*, but *Staphylococcus* is highly resistant. Gram-negative antimicrobial susceptibility to ampicillin and gentamicin can also be poor, particularly for *Klebsiella*. *E.coli* resistance to ampicillin, gentamicin, and third-generation cephalosporins in hospitals of both developed and developing countries is emerging and is raising concern. Furthermore, parenteral administration requires health care professionals that are often lacking in lower-resource settings where the majority of births and neonatal deaths occur at home.
**Table 6.23.4. Injectable antibiotics products for treating neonatal sepsis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Procaine benzylpenicillin</th>
<th>Gentamicin</th>
<th>Ceftriaxone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Neonatal sepsis, first-line</td>
<td></td>
<td>Neonatal sepsis, second-line</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>Powder for injection: 1 g (=1 mill IU); 3 g (=3 mill IU) in vial</td>
<td>Injection: 10 mg; 40 mg (as sulfate)/ml in 2-ml vial</td>
<td>Powder for injection: 250 mg and 1 g</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>Intramuscular injections 50 mg/kg of ampicillin (or comparable) every 6-8 hours – depending on age – divided 2x/day for at least 10 days</td>
<td>Intramuscular injection 7.5 mg/kg of gentamicin (or comparable) in addition to the benzylpenicillin injections – divided 2x/day for at least 10 days</td>
<td>50 mg/kg once daily for all newborns (&lt;1 week, &lt;2 kg) 75 mg/kg once daily for 10 days (&gt;1 week, &gt;2 kg)</td>
</tr>
<tr>
<td><strong>Average Cost (per treatment)</strong></td>
<td>~US$ 0.13-0.16</td>
<td>~US$ 0.17-2.03</td>
<td>~US$ 0.50-0.90</td>
</tr>
<tr>
<td></td>
<td>(dependent on weight and # days treated)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Every Woman Every Child – Injectable Antibiotics for Newborn Sepsis

Despite the existence of effective antibiotics to treat neonatal sepsis, case-fatality rates for severe bacterial infections in developing countries remain high. Although relatively low-cost treatments exist, properly trained care providers are required to administer them. There has been insufficient focus on optimizing innovative approaches to product formulation and packaging. Gentamicin administration should be monitored closely as there are risks related to toxicity that could result in permanent hearing and kidney damage. In both Asia and sub-Saharan Africa, where a large burden of neonatal sepsis lies, formulations at appropriate dosage may not be readily available. It is difficult to develop alternative delivery mechanisms for these antibiotics as procaine benzylpenicillin and ceftriaxone powders must be reconstituted with sterile water and achieving appropriate volumes with the correct formulation remains a challenge. The UN Commissioners’ Report released in 2012 for life-saving commodities for women and children have identified and recommended simple potential product innovations that demand further research particularly in the administration of gentamicin (including fixed-dose presentations for needles and syringes, auto-disable syringes, and micro-needle patch technology for administering gentamicin) (Table 6.23.5).

**Table 6.23.5. Potential product innovations for injectable antibiotics**

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Potential product innovations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable antibiotics</td>
<td>• Fixed-dose presentations for basic needles and syringes and pre-filled delivery devices for administering gentamicin</td>
</tr>
<tr>
<td></td>
<td>• Auto-disable syringes for administering gentamicin</td>
</tr>
<tr>
<td></td>
<td>• Micro-needle patch technology for administering gentamicin</td>
</tr>
</tbody>
</table>

Source: UN Commission on Life-Saving Commodities for Women and Children
2.4.3 Birth Asphyxia

Several pharmaceutical interventions have been identified to reduce the risk of neonatal mortality from respiratory distress syndrome (RDS) (Figure 6.23.12). Respiratory distress syndrome is associated with a deficiency or dysfunction of pulmonary surfactant that lines the alveolar surface and prevents atelectasis at the end of expiration. Surfactant therapy has been shown to improve the immediate need for respiratory support and the clinical outcome of very preterm newborns. Studies have been conducted on a variety of surfactant preparations used to prevent (prophylactic or delivery room administration) or treat (very early, selective or rescue administration). Use of surfactant therapy have demonstrated decreases in the severity of respiratory distress, decreases in the frequency of pneumothorax, increases survival without chronic lung disease, and decreases mortality. Cochrane systematic reviews, show that the use of animal derived surfactant extract showed reduced risk of neonatal mortality from RDS (RR=0.68, 95% CI:0.57 to 0.82). Inositol is an essential nutrient which promotes maturation of several components of surfactant and may play a critical role in reducing neonatal mortality in neonates with RDS. Cochrane Reviews of inositol supplementation resulted in statistically significant reductions in neonatal mortality (RR=0.53, 95% CI:0.31 to 0.91). Furthermore, lung edema may complicate RDS in preterm infants and for this reason, treatment with diuretics like furosemide may help remove the excess fluid from the lungs that can cause breathing problems. However, the data did not support routine administration of furosemide in preterm infants with RDS as it did not reduce the risk of neonatal mortality (RR=1.47, 95% CI: 0.72 to 2.97) and furosemide-induced transient improvement in pulmonary function did not outweigh the increased risk for patent ductus arteriosus and hemodynamic instability.

Prophylactic administration of pulmonary surfactant to newborns at risk of developing RDS is also another treatment option. The Cochrane Reviews of this intervention shows a decrease in the risk of neonatal mortality in infants who receive prophylactic animal derived surfactant extract compared to administration of normal saline or air placebo (RR=0.60, 95% CI:0.47 to 0.77). A variety of synthetic surfactant products have also been developed and administered prophylactically. Cochrane Reviews, supports prophylactic administration of protein free synthetic surfactant in reducing the risk of neonatal mortality (RR=0.70, 95% CI:0.58 to 0.85).
A variety of surfactant preparations have been developed and tested including synthetic surfactants and surfactants derived from animal sources for treatment and prophylactic use in infants at risk for or having RDS (Figure 6.23.13). Although both surfactant preparations are effective, comparative reviews show that natural surfactants seem to have greater efficacy, perhaps due to the protein content that is lacking in synthetic surfactants.\textsuperscript{96,98} Cochrane Reviews comparing natural surfactant extract versus synthetic surfactant show that there is greater efficacy of natural surfactant products (RR=0.87, 95% CI:0.76 to 0.98).\textsuperscript{96} Recent developments in synthetic surfactant preparations include peptides or whole proteins that mimic endogenous surfactant protein.\textsuperscript{97} Comparisons of synthetic surfactant containing surfactant protein mimics compared to animal derived surfactant extract showed comparable results in reducing the risk of neonatal mortality (RR=0.79, 95% CI:0.61 to 1.02).\textsuperscript{97} Furthermore, it has been suggested that multiple doses of surfactant may lead to improved outcome due to surfactant inactivation.\textsuperscript{99} Meta-analysis of trials comparing multiple doses with only a single dose of animal derived surfactant extract as treatment in established RDS suggests a reduction in the risk of mortality, but did not reach statistical significance (RR=0.63, 95% CI:0.39 to 1.02). However, statistical significance was reached in a similar trial comparing multiple doses with a single dose of prophyllactic exogenous surfactant in infants at high risk of RDS for reducing risk of neonatal death (RR=0.56, 95% CI:0.39 to 0.81).\textsuperscript{99}

Although animal derived surfactant preparations seem to be the most effective in the treatment of premature infants with RDS, they are expensive to produce and supplies are limited.\textsuperscript{100} Table 6.23.6 highlights the cost of the bovine lung extract, beractant, and the

---

### Figure 6.23.12. Pharmaceutical interventions for preventing neonatal mortality from RDS

<table>
<thead>
<tr>
<th>Intervention</th>
<th>OUTCOME: Neonatal mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human amniotic fluid extract, calf lung surfactant extract, modified bovine surfactant extract, porcine surfactant extract (2)</td>
<td></td>
</tr>
<tr>
<td>Inositol (3)</td>
<td></td>
</tr>
<tr>
<td>Animal derived surfactant extract (4)</td>
<td></td>
</tr>
<tr>
<td>Protein free synthetic surfactant (5)</td>
<td></td>
</tr>
</tbody>
</table>

#### Table 6.23.6

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome: Neonatal mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide (1)</td>
<td></td>
</tr>
<tr>
<td>Inositol (3)</td>
<td></td>
</tr>
<tr>
<td>Animal derived surfactant extract (4)</td>
<td></td>
</tr>
<tr>
<td>Protein free synthetic surfactant (5)</td>
<td></td>
</tr>
</tbody>
</table>

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\textsuperscript{1} Cochrane Review (year): trials (subjects)

porcine lung phospholipid fraction, poractant alfa, in the United Kingdom in 2012. Reimbursement prices for other European countries can be found in Annex 6.23.1. In order to widen the availability of surfactant treatment, synthetic preparations need to be developed that can be produced in large quantities and at a reasonable cost. Although some effective synthetic surfactants have been developed, the development of the key hydrophobic surfactant proteins involved in increased alveolar stability, SP-B and SP-C, are too big to synthesize, structurally complex, or unstable in pure form. Development of clinically active synthetic surfactants has turned out to be more complicated than initially anticipated and further research and development need to be undertaken.

Table 6.23.6. The reimbursed price for animal derived surfactants in the United Kingdom in 2012

<table>
<thead>
<tr>
<th>Molecule List</th>
<th>Pack</th>
<th>£ per unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poractant alfa</td>
<td>VIAL 80 MG 3 ML</td>
<td>547.40</td>
</tr>
<tr>
<td>Poractant alfa</td>
<td>VIAL 80 MG 1.5 ML</td>
<td>281.64</td>
</tr>
<tr>
<td>Beractant</td>
<td>VIAL 25 MG 8 ML</td>
<td>306.43</td>
</tr>
</tbody>
</table>

Source: National Health Service England and Wales: Electronic Drug Tariff

Figure 6.23.13. Comparison of pharmaceutical surfactant interventions and regimens in reducing risk of neonatal mortality from RDS

Pharmaceutical Interventions for RDS
OUTCOME: Neonatal mortality

Relative Risk with 95% confidence interval

3. Research and Development

Neonatal conditions have multiple causes; therefore, solutions will not come through a single discovery, but will depend on an array of discoveries addressing multiple biological, clinical, and social-behavioral risk factors. The pipeline will need to address both the prevention of neonatal conditions and the care and survival gap. This will involve different approaches along the pipeline of innovation.

3.1 Pharmaceuticals

3.1.1 Preterm

The Global Action Report on Preterm Birth released by the WHO, emphasized descriptive and discovery learning to better understand preventative methods to preterm birth in various contexts while development and delivery research is emphasized for premature baby care.3

Based on the United States National Institutes of Health, 498 clinical trials were found for preterm and premature conditions in which 235 of them are open studies.103 In 2005, the March of Dimes initiated the Prematurity Research Initiative which funds research into the causes and treatments of prematurity.104 More than US$ 15 million have been awarded to 43 grantees over the past six years.104

Researchers are working to identify the causes of premature birth and new treatments to prevent or halt preterm labor. A recent development shows promise, but only for a minority of high-risk women with premature cervical shortening. Clinical trials suggest that progestational agents (PA) may modify the signal transduction pathways that are involved in cervical ripening.105 Progestational agents seem to regulate pathways which prevent preterm birth, specifically claudin proteins.106 However, how PAs helps prevent preterm labor and which forms of progesterone may be most effective is still to be determined.104 It should be noted that Makena® (17-alpha-hydroxyprogesterone caproate) was approved by the FDA in the USA only in 2011 for women with a history of at least one previous spontaneous preterm birth.41

Several factors are hypothesized to help regulate the timing of labor including the drop in enzyme levels of caspase-3 triggering labor and the closing of SK3 (potassium) channels in the cell membranes preventing potassium flow out of the uterine muscle cells.106,107 The enzyme, caspase-3, may help prevent contractions until term when levels drop sharply triggering labor. Prior to the onset of labor, active caspace-3 levels and fragmentation of the uterine myocyte contractile proteins decline suggesting that uterine caspase-3 acts as an anticontractile agent.108 If this is true, it may be possible to develop drugs to regulate enzyme levels and prevent preterm labor. Additionally, the SK3 channels in cell membranes that allow potassium to flow out of the uterine muscle cells are believed to relax the uterus, allowing pregnancy to continue to term. These channels may close, prompting labor to begin.106 If this proves correct, it could lead to the development of drugs that open the channels to prevent or half preterm labor.
A simple approach that is being investigated is the administration of vitamin D supplements for women with uterine infections. This may help prevent preterm labor by suppressing inflammation.\textsuperscript{105}

### 3.1.2 Sepsis

Based on the US National Institutes of Health, 96 clinical trials were found for neonatal sepsis in which 38 of them are open studies.\textsuperscript{87}

Many cases of neonatal sepsis never reach a health care facility and oral antibiotic therapy must be considered where no health care providers trained to give parenteral antibiotics are available.\textsuperscript{83} The incremental benefit of injectable over oral antibiotics is not clear, but oral antibiotic therapy is certainly better than no antibiotic therapy at all.\textsuperscript{8} A series of trials are evaluating the impact of home and clinic-based seven-day intramuscular and oral antibiotic therapy for neonatal sepsis in low-income countries.\textsuperscript{85} The available data on the effect of oral cotrimoxazole in community-based treatment of serious neonatal bacterial infections are promising, but concerns of high resistance rates and side effects such as neonatal jaundice have been reported.\textsuperscript{84}

New, better absorbed oral antibiotics should be considered. Second-generation cephalosporins (e.g. cefadroxil and cefuroxime) have shown excellent safety profile, a spectrum of activity similar to cotrimoxazole, and may be more effective given the high resistance of neonatal pathogens to cotrimoxazole.\textsuperscript{8} Ciprofloxacin is also becoming increasingly accepted as safe for neonate use, but warrants further investigation for treatment of infections in newborns.\textsuperscript{8} However, the current costs for these agents and the potential for exacerbating antimicrobial resistance may limit widespread use.\textsuperscript{83} Newer antibiotics that are effective when given orally, as well as the safety and efficacy of oral plus injectable antibiotics were also identified as research priorities by technical experts to reduce global newborn infection-related mortality by 2015.\textsuperscript{109}

### 3.1.3 Birth Asphyxia

Based on the United States National Institutes of Health, 39 studies were found for birth asphyxia in which 19 of them are open studies.\textsuperscript{110}

One of the most common birth complications is RDS where babies struggle to breathe because their immature lungs do not produce enough surfactant, a protein that keeps small air sacs in the lungs from collapsing.\textsuperscript{111} Since the introduction of surfactant therapy in 1990, deaths from RDS have been reduced by two-thirds.\textsuperscript{111} Despite these advancements, about 20% of babies with RDS do not respond to surfactant treatment and further discovery and development is needed.\textsuperscript{111} Natural surfactant contains four known proteins – SP-A, SP-B, SP-C, and SP-D – but surfactant treatments only contain SP-B and SP-C.\textsuperscript{111} Research is being conducted to study the structure and function of SP-B to improve the synthetic surfactant to mimic the activity of the natural protein and be effective when the one currently available fails.\textsuperscript{111, 112} Furthermore, a new generation of synthetic surfactants containing simplified phospholipid mixtures and small amounts of peptides replacing the hydrophobic proteins is currently under development and should be introduced into the market in the near future.\textsuperscript{100}
In addition to surfactants, many newborns with RDS receive additional oxygen and mechanical breathing assistance. However, these treatments can contribute to lung injury and bronchopulmonary dysplasia. Research is being done to see whether adding SP-D to commercial surfactant treatments can help the immune system fight off lung infections and prevent the inflammation that contributes to lung injuries and bronchopulmonary dysplasia.

Further research have been conducted in animals to test the effects of administration of caffeine on metabolic variables with peripartum asphyxia. Findings suggest that administering caffeine immediately after birth to neonatal pigs with severe oxygen restriction resulted in significant improvements in metabolic variables such as triglyceride and lactate concentrations.

3.2 Diagnostics

3.2.1 Sepsis

Recent developments in microtechnologies, particularly microfluidics, have provided the greatest contribution to the diagnosis of neonatal sepsis. This technology uses the unique properties of continuous flow micro-volume channels to study the behavior, precise control, and manipulation of fluids. When applied to bacterial DNA protein microarray hybridization, DNA probes specific to selected targets that are spotted on a glass or silicon slide in a known order. Target DNA fragments are labeled with a reporter molecule, combined into a single hybrid, and measured using fluorescent signals to identify specific sepsis pathogen such as bacterial meningitis, acute viral respiratory tract infections, and neonatal sepsis. This method has also been used to detect antimicrobial resistance and virulence genes in research settings.

Microfluidic technology has also developed small, disposable, single-use diagnostic cartridges or cards that have been called “lab-on-a-chip” (LOC). Some LOCs have combined sample preparation, biomarkers, real-time PCR, and DNA microarrays to determine indices of inflammation, pathogen identification, and antimicrobial susceptibility patterns at the point of care. Its performance for sensitivity, specificity, and reproducibility levels are comparable to those of central laboratory analyzers and requires little user input other than the insertion of the sample. Samples as little as a single drop of blood, faeces, and saliva have been tested with encouraging results. Currently, LOCs are being evaluated for use in sepsis and are not yet in clinical use nor are they licensed by regulatory authorities.

3.3 EC Framework Programme

There have been 13 projects on research and development for neonatal conditions funded by the EC Framework Programme since 2004. One project was funded by the Sixth EC Framework Programme (FP6) and 12 projects by the Seventh EC Framework Programme (FP7). The complete list of projects funded by the EC Framework Programme since 2004 is listed below sorted by each neonatal condition. Starred projects indicate an overlap between neonatal conditions and are listed in all relevant categories.
Preterm (11 projects total)\textsuperscript{117}: 

Treatment (8 projects) 
- New approach to treatment of the blinding disease retinopathy of prematurity (ROP) (FP7)  
- Efficacy and safety of inhale budesonide in very preterm infants at risk for bronchopulmonary dysplasia (FP7)  
- Management of hypotension in the preterm extremely low gestational age newborn (FP7)  
- Evaluation of antibiotics (ciprofloxacin and fluconazole) for the treatment of infections in preterm and term neonates (FP7)*  
- No pain during infancy by adapting off-patent medicines (FP7)  
- Documentation of lung growth after tracheal occlusion to reverse pulmonary hypoplasia in congenital diaphragmatic hernia. Experimental studies in the rat and clinical implications of fetal therapy (FP7)  
- Treat Infections in Neonates 2 – Evaluation of an infective agent (azithromycin) for the treatment of infections in preterm and term neonates (FP7)*  
- Does vascular endothelial growth factor gene therapy safely improve outcome in severe early-onset fetal growth restriction? (FP7) 

Diagnostics (2 projects) 
- Brain diagnostics and monitoring in early neonatal period (BraDiMo) (FP7)  
- Special non-invasive advances in foetal and neonatal evaluation network (FP6) 

Basic science and other fields of research (1 project) 
- Effective perinatal intensive care in Europe: translating knowledge into evidence based practice (FP7) 

Sepsis (4 projects total)\textsuperscript{118}: 

Treatment (3 projects) 
- European multicenter network to evaluate pharmacokinetics, safety and efficacy of meropenem in neonatal sepsis and meningitis (FP7)  
- Evaluation of antibiotics (ciprofloxacin and fluconazole) for the treatment of infections in preterm and term neonates (FP7)*  
- Treat infections in NeoNates 2 – Evaluation of an infective agent (azithromycin) for the treatment of infections in preterm and term neonates (FP7)* 

Diagnostics (1 project) 
- Fast automated multiplex analysis of neonatal sepsis markers on a centrifugal microfluidic platform (FP7) 

Birth Asphyxia (0 projects total)\textsuperscript{119}
4. Existing Resource Flows

4.1 Finance for Research and Development

Global spending on maternal, newborn, and child health (MNCH) has been increasing from US$ 2.1 billion in 2003 to almost US$ 3.5 billion in 2006, with child health accounting for more than two-thirds of total aid to MNCH. In 2006, the two leading contributors supporting MNCH were the United States government and the World Bank, which collectively contributed US$ 1.4 billion. Although donor funding has increased for maternal, newborn, and child health, no analysis to date has disaggregated aid specifically for newborns.

Based on the analysis of donor-reported data, donor attention to newborn survival has increased since 2002, but does not appropriately reflect the aid needed with over three million newborn deaths each year. For low- and middle-income countries (LMIC), where the majority of total neonatal deaths occur, the investment in research funding for neonatal survival is extremely low. It is estimated that only around US$ 20 million per year is invested into research for neonatal survival. Defining specific funding allocations for research on neonatal conditions is not possible in current research resource reporting for either high- or low-income countries. The low investment suggests a large potential for public-private partnership (PPP) collaborations. Identifying incentives to foster research funding is recommended and necessary (See Chapter 8).

Currently, none of the neonatal conditions – preterm birth, neonatal sepsis, and birth asphyxia – are listed as one of the diseases on G-FINDER. Donors interested in funding research and development for neonatal conditions need to be able to make substantial investment decisions based on accurate data regarding funding flows, gaps, and duplications. The inclusion of neonatal conditions on funding surveys such as G-FINDER can provide funders with better information and hopefully stimulate increased efficiency and investment to improve neonatal health.

According to a recent 2012 UN commission report on life-saving commodities for women and children, an investment of US$ 2.6 billion over five years to scale up 13 key commodities would cumulatively save over six million women and children. The list includes a preliminary sample of overlooked life-saving commodities that represent common challenges and require a priority response, but are not exhaustive. Of the 13 recommended commodities, four of them focus on interventions for newborn conditions that can have a large potential impact (Table 6.23.7).

Within the European Union, following the requirements of the Paediatric Regulation, the EMA produces a yearly updated "priority list" of medicines in need for children. Neonates are included in these pan-European efforts. These Paediatric Regulations require that any new drug, whatever its main target, should also be considered for potential paediatric use which forces all pharma companies to think strategically in terms of paediatric medicines.
Table 6.23.7. Newborn health commodities recommended in the 2012 Commissioners’ Report

<table>
<thead>
<tr>
<th>Newborn health commodity</th>
<th>Examples of key barriers</th>
<th>Potential 5-year impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injectable antibiotics</strong> – neonatal sepsis</td>
<td>Poor compliance by health workers</td>
<td>1.22 million neonatal lives saved</td>
</tr>
<tr>
<td><strong>Antenatal corticosteroids</strong> – preterm RDS</td>
<td>Low awareness of product impact</td>
<td>466 000 neonatal lives saved</td>
</tr>
<tr>
<td>Chlorhexidine – newborn cord care</td>
<td>Limited awareness and demand</td>
<td>422 000 neonatal lives saved</td>
</tr>
<tr>
<td><strong>Resuscitation devices</strong> – newborn asphyxia</td>
<td>Requires trained health workers</td>
<td>336 000 neonatal lives saved</td>
</tr>
</tbody>
</table>

Source: Every Woman Every Child. UN Commision on Life-Saving Commodities for Women and Children: Commissioners’ Report September 2012; 2012 Sept. 89

Despite the large global burden from neonatal conditions, a recent global analysis suggests that newborn survival will remain vulnerable on the global agenda without adequate funding and without high-level engagement of policy-makers.3 For this reason, it becomes imperative that more funding is allocated towards research and development addressing neonatal conditions.

5. **Challenges and Research Opportunities**

- Although the overall under-five mortality has been declining, neonatal mortality are lagging in improvements and is becoming a larger contributor in the under-five deaths
- The latest data in 2011 indicate that neonatal deaths account for 43% of under-five deaths worldwide. The highest share (55%) of neonatal deaths for under-five deaths is seen in developed regions
- Each neonatal condition has numerous confirmed and hypothesized etiology and contributing risk factors which makes addressing these conditions complex
- Pharmaceutical gap which presently exist offer research opportunities:

**Preterm Birth:**

- Development of a more simplified dosing regimen and single dose packaging of tocolytics to prevent or delay premature labour.
- Development of tocolytics with side-effects in mothers and newborns.
- Evidence-based protocols for use of injectable antenatal corticosteroids to prevent respiratory distress syndrome.
- Clearly labeled, pre-packaged or pre-filled delivery systems of antenatal corticosteroid products.

**Sepsis:**

- Rapid diagnostics for neonatal sepsis to prevent late or inadequate administration of necessary antibiotics.
Update on 2004 Background Paper, BP 6.23 Neonatal Conditions

- Appropriate product formulation and packaging for treating neonatal sepsis, especially low-dose injectable gentamicin.
- Development of shorter course antibiotics, oral antibiotics, and antibiotics with fewer side effects for newborns.
- Development of diagnostic tools for neonatal conditions, which can help reduce the inappropriate use of antibiotics.
- Development of new and effective antibiotics to treat bacterial infections that are or will soon become resistant to current antibiotics (see Chapter 6.1).

**Birth asphyxia:**

- Development of effective and lower-cost synthetic surfactants
- Development of a more stable oral surfactant

- Many of the current treatment regimens require properly trained care providers to administer these technologies. The best methods to train these providers need to be researched.

### 6. Conclusions

Neonatal conditions need to be prioritized to achieve MDG 4. Addressing neonatal conditions can have a major impact in reducing the global burden of disease as these conditions have the most effect on potential years lived with disability (YLD) and years of life lost (YLL). Although the burden of disease is largest in developing countries, neonatal conditions are of a global concern as the share of neonatal deaths in under-five deaths are highest in developed countries.

Further research and development for rapid diagnostic tools and appropriate treatments should be prioritized. Simple product innovations such as fixed-dose technology for simple treatment administration can increase treatment usage in lower-resource settings, as well as the need for continuous innovation in developing new effective antibiotics to treat infections resistant to current antibiotics. A large challenge also remains that most of the current research and development are focused on treatments and not on prevention, in part due to the lack of understanding of the multiple etiology for each of these neonatal conditions. Furthermore, most published research has been conducted in high-income countries and research in developing, delivering, and testing community-based interventions in lower-resource settings are needed.

Research and development of new or more affordable pharmaceuticals, such as synthetic surfactants, to address neonatal conditions require substantive investment and long-term support. Increased support from the European Commission is imperative to reduce the burden of neonatal conditions such as preterm birth, neonatal sepsis, and birth asphyxia in Europe and the world.
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Annex

Annex 6.23.1: The reimbursed price for animal derived surfactants in European countries in 2012


<table>
<thead>
<tr>
<th>Country</th>
<th>Product name</th>
<th>Package</th>
<th>Dosage form</th>
<th>ATC</th>
<th>Route of admin.</th>
<th>Inn. &amp; Strength</th>
<th>No. of units</th>
<th>Manufacturer price/unit</th>
<th>Wholesale price/unit</th>
<th>Net retail price/unit</th>
<th>Gross retail price/unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>curosurf</td>
<td>1fl 3 ml 80 mg/ml</td>
<td>intratracheal suspension</td>
<td>R07AA02</td>
<td>inhalation</td>
<td>natural phospholipids 240 mg</td>
<td>1</td>
<td>775.760000 €</td>
<td>-</td>
<td>955.970000 €</td>
<td>1280.320000 €</td>
</tr>
<tr>
<td>Italy</td>
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<td>inhalation</td>
<td>natural phospholipids 120 mg</td>
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<td>387.880000 €</td>
<td>-</td>
<td>581.965000 €</td>
<td>640.160000 €</td>
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<tr>
<td>Spain</td>
<td>curosurf 120 ; 1 vial 1.5 ml</td>
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<td>intratracheal suspension</td>
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<td>310.470000 €</td>
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<td>Belgium</td>
<td>curosurf 120 mg</td>
<td>1.5 ml suspension pour instillation x 80 mg/ml surfactant pulmonaire porcin en 1 récipient unidose</td>
<td>endotracheopulmonary instillation, suspension</td>
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<td>Greece</td>
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<tr>
<td>United Kingdom</td>
<td>curosurf 120 mg/1.5 ml endotracheopulmonary suspension vials (chiesi ltd) 1 vial</td>
<td>1x</td>
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<tr>
<th>Country</th>
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### Update on 2004 Background Paper, BP 6.23 Neonatal Conditions

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<td>1 bottle</td>
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<td>UK** 357.561260 €</td>
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<td>-</td>
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</table>

**UK** This is the reimbursement price to community pharmacies for dispensing the medicine against a NHS prescription. For branded medicines, the price is the NHS list price, set by the PPRS. For most generic medicines, this is the reimbursement price listed in Part VIII of the Drug Tariff. But where a supplier name is specified on the prescription e.g. omeprazole AAH or a product is not listed in Part VIII, the pharmacist is reimbursed the supplier's list price. The price includes
wholesaler and pharmacy margins that are not regulated. The United Kingdom does not hold information on the manufacturer or wholesale price. Community pharmacies and hospitals may be able to purchase medicines at a discount to these prices. (United Kingdom)
Update on 2004 Background Paper

Background Paper 6.24
Low back pain

By Béatrice Duthey, Ph.D

15 March 2013
Update on 2004 Background Paper, BP 6.24 Low back pain

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Executive Summary

Low back pain is a very common health problem amongst population and a major cause of disability that affects work performances and well-being. Low back pain can be acute, subacute or chronic. Though several risk factors have been identified such as occupational posture, depressive moods, obesity, body height or age, the causes of the onset of low back pain remain obscure and diagnosis difficult to make.

Low back pain affects children to elderly and is a very common reason for medical consultations. The Global Burden of Disease (GBD) 2010 estimated that low back pain is amongst the top ten DALYs (disability-adjusted life years) causing diseases and injuries.

Socioeconomic impacts are considerable in terms of work loss. Estimating the incidence of low back pain is difficult as the incidence of first-ever episodes of low back pain is already high by early adulthood and symptoms tend to recur over time. The lifetime prevalence of non-specific (common) low back pain is estimated at 60–70% in industrialized countries (one-year prevalence 15–45%, adult incidence 5% per year). The prevalence rate for children and adolescents approaches that seen in adults. It then increases and peaks between ages 35 and 55. As the world population ages, low back pain will increase substantially due to the deterioration of disc bones.

Low back pain (LBP) is the leading cause of activity limitation and work absence throughout much of the world, and it causes an enormous economic burden on individuals, families, communities, industry and governments. Several studies have been performed in Europe to evaluate the social economic impact of low back pain. In the United Kingdom, low back pain was identified as the most common cause of disability in young adults: with more than 100 million work days lost per year. In Sweden a survey suggested that low back pain increased the number of work days lost from seven million in 1980 to four times that (28 million) by 1987; however, authors state that social compensation systems might account for some of this increase. In the United States an estimated 149 million days of work per year are lost because of LBP. The condition is therefore costly, with total costs estimated to be between US$ 100 and US$ 200 billion annually, two-thirds of which are due to decreased wages and productivity.

At present low back pain is being treated with analgesics, alternatively rehabilitation can be prescribed. Causes of LBP are rarely being addressed. Disc surgery remains the last option when all other strategies have failed.

European Guidelines for the Management of Chronic non-specific Low Back Pain have been developed by experts in the field and provide guidance for diagnosis and treatment. The European Commission is also funding the project ‘Genodisc’ to identify risks factors, biomarkers and improve diagnosis of low back pain.

Research performed these past few years on biomaterial, growth factors or stem cells in the intra vertebral disc space brings new hopes for delaying the time before surgery.

Also, 3D imaging and using more resistant biomaterials for the development of more adapted disc prosthesis should help better addressing the issue of low back pain.
1. Introduction

Low back pain (LBP) is a very common health problem and affects all ranges of the population, however, its burden is often considered trivial. Low back pain occurs in similar proportions in all cultures, interferes with quality of life and work performance, and is the most common reason for medical consultations. Few cases of back pain are due to specific causes; most cases are non-specific.

As part of the Global Burden of Disease Study (GBD) 2010, the Expert Group showed that low back pain is among the top ten high burden diseases and injuries, with an average number DALYs (disability-adjusted life years) higher than HIV, road injuries, tuberculosis, lung cancer, chronic obstructive pulmonary disease and preterm birth complications.1

1.1 Common symptoms experienced by people with low back pain

Low back pain is defined as pain and discomfort below the the costal margin and above the inferior gluteal folds, with or without referred leg pain. It may be experienced as aching, burning, stabbing, sharp or dull, well-defined, or vague with intensity ranging from mild to severe. The pain may begin suddenly or develop gradually. Non-specific low back pain is defined as low back pain not attributed to recognisable, known specific pathology (e.g. infection, tumour, osteoporosis, ankylosing spondylitis, fracture, inflammatory process, radicular syndrome or cauda equina syndrome). This background paper does not deal with specific and attributable low back pain that results from trauma, osteoporotic fractures, infections, neoplasms, and other mechanical derangements as such causes can be identified and must be dealt with appropriately.

1.2 Low back pain subtypes

Substantial heterogeneity exists among low back pain that can be classified into three categories: chronic, acute and subacute back pain.1

- **Chronic back pain** (CLBP) is defined as low back pain persisting for longer than 7-12 weeks, or after the period of healing or recurring back pain that intermittently affects an individual over a long period of time.
- **Acute back pain** is defined as low back pain lasting for less than 12 weeks.
- **Subacute pain** is defined low back pain lasting between six weeks and three months.

While many patients with LBP recover quickly, LBP commonly follows a recurrent course, with exacerbations occurring over time.

1.3 Causes of low back pain

Low back pain can be due to a number of factors including: individual characteristics, working conditions such as heavy physical work, awkward static and dynamic working postures, as well as manual handling and lifting, lifestyle factors and psychological factors. A minority of cases of low back pain results from trauma to the back, osteoporosis or prolonged corticosteroid use. Relatively less common are vertebral infections, tumors and bone metastasis.
The exact source of low back pain is often difficult to identify. Non-specific back pain is thus a major problem for diagnosis and treatment. Low back pain can be produced by different tissues including muscles, soft connective tissue, ligaments, joint capsules cartilage, and blood vessels. These tissues may be pulled, strained, stretched or sprained and rapidly produce an inflammation with the release of inflammatory chemicals such as cytokines and/or chemokines. These chemicals stimulate the surrounding nerve fibers resulting in the sensation of pain. Inflammatory process perpetuates the process of swelling. A reduction on blood supply to the affected area may occur so that nutrients and oxygen are not optimally delivered and removal of irritating byproducts of inflammation is impaired, creating thereby a feedback loop of inflammation and pain.

The diagnosis of low back pain is complicated because of the complex nature of pain and the nonstandardized approach by physicians to clinical decision making.

1.4 Risk Factors

In approximately 5–15% low back pain can be attributed to a specific cause such as an osteoporotic fracture, neoplasm or infection.\(^1\)\(^2\) For the remaining 85–95% of cases, the specific cause of low back pain is unclear.\(^3\)\(^4\)

1.4.1 Psychological

Psychosocial factors appear to play a substantial role in the frequency of low back pain. Persons with negative affectivity, low levels of social support in the workplace, low level of job control, high psychological demands and work dissatisfaction as well as stress, anxiety, depression are more prone to low back pain.

1.4.2 Body height and weight

Studies demonstrated an association between body height and LBP. Results suggest that being tall is a predictor for back surgery.\(^2\) Taller people appear to have more potential risk for disk instability under external loading.\(^3\) Alterations of facet joints in patients with lumbar disc hernia were shown to be more evident in taller patients.\(^4\)

Several studies have clearly shown that people with high BMI are more prone to LBP. A meta-analysis including 33 studies showed that obesity was associated with increased prevalence of LBP in the past 12 months (pooled odds ratio, OR = 1.33 (95% CI: 1.14-1.54)).\(^5\)

1.4.3 Occupational

In the world, 37% of LBP are attributed to occupation.\(^6\) Professionals who are exposed to vibrations, or long standing positions such as health-care workers, occupational drivers, and construction workers are more prone to LBP. Low back pain is associated with working postures which included bending heavily with one’s trunk, bending and twisting simultaneously with one’s trunk, a bent and twisted posture for long periods, and making repetitive movements with the trunk. This finding was consistent with other studies.\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\) Repetitive twisting or bending with the trunk, as well as prolonged twisting or bending, can increase the risk of LBP because of unrecovered fatigue. To some extent, these results reflect...
that LBP risk may be higher in some industries, in which the workers need to take heavy physical work, or work with awkward posture.

Sociodemographic factors, such as age, lifestyle factors, such as smoking and physical conditioning are other potential risk factors for low back pain.7

2. Size and Nature of Disease Burden

2.1 Incidence and prevalence

Low back pain is well documented to be an extremely common health problem; WHO, whose Community Oriented Programme for the Control of Rheumatic Disease showed convincingly that it is present in similar proportions in several countries. Until recently it was largely thought of as a problem confined to western countries but research performed during the last decade clearly showed that low back pain is also a major problem in low- and middle-income countries.13

As part of the Global Burden of Disease Study (GBD) 2010, Expert Group showed that low back pain is among the top ten high burden diseases and injuries, with an average number of DALYs (disability-adjusted life years) higher than HIV, road injuries, tuberculosis, lung cancer, chronic obstructive pulmonary Disease and preterm birth complications.1

Figure 6.24.1: Absolute DALYs caused by low back pain by age group and European region

Source: Institute of Health Metrics and Evaluation (IHME)
http://ghdx.healthmetricsandevaluation.org
Figure 6.24.2: Absolute DALYs caused by low back pain in the world, by age group

Source: Institute of Health Metrics and Evaluation (IHME)
http://ghdx.healthmetricsandevaluation.org

Figure 6.24.3: DALY rate by European region and gender

Source: Institute of Health Metrics and Evaluation (IHME)
http://ghdx.healthmetricsandevaluation.org

Estimating the incidence of low back pain is difficult as the incidence of first-ever episodes of low back pain is already high by early adulthood and symptoms tend to recur over time. The lifetime prevalence of non-specific (common) low back pain is estimated at 60–70% in industrialized countries (one-year prevalence 15–45%, adult incidence 5% per year). The prevalence rate for children and adolescents approaches that seen in adults.\textsuperscript{14, 15} It then increases and peaks between ages 35 and 55.\textsuperscript{16, 17}
While substantial heterogeneity exists among low back pain epidemiological studies show that low back pain country prevalence ranges from 1.0% to 58.1% (mean: 18.1%; median: 15.0%), and one-year prevalence from 0.8% to 82.5% (mean: 38.1%; median: 37.4%). Due to the heterogeneity of the data, mean estimates need to be interpreted with caution. Longitudinal studies, which measure incidence, are more expensive than cross sectional studies, which measure prevalence. As a result, there is a substantial amount of literature on the prevalence of low back pain, but much less information on low back pain incidence and remission.

Table 6.24.1: Incidence of low back pain in the general population.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Country</th>
<th>Age range (years)</th>
<th>Inclusion criteria at baseline</th>
<th>Case definition</th>
<th>Incidence (%)</th>
<th>Standard error (%)</th>
<th>Risk of bias</th>
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</thead>
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<td>30–60</td>
<td>Never had low back pain</td>
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<td>6.3</td>
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<tr>
<td>Croft et al. [24]</td>
<td>United Kingdom</td>
<td>18–75</td>
<td>Never had low back pain</td>
<td>Low back pain over past year</td>
<td>15.4</td>
<td>0.9</td>
<td>Moderate</td>
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<tr>
<td>Mustard et al. [30]</td>
<td>Canada</td>
<td>21–34</td>
<td>Never had back pain &gt;1 day</td>
<td>Back pain &gt;1 day over past year</td>
<td>7.5</td>
<td>0.6</td>
<td>High</td>
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</tbody>
</table>


In many instances, people with low back pain will go on to have recurrent episodes that may last longer and cause greater disability. Consequently, low back pain can become chronic. In the majority of cases, true remission in the sense that a single episode of low back pain never recurs, is rare.
Studies have found the incidence of low back pain is highest in the third decade, and overall prevalence increases with age until the 60–65 year age group and then gradually declines.

China is the world’s largest developing country with a huge number of occupational populations. The prevalence rates of LBP among the Chinese occupational population were from 26.4% to 84.6%. The latest LBP data obtained from articles written in English in the mainland of China showed that the 1-year prevalence of LBP in rural working populations was 64%.19
2.2 Economic impact: the global societal cost of low back pain

Low back pain is the leading cause of activity limitation and work absence throughout much of the world, and it causes an enormous economic burden on individuals, families, communities, industry and governments.\textsuperscript{20,21,22,23,24,25,26,27}

Several studies have been performed in Europe to evaluate the social economic impact of low back pain. In the United Kingdom, low back pain was identified as the most common cause of disability in young adults: with more than 100 million work days lost per year.\textsuperscript{28} In Sweden a survey suggested that low back pain increased the number of work days lost from seven million in 1980 to four times that (28 million) by 1987; however, authors state that social compensation systems might account for some of this increase. Research scientists found that 35–37\% of workers experienced back pain in the month before their survey, with a peak in the incidence seen among those aged 49–59 years.\textsuperscript{29} Low back pain is the second most common cause of disability in adults from the USA and a common reason for lost work days. An estimated 149 million days of work per year are lost because of LBP.\textsuperscript{30,31,32,33} The condition is costly, with total costs estimated to be between $100 and $200 billion annually, two-thirds of which are due to decreased wages and productivity.\textsuperscript{34,35}

Many patients have self-limited episodes of acute low back pain and do not seek medical care.\textsuperscript{36} However, up to one third of patients report persistent back pain of at least moderate intensity one year after an acute episode, and one in five report substantial limitations in activity.\textsuperscript{37}

Approximately 5\% of the people with back pain disability account for 75\% of the costs associated with low back pain.\textsuperscript{38}

3. Control Strategy

3.1 Diagnosis

Guidelines for the management of acute non specific low back pain in primary care were developed within the framework of the COST ACTION B13 ‘European Guidelines for the Management of Low Back Pain’, issued by the European Commission, Research Directorate-General, Department of Policy, Co-ordination and Strategy. The guidelines were developed by experts in the field of low back pain research in primary care who had been involved in the development of national guidelines for low back pain in their countries. The primary objective of these European evidence-based guidelines was to provide a set of recommendations that can support existing and future national and international guidelines or future updates of existing guidelines.

Diagnosis depends on physical examination. For most patients pain a thorough history taking and brief clinical examination to exclude any other serious disorders causing back pain (tumor, infection, fracture) is sufficient. Low back pain is categorised based on pain distribution, pain behaviour, functional disability and clinical signs.\textsuperscript{7}
Clinical examination can be followed by magnetic resonance imaging, radionuclide scanning, computed tomography, and/or radiography. Recent studies showed however that for adults younger than 50 years of age with no signs or symptoms of systemic disease, diagnostic imaging does not improve treatment of low back pain. For patients 50 years of age and older or those whose findings suggest disc space narrowing, osteophytes and sclerosis, plain radiography and simple laboratory tests are sufficient to make a diagnosis. The authors concluded that advanced imaging should be reserved for patients who are considering surgery or those in whom systemic disease is strongly suspected (level A). The risks of the high doses of radiation in X-rays of the lumbar spine do not justify routine use.

The lack of effective biomarkers makes LBP is difficult to diagnose, track progression of, and monitor improvements in the patient’s condition. These issues are especially important to address because low back pain is a condition that requires long-term careful management, so detailed information regarding the effectiveness of therapies 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 therapies that can reverse the progression of this high-burden condition.

3.2 Management of low back pain

3.2.1 Analgesics

Currently, the main treatment goal for low back pain is to control the pain, maintain function and prevent exacerbation. Low back pain is being treated with analgesics such as paracetamol, NSAIDs or weak opioids. The difficulty is to manage pain when it becomes chronic because of the side events of these medicines on the long term. For example, treatment with opioids can become problematic on a long term basis because of the possible risk of addiction. To reduce the risk of dependence, slow release forms of opioids are preferred to immediate release opioids for the treatment of chronic back pain.\(^{40,41}\)

Table 6.24.3: Classification of non steroidal anti inflammatory medicines.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Products</th>
</tr>
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<tbody>
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<td>Salicylates</td>
<td>Aspirin, diffusinal, salsalate</td>
</tr>
<tr>
<td>Propionic acid derivatives</td>
<td>ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin, loxoprofen</td>
</tr>
<tr>
<td>Enolic acid (oxicam)</td>
<td>Piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam, phenylbutazone</td>
</tr>
<tr>
<td>Fenamic acid derivatives</td>
<td>Mefenamic acid, meclofenamic acid, flufenamic acid, tolkenfamic acid</td>
</tr>
<tr>
<td>Alkanones</td>
<td>Nabumetone</td>
</tr>
<tr>
<td>Acetic acid derivatives</td>
<td>Indomethacin, sulindac, etodolac, ketorolac, diclofenac, nabumetone</td>
</tr>
<tr>
<td>Diaryl heterocyclic compounds</td>
<td>Celecoxib, valdecoxib, rofecoxib, etoricoxib</td>
</tr>
<tr>
<td>Sulphonanilides</td>
<td>Nimesulide</td>
</tr>
<tr>
<td>Others</td>
<td>Licoferone</td>
</tr>
</tbody>
</table>

Source: Kuritski and Samraj 2012.\(^{40}\)
Management of low back pain involves musculoskeletal rearrangement through manipulations by various health care providers. These include physiotherapists, manual therapists, chiropractors, exercise therapists.\textsuperscript{7}

According to the European Guideline for the Management of Chronic non-specific Low Back Pain:\textsuperscript{7}

“\textit{There is moderate evidence that manipulation is superior to sham manipulation for improving short-term pain and function in CLBP (level B).}”

- \textit{There is strong evidence that manipulation and GP care/analgesics are similarly effective in the treatment of CLBP (level A).}

- \textit{There is moderate evidence that spinal manipulation in addition to GP care is more effective than GP care alone in the treatment of CLBP (level B).}

- \textit{There is moderate evidence that spinal manipulation is no less and no more effective than physiotherapy/exercise therapy in the treatment of CLBP (level B).}

- \textit{There is moderate evidence that spinal manipulation is no less and no more effective than back-schools in the treatment of CLBP (level B).}”

An active approach is the best treatment option for acute low back pain. Prolonged bed rest should be avoided as it may increase the risk of chronicity.

Massage, ultrasounds, heat/cold, electrotherapy, laser and traction can substantially improve in certain cases the treatment of low back pain.\textsuperscript{7}

3.2.2 Surgery and intradiscal injection

Often, surgery is offered as an ultimately desperate last measure, but almost always it is unjustifiable and usually fails to provide permanent relief.\textsuperscript{42} Disc herniation and spinal canal narrowing are common in most of the population in their later years, and in most cases, such conditions are not responsible for the pain. Patients undergo surgery, but only rarely are operations successful in alleviating the pain definitively.\textsuperscript{43}

Treatment of intervertebral disc herniations and degenerated discs is still spinal fusion. Mechanical prostheses, which are currently implanted, have medium outcome success and have relatively high re-operation rates. Intradiscal injections of steroids or glucocorticoids have been used to treat discogenic pain or reduce inflammation in the disc. Injections can be potentially dangerous and cause infection (discitis or spondylodiscitis).\textsuperscript{44}

3.2.3 Neuro-reflexotherapy intervention (NRT)

Neuro-reflexotherapy intervention (NRT) is defined as the temporary implantation of epidermal devices in trigger points defined by their innervations to desensitize neurons involved in the persistence of pain, neurogenic inflammation, and muscle contracture.\textsuperscript{45} NRT is performed without anaesthesia, on an outpatient basis. In a systematic review quoted by the European Guidelines for the Management of Chronic Non-Specific Low Back Pain, NRT
was shown to be substantially more effective than a sham procedure in providing pain relief up to 30-45 days.\(^7\)

### 3.2.4 Implants

Implants for closing altered intra vertebral disc are also been used. They act by bridging defects of the intravertebral disc. Several implants are commercially available. The implants reinforce the altered area and therefore prevent contralateral herniation. However, the materials cannot maintain the disc in the long-term. Other types of more resistant materials are under investigation.\(^{46}\)

### 4. Major Problem and Challenges for Disease Control: why does the Disease Burden Persist?

Low back pain is becoming more prevalent in our societies because of a number of factors that could be modified and other inherent to the individuals. Factors such as prolonged sitting position at the work place, lack of exercise, obesity and high body weight account for factors that can be modified.

Other risk factors such as anthropomorphic characteristics, 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, although there is a wide range of analgesics available that relieve pain and improve quality of life for patients.

With the rapidly ageing of the world population, the disease burden of low back pain consequent to deterioration of bones and discs will naturally increase accordingly unless (1) primary prevention efforts such as healthy diet, exercise, and adequate positions at the work place are scaled up around the world and (2) early diagnostics to identify and resolve possible causes of low back pain are clearly identified and can be modified.

There is evidence suggesting that prevention of various consequences of back pain is feasible. However, for those interventions where there is acceptable evidence, the effect sizes are rather modest. The most promising approaches seem to involve physical activity/exercise and appropriate (biopsychosocial) education, and support at the work place.

### 5. Current Pharmaceutical Product “Pipeline” for Low Back Pain treatment

Treatment for low back pain aims to relieve pain, improve functional ability, and prevent recurrence and chronicity. Pharmacological treatments will be prescribed based on the pain intensity and back pain specific functional status. Intervention-specific outcomes may also be relevant, for example behavioural treatment, exercise therapy, antidepressants, and muscle relaxants. The following text is extracted from the European Guidelines for the Management
of Acute non-specific Low Back Pain in primary care. This summarizes the effectiveness of pharmaceutical compounds in treating pain associated to low back pain.

5.1 Paracetamol

Two systematic reviews found strong evidence that paracetamol is not more effective than NSAIDs. There is strong evidence from a systematic review in other situations that analgesics (paracetamol and weak opioids) provide short-term pain relief.

Six RCTs (total n=329) reported on acute low back pain. Three compared analgesics with NSAIDs. Two of these (n=110) found that meptazinol, paracetamol, and diflunisal (an NSAID) reduced pain equally. The third trial found that mefenamic acid reduced pain more than paracetamol, but that aspirin and indomethacin were equally effective.

5.2 NSAIDs

Two systematic reviews found strong evidence that regular NSAIDs relieve pain but have no effect on return to work and natural history or chronicity. NSAIDs do not relieve radicular pain. Different NSAIDs are equally effective. Statistical pooling was only performed for NSAIDs versus placebo in acute low back pain. Compared to placebo, nine RCTs (n=1135) found that NSAIDs increased the number of patients experiencing global improvement (pooled OR after 1 week 2.00, 95% CI 1.35 to 3.00) and reduced the number needing additional analgesic use (pooled OR 0.64, 95% CI 0.45 to 0.91). Four RCTs (n=313) found that NSAIDs did not relieve radicular pain.

When compared to paracetamol, three trials (n=153) found conflicting results. Two RCTs (n=93) found no differences in recovery, and one RCT (n=60) found more pain reduction with mefenamic acid than paracetamol.

Five out of six RCTs (n=399 out of 459) found no differences in pain and overall improvement when comparing muscle relaxant and opioid anagesics with NSAIDs. One RCT (n=60) reported more pain reduction with mefenamic acid than with dextropropoxyphene plus paracetamol.

Three trials (n=461) were done with non-drug treatments. One RCT (n=110) found that NSAIDs improved range-of-motion more than bed rest and led to lesser need for treatment. One trial (n=241) found no statistically significant difference. Two studies (n=354) found no differences between NSAIDs and physiotherapy or spinal manipulation in pain and mobility.

Fifteen RCTs (n=1490) found no difference in efficacy of different NSAIDs when compared to one another. One recent trial (n=104) found somewhat better improvement of functioning with nimesulide, a COX-2 inhibitor, compared with ibuprofen 600 mg, but no differences on pain relief.

5.3 Muscle relaxants

Three systematic reviews (24 RCTs; n=1662) found strong evidence that muscle relaxants reduce pain and that different types are equally effective.
Twenty-four trials on acute low back pain were identified. Results showed that there is strong evidence that any of these muscle relaxants (tizanidine, cyclobenzaprine, dantrolene, carisoprodol, baclofen, orphenadrine, diazepam) are more effective than placebo for patients with acute LBP on short-term pain relief. The one low quality trial on benzodiazepines for acute LBP showed that there is limited evidence (one trial; 50 people) that an intramuscular injection of diazepam followed by oral diazepam for 5 days is more effective than placebo on short-term pain relief and better overall improvement (level C). The pooled RR (relative risk) for non-benzodiazepines versus placebo after two to four days was 0.80 [95% CI; 0.71 to 0.89] for pain relief and 0.49 [95% CI; 0.25 to 0.95] for global efficacy (level A). The various muscle relaxants were found to be similar in performance.

5.4 Opioids
Opioids can be also prescribed for the treatment of low back pain. The WHO's analgesic ladder, originally developed for the treatment of cancer pain, is applicable here. The WHO's analgesic ladder recommends the following ladder scheme in using opioids for pain treatment:
• Non-opioid analgesics with adjuvant therapy where needed;
• Addition of a weak opioid;
• Where necessary, a stronger opioid in addition to the non-opioid and adjuvant therapy

Clinicians must prescribe opioids following specific guidelines and make sure that their patients do not fall on habituation and addiction.

5.5 Antidepressants
Small doses of tricyclic antidepressants (mood elevators) given up to an hour before bedtime can help regulate the sleep cycle, which seems to help in some cases. Psychotropic drugs are otherwise of no avail.

6. Past/Current Research into New Therapeutic Options for Low Back Pain
Currently all the treatment advances in low back pain offer palliative care and help to reduce the symptoms of pain and help mobility. There are at present no new drugs that can prevent, halt, or reverse low back pain progression. Several new technologies, devices, as well as advances in the area of stem cell therapy offer alternative and new hope for the treatment of low back pain. The following information summarizes the highlights of treatment of low back pain:

Intervertebral disc (IVD) degeneration plays an important role in its epidemiology. Recent approaches for biologic repair and regeneration of the IVD are under investigation including cell transplantation, administration of growth factors, and gene therapy. Mesenchymal stem cells (MSCs) may be ideal candidates for cell therapies and tissue
engineering because of their high proliferation rate and potential for multilineage Differentiation.\textsuperscript{61,62}

Healthy discs function as load-absorbers between all vertebrae, allowing for bending, flexion and torsion of the spine. As the global population ages, the incidence of intervertebral disc (IVD) degeneration and low back pain (LBP) increases. The occurrence of LBP has been associated in many cases with degenerative disc disease. New treatments are being investigated to normalise disc cell homeostasis and restore full disc function.

Discs can be subdivided into two different tissue types, the nucleus pulposus (NP) and the annulus fibrosus (AF). The AF is a ring of highly oriented densely packed collagen fibril lamellae. It anchors to the cartilaginous endplates connecting to the vertebral bodies and keeps the NP in the centre position. At present, when discs deteriorate, the IVD are excised and the vertebral bodies are fused. The surgery is very traumatic and the non-biological prosthesis wears with time. A solution using tissue engineering approaches for disc regeneration and repair is the recent focus to restore the disc function by the introduction of functional cells and supporting biomaterials to augment or replace the degenerated disc.

One of the characteristic of disc degeneration is the loss of matrix in the nucleus pulposus (NP). There are several strategies under investigations to restore the function of the nucleus pulposus such as injection of shock absorbing hydrogels and matrix producing cells and molecules which stimulate the endogenous cells to replenish the lost matrix. Treatment strategies may vary depending on the severity of the degeneration.

6.1 Repair of the nucleus pulposus using hydrogels

Photo-crosslinking of natural polymers, performed by chemical reactions, generates considerable amount of heat. A recent study has shown good cytocompatibility and injectability of the polymer in combination with human disc cells for NP repair.\textsuperscript{63,64,65} Polymers enriched with collagen, hyaluronic acid (HA), and chondroitin sulfate are potential candidates as an injectable system for NP repair.\textsuperscript{66,67} Although tested in animal models only, hyaluronic acid appears to be a good candidate material as it is an abundant water absorption molecule, which is able to dehydrate and rehydrate under a range of mechanical loading parameters. However, hyaluronic acid and collagen are degraded relatively fast in vivo, further research is necessary to ensure better stability and mechanical properties.\textsuperscript{68}
Table 6.24.4: Overview of potential molecular/growth factor for IVD treatment. (adapted from Chan et al.).

<table>
<thead>
<tr>
<th>Protein</th>
<th>Overview of potential molecular/growth factor for IVD treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercellular regulator</td>
<td>SOX-9LIM mineralization protein (LMP-1) \nDexamethasone \nTissue inhibitor of matrix metalloproteinase (TIMP) \nSynthetic peptide (Link-N)</td>
</tr>
<tr>
<td>Inflammatory cytokines antagonist</td>
<td>Interleukin-1 receptor antagonist (IL-1 ra) \nTumor necrosis factor antagonist (TNF-a)</td>
</tr>
<tr>
<td>Growth factor</td>
<td>Growth and differentiation factor-5 (GDF-5) or (BMP-14) \nInsulin-like growth factor (IGF-1) \nTransforming growth factor ? (TGF-?) \nEpidermal growth factor (EGF) \nOsteogenic protein-1 (OP-1)/ BMP-7 \nBone morphogenetic protein (BMP-2) \nPlatelet-rich plasma (PRP) \nPlatelet derived growth factor (PDGF) \nBasic fibroblast growth factor (bFGF)</td>
</tr>
</tbody>
</table>


6.2 **Stem cell therapy**

Stem cell research offers exciting possibilities for restoring intervertebral discs. Although much of this research has been performed on animal models they offer exciting possibilities for regenerating altered intervertebral discs. Stem cells can be obtained from autologous transplant mainly from the bone marrow, but also from adipose-tissue and synovium. An increasing number of studies have been published on the use of mesenchymal stem cells (MSC) for disc regeneration. These cells can be obtained from the bone marrow. The autologous transplant prevents any risk of immunoreaction and showed promising results in terms of improvement of pain and disability when injected in the IVD.

The IVD environment is a quite hostile environment for such cells to grow as there is low oxygen content, high lactic acid concentration, and relatively high hydrostatic pressure. Several strategies are being investigated to improve the survival of the injected MSC by preconditioning or using different hydrogel cell carriers.

Researchers have hypothesised that the IVD (invertebral disc) might itself contain a population of “intervertebral-disc stem cells” that could offer a better alternative since they are perfectly adapted to these particular conditions.
6.3 Modulation of matrix production through IVD injection of growth factors

Another area of investigation for disc regeneration is the use of molecules that could help regenerate the extracellular matrix in the IVD. These molecules include growth factors, inflammatory cytokine antagonists, proteinase inhibitors or intercellular, bone morphogenetic protein (BMP-2, -7, -14), platelet derived growth factor (PDGF), platelet-rich plasma (PRP), and transforming growth factor beta (TGF-β) (Table 6.24.4). More research has to be done in this area to improve the delivery systems, and a longer term delivery within the IVD.78

6.4 Disc renutrition

To ensure that the injected stem cells and other growth promoting factors can effectively replenish the altered IVD, sufficient nutrients and oxygen must be supplied to the targeted area. In this regard, several molecules have been identified as able to increase blood flow to the nerve with success, such as a receptor antagonist 5-hydroxytryptamine (5-HT) and nimodipine, which enhances vascularisation of the cartilage endplates in the disc.79,80

6.5 Disc replacement using synthetic material

Replacing the altered annulus fibrosus instead of the whole disc by injecting shock absorbing materials is another alternative that is being investigated. Injection of material of high compressive resistance such as polyacrylonitrile and polyacrylamide materials made of silicone, polymethyl methacrylate (PMMA) – hydroxyethyl methacrylate (pHEMA), polyurethane, polyvinyl alcohol (PVA) based polymer, N-vinyl-2-pyrrolidinone copolymerised with 2-(40-iodobenzoyl)-oxo-ethyl methacrylate and photo-crosslinked gellan gum – glycidyl methacrylate are being investigated. Other materials that could bridge the deteriorated annulus fibrosus or serve as cell carrier are also under research.81
Table 6.24.5. Overview of classical biomaterials and examples used for intervertebral disc engineering. (adapted from Chan et al.)

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic degradable polymers</td>
<td>Polylactides/glycolides</td>
</tr>
<tr>
<td></td>
<td>Polycaprolactone</td>
</tr>
<tr>
<td></td>
<td>Polyhydroxyalkanoates</td>
</tr>
<tr>
<td></td>
<td>Poly(propylene fumarates)</td>
</tr>
<tr>
<td>Natural biopolymers</td>
<td>Proteins</td>
</tr>
<tr>
<td></td>
<td>Collagen</td>
</tr>
<tr>
<td></td>
<td>Elastin</td>
</tr>
<tr>
<td></td>
<td>Fibrin/fibrinogen</td>
</tr>
<tr>
<td></td>
<td>Silk</td>
</tr>
<tr>
<td></td>
<td>Polysaccharides</td>
</tr>
<tr>
<td></td>
<td>Alginites</td>
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<tr>
<td></td>
<td>Chitosan</td>
</tr>
<tr>
<td></td>
<td>Hyaluronic acid</td>
</tr>
<tr>
<td>Bioactive ceramics</td>
<td>Calcium phosphates</td>
</tr>
<tr>
<td></td>
<td>Bioactive glasses</td>
</tr>
<tr>
<td>Composites</td>
<td>Synthetic polymers/bioactive ceramics</td>
</tr>
<tr>
<td></td>
<td>Biopolymers/bioactive ceramics</td>
</tr>
<tr>
<td>Tissue derived ECM</td>
<td>Small intestine submucosa</td>
</tr>
<tr>
<td></td>
<td>Skin extracellular matrix</td>
</tr>
</tbody>
</table>


7. Gaps between Current Research and Potential Research Issues That Could Make a Difference

Opportunities for research can be divided into three categories:
- a) Identify relevant sub-groups of patients with a high risk of chronicity
- b) Prolong the treatment window before surgery
- c) Improve research in disc replacement therapy

7.1 Identify relevant sub-groups of patients with a high risk of chronicity

There have been a number of clinical trials within the past ten years, which have identified risks factors such as lifting of heavy loads, long standing positions, vibrations, work related factors, psychosocial distress, depressive mood, as well as body height, obesity, and age. However, there is a lack of research in the area of anthropometric criteria and genetics.
Posture in humans is affected by several factors including anatomical structural impairments, postural habits, and occupations. Posture prevents the body from injuries and deformations that can lead to muscle stress and pain.

It would be important to establish a relation between postural balance and anthropometric measurements for each individual and develop programs to determine how to correct postural deviations accordingly. Imaging as well as clinical assessments should help determine anthropomorphic parameters that lead to low back pain (muscle and bones length, density, ratios between BMI and bones, etc).

Prevention of low back pain at an early age and thorough lifetime should help lower substantially the burden of disease. Screenings of children and adolescents at school and adults at the work place and proposing exercise rehabilitation that would halt the progression of spinal deviations and reduce the rates of chronicity.

As BMI plays an important role in the onset of low back pain, it would be important to better sensitize the populations to the importance of a healthy diet.

Low back pain consecutive to occupational postures has been the subject of several studies. Ergonomic types of furniture are being proposed to workers and school children. However, these measures are not systematically applied in reality and employers are rarely aware of the impact that this can have on low back pain and work loss. Ergonomic furniture at the work place has been shown to substantially reduce the musculoskeletal stress and maintain a more physiological posture.

7.2 Prolonging the treatment window before surgery

One of the fast growing areas of research for low back pain therapies is applications of stem cells and biomaterials. 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 are the best mechanisms of action, which patients will benefit most, when the optimal timing to apply the stem cells is, and what would be the best way to deliver and track the cells. More research and funding are urgently needed in this emerging area of research.

The disease burden of low back pain 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.

7.3 Surgery and disc replacement

Although surgery for disc replacement already exists, considerable improvement could be made in the area of prostheses with the development of new more adapted and resistant materials and the 3D imaging technologies.
8. **European Union Funding Opportunities for Low Back Pain**

European Guidelines were published in 2004. These guidelines are intended to offer guidance on diagnosis and treatment of chronic non-specific low back pain. They aim to inform professional associations, health care providers, health promotion agencies, industry/employers, educationalists, and policy makers in Europe.

The following text has been extracted from the European Guidelines:

“The primary objective of the European evidence-based guidelines is to provide a set of recommendations that can support existing and future national and international guidelines or future updates of existing back pain guidelines. This particular guideline intends to foster a realistic approach to improving the treatment of common (non-specific) chronic low back pain (CLBP) in Europe by:

1. Providing recommendations on strategies to manage chronic low back pain and/or its consequences in the general population and in workers.
2. Ensuring an evidence-based approach through the use of systematic reviews and existing evidence-based guidelines, supplemented (where necessary) by individual scientific studies.
3. Providing recommendations that are generally acceptable to a wide range of professions and agencies in all participating countries.
4. Enabling a multidisciplinary approach, stimulating collaboration between the various players potentially involved in treatment, thus promoting consistency across countries in Europe.
5. Identifying ineffective interventions to limit their use.
6. Highlighting areas where more research is needed.

A research project called Genodisc under the FP7 programme is being funded by the European Commission with a total budget of 2,997,144 Euros.

The following text has been extracted from the Educell (an SME that is a participant in the Genodisc consortium) website:

“Genodisc aims to contribute to improvement of patient care through improving diagnosis of disc-related pathologies both by more effective utilisation of present diagnostic information and by developing novel diagnostic tools. Through these new diagnostic methods, it aims to select patients at risk of chronic low back pain and spinal stenosis. It also aims to develop criteria for selecting patients who will benefit from newly emerging biological therapies for treating disc degeneration. The scientific advances underpinning improved diagnosis will arise from genotyping carefully phenotyped patients, from research into the processes of disc degeneration and from models of how these molecular processes lead to disc failure. This research will potentially provide biomarkers which will increase diagnostic specificity and provide targets for development of drug therapies. (...) The researchers include surgeons and other clinicians as well as research scientists specialising in genetics, cell physiology, regenerative medicine, engineering and computational analysis. The research will be led by a group from the University of Oxford but carried out in nine countries including the UK, Israel, Germany, Finland, Greece, the Netherlands, Hungary, Italy and Slovenia. Educell, a Slovenian biotechnology company and a 'Tissue Establishment', has also been invited by Dr Jill Urban from the University of Oxford - coordinator of Genodisc, to participate in the project. Research in Educell is led by Dr Nevenka Kregar Velikonja and Dr Mirjam Fröhlich and focuses on one of novel potential repair
treatments, which is development of tissue engineering approach aiming for functional and long lasting replacement of the removed damaged nucleus pulposus tissue. Genodisc recruits thousands of patients into the study as large numbers are required to determine any genetic link to complex disorders like back pain.”

Future research funded by the European Commission should be on carefully chosen topics that can make important contributions to improving care and prevention for low back pain. Future areas for public sector research to explore include; (a) searching for biomarkers (b) searching for anthropometric risk factors and adapted rehabilitation (c) development of biomaterials and (d) stem cell research.

9. Conclusions

Back pain is not a disease but a constellation of symptoms which origins remain in most cases unknown even though risks factors have been identified. Low back pain is disabling and causes enormous socioeconomic impacts on societies. Treatments for now are focused on reducing the pain. Back pain is both a major cause of temporary disability and a challenge to medical and surgical treatment decisions. It imposes high socio-economic burden in modern western countries, since it not only affects the elderly population but also the working population from 25–60 years.

The management of patients with low back pain requires multiple interventions, an accurate initial diagnosis, close monitoring of potential complications, and appropriate rehabilitation by trained professionals.

There is a still long way to go to improve diagnosis and identify other potential risks factors. As the world population ages, low back pain burden of disease will increase substantially. If surgery and discs replacement therapies remain at present the last option to relieve when all other strategies have failed, new developments in 3D imaging, biomaterials and disc renutrition or stem cell therapies may bring new hope for the treatment of low back pain.

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Update on 2004 Background Paper, BP 6.24 Low back pain