GLOBAL REPORT
FOR RESEARCH ON INFECTIOUS DISEASES OF POVERTY

2012

WITH FINANCIAL SUPPORT OF

European Union

World Health Organization

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

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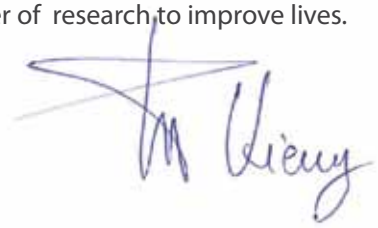
Foreword

Infectious diseases remain major causes of ill health among poor people. Almost 3 billion people live on less than US$ 2 a day, and they continue to be at the greatest risk for these diseases. How can this be possible when global health funding is increasing and new drugs and other health tools are being developed? How is research being prioritized to meet these needs, and can it be done better?

The *Global Report* is an important tool in raising these questions and providing some ideas. Its value is in its cross-disciplinary perspective, bringing together issues from environmental changes, lack of innovation support in low and middle income countries, poor health systems and inequitable funding patterns. While the report focuses on infectious diseases of poverty, many of the issues raised are also relevant for other communicable and non-communicable diseases. It is essential reading for policy-makers, funders and research leaders.

TDR, the Special Programme for Research and Training in Tropical Diseases, which initiated this independent report and brought together worldwide experts to author it, is one of two Special Programmes based at and executed by the World Health Organization (WHO). The *Global Report* provides valuable contributions to meet the goals of WHO's Research for Health Strategy, which was adopted at the 63rd World Health Assembly in 2010.

National, regional and international stakeholders were invited by TDR to come together to identify research priorities so that they can own these priorities and take them forward. My hope is that the discussions generated from this report will help make important changes, so that we break the terrible cycle of poverty and disease and start to experience the real power of research to improve lives.



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How the report was developed

The world's poor are still not reaping the full benefits of research outcomes, despite an increasing global commitment to health research. While research funding to combat HIV/AIDS, malaria and TB has increased, other infectious diseases associated with poverty, such as Chagas disease, leishmaniasis, human African trypanosomiasis and Buruli ulcer, have not had the same attention. This key fact is at the heart of this report, which began after TDR initiated a concerted Stewardship effort to investigate and support more equitable approaches to funding and support for research.

Supported by the European Commission, TDR set up a global "Think Tank" of over 130 experts in 2008, and from the outset, the concept was to ensure disease endemic country input, with these countries playing active roles in developing the research agenda on infectious diseases of poverty.

Experts were convened from across the globe to work in ten disease-specific and thematic reference groups to carry out a review and consultation process and identify top research priorities. Each reference group was jointly led by a disease endemic country and international chair or co-chair, and each was hosted by a disease endemic country with WHO country or regional offices acting as the secretariat. The analysis and research priorities developed by these expert groups and followed by regional and national consultations with stakeholders and workshops underpins this *Global Report*.

Developed over three years and in three phases (see Box 1), The *Global Report for Research on Infectious Diseases of Poverty* identifies research-related actions that policy-makers, funders and researchers should focus on if the public health challenges of infectious diseases of poverty are to be met. The report details the drivers of infectious diseases in poor populations and highlights how advances in science and technology can be used to meet the challenges of controlling these diseases.

Themes selected for close attention in this report represent some of the most contemporary global discussions as they relate to infectious diseases of poverty, the aim being to draw particular attention to their implications for infectious

BOX 1. GLOBAL REPORT FOR RESEARCH ON INFECTIOUS DISEASES OF POVERTY: DEVELOPMENT PHASES

PHASE I: Expert discussions and literature reviews

Convened by the Special Programme for Research and Training in Tropical Diseases (TDR), a "Think Tank" of world experts reviewed and deliberated on infectious diseases of poverty – particularly social and economic drivers and the communities affected – to produce 10 disease and thematic reference group reports identifying top research priorities.

PHASE II: National, regional and global stakeholder consultations

A cross-section of national, regional and global stakeholders, including researchers, funders, decision-makers and representatives from public and private organizations, were convened in a forum hosted by ministers of health or regional health organization leaders for each reference group. Here, the findings and recommendations emerging from each Think Tank report were discussed and debated. The outcomes and input from this process were used to update and finalize the priorities outlined in the Think Tank reports.

PHASE III: Synthesis of ideas

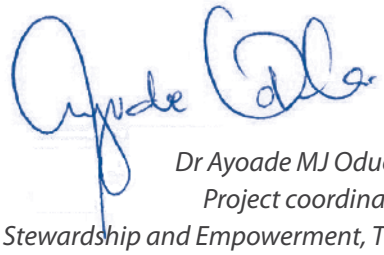
International leaders were invited to be authors of the *Global Report* and included former ministers of health and of science and technology, policy-makers, research leaders and experts in public health. Supported by research fellows, these authors reviewed the 10 Think Tank reports, conducted additional literature research, and worked together to agree on core themes and develop options for actions.

The TDR secretariat and external consultants provided support for the development, writing and production phases of the *Global Report*.

diseases of poverty. They include "innovation and new technologies" in line with the call for an agreed set of research priorities in the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPOA)[1]. The focus on "environment and climate change" highlights disease vulnerability of poor communities, while the "health delivery systems for universal coverage" theme was chosen following the call to action from the Bamako Global Ministerial Forum on Research for Health, November 2008[2], (further addressed by deliberations at the Health Systems Research and Universal Coverage Symposium in 2010)[3].

Presented in six chapters, this report is a distillation of the evidence, ideas and priorities that emerged from the stewardship initiative and provides an ambitious set of options for action. The report is essential reading for policy-makers, funders and research leaders.

Implementation of the actions proposed in this report should help improve current research prioritization processes, guide investment strategies and enhance commitment to using research to promote global health equity. If, like the MDGs, these options for action are focused on by policy-makers, funders and researchers, they should lead to well-planned, effective, and powerful health interventions. The task now is to develop and focus attention on key actions that are most likely to have a significant public health impact on poor populations.



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1 http://www.who.int/phi/implementation/phi_globstat_action/en/, accessed 20 February 2012.

2 http://www.tropika.net/svc/specials/bamako2008/call-for-action/call, accessed 20 February 2012.

3 http://www.hsr-symposium.org/hsr2010/, accessed 20 February 2012.

Acknowledgements

The *Global Report* was initiated and facilitated by TDR, the Special Programme for Research and Training in Tropical Diseases, based on wide contributions from stakeholders at various stages of the work. Under the leadership of the TDR Stewardship function, high level experts from around the globe were brought together for research, analysis and consultations. The result is an independent publication comprising different viewpoints written by expert authors in each chapter.

Much valuable advice and support was received from the TDR Think Tank members, chairs and co-chairs, who prepared the 10 disease and thematic reference group reports that provided the technical foundation for this report. Two major report development workshops were organized in Bellagio (July 2010) and Shanghai (January 2011).

Consultations on the report findings were held with national and regional experts and policy-makers at World Health Organization regional and country offices. The report was also peer reviewed by external consultants and reviewed by TDR's Scientific and Technical Advisory Committee (STAC) and TDR co-sponsoring bodies: UNICEF, UNDP, the World Bank and WHO.

Report editors were Dr Margaret Harris and Dr Julie N Reza, with further editing and proofreading provided by Jo Woodhead and Tony Murdoch. Graphic design and guidance on illustrations in the report was provided by Lisa Schwarb.

The Stewardship team which facilitated this work include: Dr Ayoade Oduola, (Stewardship Coordinator), Dr Shenglan Tang, Ms Edith Certain, Dr Deborah Kioy, Dr A Lee Willingham, Dr Michael Wilson, Dr Johannes Sommerfeld, Ms Lynn Hollies and Ms Elisabetta Dessi.

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The *Global Report* was funded by TDR and the European Commission. Additional financial and structural support was provided by the Rockefeller Foundation, which hosted the first drafting meeting at its Bellagio Center, and the People's Republic of China, which co-hosted a stakeholder consultation and the fourth production meeting. Hughes Hall, University of Cambridge, UK, also hosted a production workshop.

Abbreviations

ACT	artemisinin-based combination therapy
Aeras	Aeras Global TB Vaccine Foundation
ANDI	African Network for Drugs and Diagnostics Innovation
APOC	African Programme for Onchocerciasis Control
BIREME	Biblioteca Regional de Medicina, Brazil
BRAC	Bangladeshi Rural Advancement Committee
BSE	bovine spongiform encephalopathy
CARTA	Consortium for Advanced Research Training in Africa
CDT	community-directed treatment
CDTI	community-directed treatment with ivermectin
COHRED	Council on Health Research for Development
CONICET	National Council for Scientific and Technical Research, Argentina
DALY	disability-adjusted life-year
DDT	dichlorodiphenyltrichloroethane
DFID	Department for International Development (UK)
DNDi	Drugs for Neglected Diseases initiative
EDCTP	European and Developing Countries Clinical Trials Partnership
EPI	Expanded Programme on Immunization
ERR	economic rate of return
EVIPNet	Evidence-Informed Policy Network
FAO	Food and Agriculture Organization of the United Nations
FIND	Foundation for Innovative New Diagnostics
FIOCRUZ	Oswaldo Cruz Foundation
GAELF	Global Alliance to Eliminate Lymphatic Filariasis
Gates Foundation	The Bill & Melinda Gates Foundation
GBS	general budget support
GIZ	Deutsche Gesellschaft für Internationale Zusammenarbeit
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GREP	The Global Rinderpest Eradication Programme
GSPOA	Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property
HHVI	Human Hookworm Vaccine Initiative
IAVI	International AIDS Vaccine Initiative
ICMR	Indian Council of Medical Research
IMF	International Monetary Fund
IPM	International Partnership for Microbicides
LMICs	low and middle-income countries
MDG	Millennium Development Goal

MPI	Multidimensional Poverty Index
MDR-TB	multidrug-resistant TB
MEXT	Ministry of Education, Culture, Sports, Science and Technology
MMV	Medicines for Malaria Venture
MPI	Multidimensional Poverty Index
MRC	Medical Research Council (UK)
NCD	noncommunicable disease
NGO	nongovernmental organizations
NHMRC	National Health and Medical Research Council
NIH	National Institutes of Health (USA)
NTD	neglected tropical disease
OECD	Organisation for Economic Co-operation and Development
ORS	oral rehydration salts
OTEP	Oral Therapy Extension Programme
PATH	Program for Appropriate Technology in Health
PEPFAR	President's Emergency Plan for AIDS Relief (USA)
PDP	product development partnership
PPP	public–private partnership
RBM	Roll Back Malaria
R&D	research and development
SARS	severe acute respiratory syndrome
SIDA	Swedish International Development Cooperation
SWAps	sector-wide approaches
TB	tuberculosis
TB Alliance	The Global Alliance for TB Drug Development
TDR	The Special Programme for Research and Training in Tropical Diseases
TREES	Tropical Ecosystem Environment Observation by Satellites
TRIPS	trade-related aspects of intellectual property rights
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
XDR-TB	Extensively drug-resistant TB

Summary

Infectious diseases remain key agents of the debilitating poverty afflicting so much of the world today. Each year these diseases kill almost 9 million people, many of them children under five, and they also cause enormous burdens through life-long disability. Stepping up research into their causes and how to effectively treat them and prevent them from spreading could have an enormous impact on efforts to lift people out of poverty and to build a better world for future generations.

The *Global Report for Research for Infectious Diseases of Poverty* is an independent publication comprising different viewpoints written by expert authors in each chapter. It was initiated and facilitated by TDR, the Special Programme for Research and Training in Tropical Diseases, supported by the European Commission, and based on wide contributions from stakeholders at various stages of the work. It offers new ways of improving public health in low and middle income countries, with research as the compelling foundation and driver for policies.

The first chapter sets the context and outlines ten areas where research on infectious diseases of poverty can make major improvements; these form the framework for the rest of the report. The next three chapters take these ten areas forward by focusing on specific themes: the environment, health systems, and innovation and technology. A fifth chapter discusses the research funding landscape while the final sixth chapter considers the issues and evidence presented in the rest of the report to propose high level actions, including the best research strategies against infectious diseases of poverty.

Implementation of the actions proposed in this report should help improve current research prioritization processes, guide investment strategies and enhance commitment to using research to promote global health equity. If, like the Millennium Development Goals, these options for action are focused on by policy-makers, funders and researchers, they should lead to well-planned, effective, and powerful health interventions and have a real chance of saving millions of lives in years to come.

1 Why research infectious diseases of poverty?

IN CHAPTER 1:

- Poverty and infectious disease – a problematic relationship
- Infectious disease – the true burden on communities
- The value of research: new ways to end old diseases
- Moving beyond the Millennium Development Goals
- The cost of inaction – social and economic consequences
- Tackling disease – a need for investment
- Ten reasons to research infectious diseases of poverty

1

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REPORT FELLOW

ALLISON THORPE

Research is the key to making things happen for poor populations. This introductory chapter of the *Global Report* examines the need for research into the infectious diseases that disproportionately affect poor and marginalized communities – the so-called "infectious diseases of poverty". It examines the link between poverty and disease and outlines ten reasons to support research for such diseases. Such research represents unfinished business of global relevance, work that the world can no longer afford to neglect.

According to the latest published data in 2012, infectious (including parasitic) diseases were together responsible for the death of more than 8.7 million people worldwide in 2008 (*1*). The majority of these deaths were of poor people living in low and middle-income countries, with many of the deaths occurring in children under five years of age. Given the sketchy data, misdiagnosis and under-detection that are typical of health systems in impoverished areas, these numbers are almost certainly underestimated.

Infectious diseases have shaped societies, driven conflict and spawned the marginalization of infected individuals and communities throughout history. Today they are significant agents in the appalling poverty afflicting so much of the world. Their impact is felt not only in massive loss of life but also in high-levels of morbidity and the accompanying impact on families, communities and weak and under-resourced health systems in low and middle-income countries. Stepping up research into the causes of infectious diseases and how to treat them effectively and prevent them from spreading would, if acted on, have an enormous impact on efforts to lift people out of poverty and would help build a better world for future generations.

Infectious diseases have shaped societies, driven conflict and spawned the marginalization of infected individuals and communities throughout history. Today they are significant agents in the appalling poverty afflicting so much of the world.

Poverty and infectious disease – a problematic relationship

According to The World Bank, the global rate of extreme poverty (less than US$ 1.25 a day) has been falling over the past two decades and will likely meet the Millennium Development Goal (MDG) for 2015 (*2–5*). Much of this improvement reflects rapid economic growth in China and India, yet many African countries with a high burden of infectious diseases are lagging behind. For example, almost 50% of African countries are far from halving extreme poverty.

However, from a global health perspective, often there are criteria broader than income with which to determine who is actually "living in poverty". Social and economic conditions underpin poverty and can directly and indirectly affect health status and health outcomes. Major epidemics emerge and chronic conditions cluster and persist wherever poverty is widespread. Lack of food, shelter, security and social protection make people more vulnerable to infections, while affected populations are often unable to obtain even the most basic means of prevention and care. Poverty creates conditions that favour the spread of infectious diseases and prevents affected populations from obtaining adequate access to prevention and care. Ultimately, these diseases – infectious diseases of poverty (see Box 1.1) – disproportionately affect people living in poor or marginalized communities. Social, economic and biological factors interact to drive a vicious cycle of poverty and disease from which, for many people, there is "no escape". As stated in the report of the Commission on Social Determinants of Health (*6*): "Poverty is not only lack of income. The implication, both of the social gradient in health and the poor health of the poorest of the poor, is that health inequity is caused by the unequal distribution of income, goods, and services and of the consequent chance of leading a flourishing life. This … is not in any sense a 'natural' phenomenon."

BOX 1.1. INFECTIOUS DISEASES OF POVERTY

Infectious diseases are caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi. The diseases can be spread, directly or indirectly, from one person to another[1].

"Infectious diseases of poverty" is an umbrella term used to describe a number of diseases which are known to be more prevalent among poorer populations, rather than a definitive group of diseases. It is an overarching concept, recognizing the need to focus on the poor and vulnerable, who have less power to intervene. Many such diseases are also considered "neglected tropical diseases", as defined by WHO (see list below). Infectious diseases of poverty are not restricted to low and middle-income countries, but manifest in poor populations globally. Apart from TB, malaria and HIV/AIDS, many other infectious diseases have not been high on the global agenda. However, an increasing number of organizations and partnerships are now engaged in their control.

Main neglected tropical diseases (*6*) as identified by WHO are listed below:

- dengue
- rabies
- trachoma
- Buruli ulcer
- endemic treponematoses (including yaws)
- leprosy
- chagas disease (American trypanosomiasis)
- human African trypanosomiasis (sleeping sickness)
- leishmaniasis
- cysticercosis
- dracunculiasis (Guinea-worm disease)
- echinococcosis
- foodborne trematode infections
- lymphatic filariasis (elephantiasis)
- onchocerciasis (river blindness)
- schistosomiasis (bilharziasis)
- soil-transmitted helminthiases (intestinal parasitic worms)

Infectious diseases do not respect socio-economic status. Biologically, we are all at risk – but the risk is not evenly distributed. People already living in social and economic deprivation have a greater exposure to the risk factors for disease, and the economic consequences of living with chronic infectious conditions are often more serious. Investment in controlling the spread of infectious and parasitic diseases will have a powerful impact on global human, social and economic development.

Infectious disease – the true burden on communities

For the working poor, the economic impact of infectious diseases can be catastrophic. Not only are infectious diseases causally linked to conditions of poverty; they can actually make people poor. For example, a study in Orissa, India showed that people with chronic lymphatic filariasis lost 68 working days per year and that their families spent more on treatment than the average government per capita expenditure on health (*21*). Thus, families that experience such a disease not only have death to fear but also the cost of illness in terms of treatment and lost working days. This easily perpetuates the vicious cycle of poverty and infection.

1 Infectious diseases. http://www.who.int/topics/infectious_diseases/en/, accessed 13 February 2012.

TABLE 1.1. RELATIONSHIP BETWEEN INFECTIOUS DISEASES AND POVERTY

Infectious diseases	Risks
...are a proxy for poverty and disadvantage (*7*)	Risk factors are shaped by the conditions in which people live and work, particularly poverty, conflict, gender and education levels (*8, 9*). Infectious diseases contribute to lifelong disadvantage in already disadvantaged groups. For example, the often-devastating effects on learning ability of worm infections and schistosomiasis acquired at an early age have lifelong detrimental consequences (*10, 11*).
...affect populations with low visibility and little political voice (*7*)	Infectious diseases are prevalent among populations living in conflict and war zones, internally displaced populations, refugees and those affected by the consequences of natural disasters.
...cause stigma and discrimination (*7*)	People suffering from infectious diseases (such as Buruli ulcer) often experience stigma and ostracization from society. Reasons for this can include fear of the disease or the belief that it is self-inflicted. This stigmatization can have broad economic consequences for an affected individual, particularly if that person is unable to get work as a result.
...impose a heavy health and economic burden	Infectious diseases place a substantial health and economic burden on poor populations in Africa, Asia and Latin America (*12, 13*). For example, malaria is the leading cause of mortality in children under five years of age in Africa, constituting one tenth of the continent's overall disease burden. In areas with high malaria transmission it accounts for 40% of public health expenditure, 30–50% of inpatient admissions and up to 50% of outpatient visits (*14*)[2]. Diarrhoeal diseases, respiratory infections and malaria are all closely associated with childhood mortality (*11, 15, 16, 17*). Each year, rotavirus, a common cause of childhood diarrhoea, kills over half a million children under the age of five. Most of these deaths occur in the world's poorest countries (*15*).
...are low on many research funders' agendas	While there is an urgent need for innovative new tools and technologies to combat infectious diseases, the perceived absence of a market means that limited funding has been available to develop them. Of 1393 new chemical entities introduced between 1975 and 1999, only 16 targeted "tropical diseases" or tuberculosis (*18*). An updated study in 2010 found that while there had been progress for some diseases (such as malaria), not a single new product had been approved in the previous nine years in disease categories that include Buruli ulcer, dengue, trachoma, rheumatic fever and typhoid and paratyphoid fevers (*19*).
...have greater impact where health systems are weak	Health systems in many disease endemic countries are noticeably weak. Patients either cannot afford or do not have access to adequate drugs, while human and other resources are overburdened by the volume of needs.
...burden caregivers and families	Lost labour time due to illness often means a reduction in household capacity to earn income, particularly at a time when the household needs additional money to pay for treatment (*20*). As a result, money to pay for treatments is often diverted from other expenses, such as school fees.

Source: adapted from reference (7), with selected examples summarized from the multiple references cited above.

The consequences of infectious diseases are not limited to the families whose members become infected. They also have a broader societal and economic impact, much of which could be averted by effective interventions. For example, in 2001, the Commission on Macroeconomics and Health (*22*) predicted that reducing the number of deaths from infectious diseases and maternal conditions by 8 million per year by 2015 could result in an estimated reduction of 330 million disability-adjusted life-years (DALYs)[3]. Conservative estimates of the economic impact of this reduction suggest that it would yield a monetary gain of between US$ 186 billion and US$ 500 billion to the global economy (*23*).

The value of research: new ways to end old diseases

Poverty begets poverty. Problems such as misdiagnosis, polyparasitism, fragile health services to which populations have limited access, poor transport, lack of drug availability, treatment delays, treatment costs and the social and economic consequences of inadequate management of illness all interact against a backdrop of ecological stress, migration and civil unrest.

Research has played a huge role in efforts to understand, control and prevent the spread of infectious diseases. For some diseases, such as smallpox and dracunculiasis, research has led to eradication. For others, we now have a much better understanding of pathogenesis, treatment and control.

In Box 1.2 below we outline a fictional case study, based on real issues, that illustrates the problems of the poor and highlights the essential role that research plays in helping to tackle the interrelationship between infectious diseases and poverty.

Research findings, put into practice, can do much to prevent situations like Christophe's from arising. Research can help to improve diagnosis, enable the development of new drugs and treatment regimes, monitor progress, identify how best to deliver interventions and thus lead to the strengthening of weak health systems. The whole spectrum of research – from laboratory bench to field-based, from basic science to social science – with multiple disciplines working together is needed. Some progress has already been made in disease control but there is still much more to do. New technologies, innovative ways of working and a better understanding of pathogenesis, diagnostics, clinical management, transmission prevention and vector control will all improve our future ability to respond to the challenges posed by infectious disease.

Poverty, infectious disease and policy: moving beyond the Millennium Development Goals

The MDGs are eight time-bound targets (see Box 1.3) set "to free our fellow men, women and children from the abject and dehumanizing conditions of extreme poverty" (23). If all of the MDG targets are reached by 2015, world poverty will have been halved, tens of millions of lives will have been saved and billions more people will have been able to participate in, and benefit from, the global economy (24).

While progress toward fulfilment of a number of the MDGs has been reported, the latest reports from the United Nations show that considerable challenges remain, particularly in areas related to health. Infectious diseases – clustering in impoverished communities and ignored, undertreated and under-researched – remain a substantial hurdle to MDG attainment.

2 The true burden of malaria is currently under discussion.

3 Disability-adjusted life-year (DALY) – a measure of disease burden which provides an indication of time lost due to early mortality or morbidity. Calculations of cost per DALY calculate the cost of the intervention in relation to the years of the given symptom or health condition which have been prevented.

BOX 1.2. CHRISTOPHE'S STORY: THE NEED FOR RESEARCH ON INFECTIOUS DISEASES OF POVERTY

A fictionalized compilation of real issues faced by millions of people

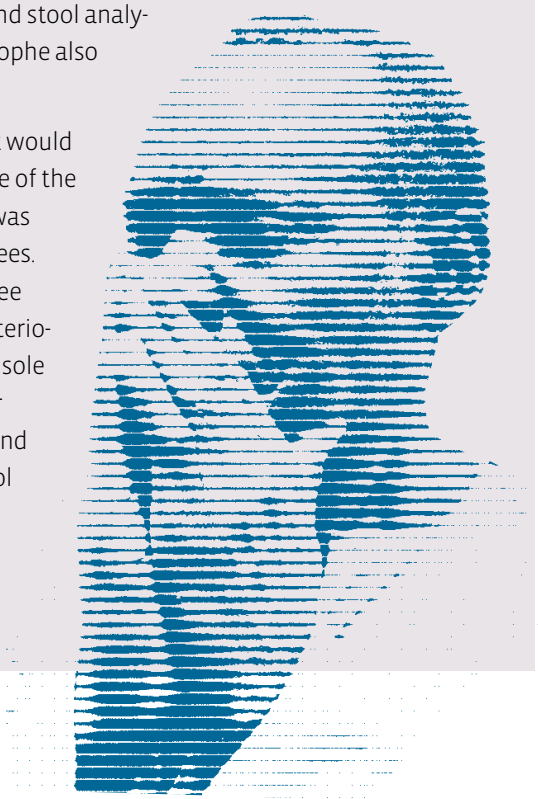
Bolebole is a region rich in alluvial diamonds, attracting migrant workers from surrounding areas. It has few functioning government services, there is chronic civil unrest and the region has a poor transport infrastructure. This situation is compounded by extensive environmental degradation – in particular, deforestation as a result of mineral exploitation. The traditional communities that previously used to live in the area have been displaced by the mining activities and the threat of violence from itinerant rebels, while traditional ways of livelihood – such as hunting for bush meat and small scale farming in the forest – have died out.

The mining community is a largely male, transitory community dependent on imported services of private traders and providers. Christophe, in his thirties, has been working as a miner for several years. Living in the mining camps, he is separated from his family who live far away in one of the largest towns in the region (where he was unable to find work). The mining work is hard and hazardous but the pay allows him to support his wife, elderly mother and young daughter.

Recently, Christophe began to develop recurrent fevers. Believing that they were caused by malaria, Christophe bought antimalarial products from the local "shop" that services the miners. However, despite taking the medicine (which may have been past its sell-by-date or even counterfeit), his fevers continued. Eventually, Christophe's fevers drove him to seek help at the health clinic in the nearest small town, some 30 km away. He spent most of his money sharing a trip on a motorcycle, but when he reached the clinic it was closed.

The following day, staff at the clinic gave him paracetamol for his fever, which he paid for with his remaining money. However, his fevers persisted; he became increasingly weak and soon he was no longer able to work. Eventually he had no option but to go back to his family home. There, his wife borrowed money to send him to a private doctor, who thought that although Christophe was most likely to have contracted malaria, further investigations were needed as Christophe's working environment put him at risk of contracting a range of other infections, including HIV. The doctor also noticed that Christophe had some neurological symptoms and swollen lymph glands. Because the hospital had a working laboratory, Christophe was given a lumbar puncture and the sample fluid confirmed that Christophe had late stage sleeping sickness (trypanosomiasis), requiring expensive drugs and hospitalization. Other tests (blood films and stool analysis) performed at the same time revealed that Christophe also had tropical eye worm, hookworm and ascariasis.

Christophe's wife attempted to raise the money that would be necessary to pay for his treatment by selling some of the family's precious assets – a radio and a bicycle. She was also obliged to stop paying their daughter's school fees. Raising the money for treatment took the family three weeks, during which time Christophe's condition deteriorated further. During that time his wife, who was his sole caregiver and was also providing care for his mother and daughter, became progressively isolated, tired and depressed. Their daughter was unable to go to school and further her education, money became increasingly tight, and Christophe began to feel that he was a burden to his family...



Source: courtesy of David Molyneux

Consider MDG4 – reduce childhood mortality – as an example. According to 2010 figures, approximately 7.6 million children die each year before reaching the age of five (*25*). Infectious diseases such as pneumonia, diarrhoea and malaria are among the leading causes of those early deaths (*25*). Malnutrition is a factor in more than one third of all child deaths and the links between lack of nutrition and infectious diseases are already well established.

Infectious diseases also prevent attainment of MDG5 – improve maternal health. Malaria, schistosomiasis and hookworm all cause anaemia, which is responsible for 20% of maternal deaths in Africa and is a key risk factor for poor pregnancy outcomes and low fetal birth weight (*26*). Moreover, though not conclusive (more research is needed), there is some evidence that other diseases such as dengue and *Trypanosoma cruzi* infections may also adversely impact maternal and fetal outcomes (*27–29*).

After a longer period of neglect, the impact of infectious diseases on attainment of MDGs is only just beginning to be truly appreciated. Their low visibility in the "other" infectious diseases category within MDG6 has no doubt delayed progress towards achieving MDGs. Fortunately, there is now explicit recognition of neglected tropical diseases within the United Nations' "Keeping the promise" resolution (*30*), signalling greater emphasis on infectious diseases in general and wider recognition of the need to address these diseases across all of the MDGs. We trust this recognition results in an enhanced commitment to using research to address the significant knowledge gaps that impede progress in reducing the incidence, prevalence and impact of infectious diseases on poor and vulnerable populations. Such commitment is critical to delivering on the MDG promise and sustaining achievements beyond 2015.

In recent years there has been an increased focus on the "epidemiological transition" – the shift from infectious diseases to non-communicable diseases (NCDs) as the major

> **"Infectious diseases – clustering in impoverished communities and ignored, undertreated and under-researched – remain a substantial hurdle to MDG attainment."**

BOX 1.3. THE MILLENNIUM DEVELOPMENT GOALS (MDGs)

There are **8** MDGs:

1. **Eradicate extreme poverty and hunger**
2. **Achieve universal primary education**
3. **Promote gender equality and empower women**
4. **Reduce child mortality**
5. **Improve maternal health**
6. **Combat HIV/AIDS, malaria and other diseases**
7. **Ensure environmental sustainability**
8. **Develop a global partnership for development.**

These eight MDGs break down into 21 quantifiable targets that are measured by 60 indicators.

Source: *Millennium Development Goals (MDGs) (http://www.who.int/topics/millennium_ development_goals/about/en/index.html, accessed 17 February 2012) and The Millennium Development Goals, Eight Goals for 2015 (http://www.undp.org/mdg/basics.shtml, accessed 17 February 2012).*

causes of morbidity and mortality in low and middle-income countries. It is now recognized that, by 2020, NCDs will be responsible for 60% of illnesses worldwide and seven out of every ten deaths (*31*). In impoverished communities, NCDs are becoming a development challenge of epidemic proportions (*32*). In many cases, infectious and parasitic diseases often contribute to the chronic NCD burden (*33*). For example: 28% of bladder cancer in Bulawayo, Zimbabwe was accounted for by urinary schistosomiasis (*34*); Chagas disease is a leading cause of chronic cardiovascular disease in Latin America (*35*); and toxocariasis is emerging as a leading cause of asthma (*36*). NCDs add to the burden of disease for individuals, communities and countries that are already struggling to cope with the infectious disease. Therefore, understanding the links between NCDs and infectious diseases through research is crucial, if progress is to be made in improving global health.

The cost of inaction – social and economic consequences

WHO data show that 1 billion people worldwide are directly affected by one or more infectious diseases (*6*). Such diseases are often wrongly characterized as a developing world problem – but in fact their contribution to the global disease burden has the potential to affect us all. Take tuberculosis (TB) as an example. TB is known to cause more than 10% of paediatric hospital admissions and deaths, particularly in countries where the HIV burden is high (*37*). In 2009, 9.4 million new cases of TB were reported and 1.7 million people died of the disease, with the highest number of deaths occurring in Africa. Meanwhile the number of cases of multi-drug-resistant TB (MDR-TB) is rising steadily: 440 000 cases of MDR-TB and 150 000 deaths were reported in 2008 (*38*). Given the increased ease of travel due to globalization and the development of modern technology, there is increasing concern that TB and, more ominously, MDR-TB could spread into new areas and ultimately lead to a global epidemic of these diseases.

The emergence of infections such as severe acute respiratory syndrome (SARS) and H1N1 influenza have vividly demonstrated global vulnerability to infectious diseases and the need for robust health care systems to respond to such threats. In 2002/2003, SARS spread to 28 countries, affected around 8500 people worldwide, and claimed 800 lives (*39*). The numbers themselves were relatively small compared with the 1.8 million people, most of them children, who die of diarrhoeal diseases each year (*40*). However, the economic impact of SARS on the global economy was enormous – an estimated US$ 50–140 billion (*41*, *42*) – and thus its impact went well beyond those who were actually infected with the virus.

In 2009, the H1N1 influenza pandemic in Mexico also had a profound economic impact. The outbreak directly affected tourism, the service sector, retail trade, transport, entertainment, the agricultural industry (particularly pig farmers) and depressed international investment. The outbreak is estimated to have reduced economic activity by 0.3% to 0.5% of gross domestic product (i.e. between US$ 2.7 and US$ 4.5 billion) (*43*).

It is therefore clear that, as well as saving and improving lives in disease endemic countries, tackling infectious diseases is also essential for sustaining the global economy.

“The emergence of infections such as severe acute respiratory syndrome and H1N1 influenza have vividly demonstrated global vulnerability to infectious diseases and the need for robust health care systems to respond to such threats.”

Tackling disease – a need for investment

There is a sound economic case for investment in research to tackle infectious diseases. Studies have shown that scaling up of previously developed, evidence-based interventions can be highly cost effective, resulting in both direct savings (such as reduced medical costs) and indirect savings (through increased productivity and reduced losses in work time). Examples are shown below.

- Ivermectin and albendazole[4] cost US$ 0.05–0.10 per person as part of mass drug administration for lymphatic filariasis, with a cost per DALY averted of US$ 5.90 (*7*).
- Oral rehydration salts (ORS) for diarrhoeal diseases cost approximately US$ 5.50 per child per episode, with a cost effectiveness ratio of US$ 1062 per DALY (*44*).
- Immunization against rotavirus and cholera deliver a cost effectiveness ratio[5] of US$ 2712 per DALY (*44*).

These examples show that the return on investment can be considerable. An analysis of more than 100 countries showed that a 1% increase in adult survival rates increases labour productivity by about 2.8%, thus strengthening economic growth (45). When the human costs of diseases are factored in, the return on investment is increased substantially.

A key strength of research is that it can provide evidence on how effectively interventions work and thus can support investment decisions and scale-up. Sometimes research can show that an intervention is unlikely to result in an effective outcome, or that the cost of intervention is not matched by the potential benefit.

4 Donated by Merck & Co. Inc. and GlaxoSmithKline.

5 Cost effectiveness ratio is a term used by health economists to describe the results of a calculation which is undertaken to investigate whether an intervention will provide value for money. At its simplest, a cost effectiveness ratio divides the costs of the intervention by the health effects. For further information see http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/Cost-effect.pdf.

At other times research can show where investments could be of most use. As well as providing evidence for what will work, research also provides a robust foundation for terminating studies and interventions, or for changing strategies. Precious resources can then be released for redistribution towards other, better and more cost-effective interventions.

Ten reasons to research infectious diseases of poverty

Research underpins and drives progress in controlling infections and improving health on a global scale. However, for many infectious diseases of poverty, progress has been too slow. For many diseases there is a paucity of effective and affordable treatments. In other cases, although effective interventions exist, often they are not readily available or accessible in communities where the need is greatest. Research has a key role to play in both scenarios – developing new products and interventions where required, and supporting health systems to implement existing interventions effectively. Research is critical to the development of a functional, innovative and sustainable health and disease control system. In Box 1.4 we outline ten compelling reasons why research is vital to break the hold of infectious diseases on populations living in poverty.

On the next page, we expand on the contexts and ideas underpinning each of these ten vital activities.

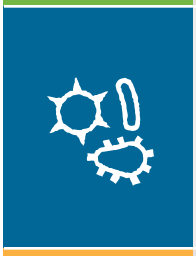
> **“Research is critical to the development of a functional, innovative, and sustainable health and disease control system...”**

BOX 1.4. TEN COMPELLING REASONS FOR RESEARCH

To meet the global health challenges of eliminating infectious diseases of poverty, it is vital that we find ways to do the following:

1. Break the vicious cycle of poverty and infectious disease. The interrelationships between health, infectious diseases and poverty are dynamic and complex. Timely, targeted research will prevent infectious diseases from driving more people into poverty.

2. Forge an escape for the poor and vulnerable. Poor people living in the areas most affected by environmental factors are least able to respond to the challenges of environmental and climate change. Interactive, interdisciplinary research can identify ways to mitigate risk factors, establish the potential impact of interventions on the environment and direct future interventions to minimize risk.



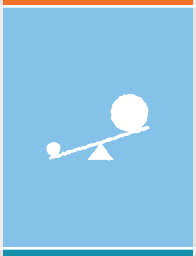
3. Tackle multiple problems. Research will help understand both causes and consequences of polyparasitism, coinfection and comorbidities with non-communicable diseases on people, societies and systems. An integrated understanding of the complex relationships underpins effective integrated health system delivery and effective disease control programmes.

4. Commute the life sentence. Many people must live with the long-term debilitating effects of past or current infection. Research can find ways to mitigate the consequences of chronic and persistent lifelong infection and its secondary complications and associated stigma.

5. Be prepared – forewarned is forearmed. Surveillance is essential at all levels to understand patterns of emergence, including the spread of drug and insecticide resistance. Mapping, monitoring and evaluation of these trends are critical. Access to such surveillance data allows us to anticipate and respond to emergent, re-emergent and drug-resistant diseases.

6. Reach the hardest to reach. By identifying ways to strengthen health infrastructure and better deliver services in impoverished areas, we can reach disenfranchised populations who continue to struggle with the burden of poverty and disease. Health systems research can create positive synergies between disease control and wider health systems in poor regions.

7. Prevent loss in translation. Progress along the route from basic research to clinical and public health practice is slow and patchy. Integrated multidisciplinary research programmes should aim to anticipate and avoid potholes along the route to the introduction of more effective interventions.



8. Identify small changes that can make a big difference. Relatively low levels of investment in evidence-based interventions can have a big impact. Small modifications in where and how we deliver treatments and care can achieve dramatic improvements. Effective research that demonstrates positive effects from small modifications should be rapidly scaled up in poor communities.

9. Stay focused on the light at the end of the tunnel. Much has been achieved to date and even the most difficult situations are not irreversible. Significant progress will continue to be made if investment in coordinated research programmes is expanded and sustained.

10. Act quickly on what we know. Policy-makers and global funders need to have access to the right information at the right time to inform decisions that draw on the evidence of what works, and feed "best buys" into health policy, health budgets and the operations of health systems. Research data must therefore be rapidly translated into effective tools for policy-makers.

1. BREAK THE VICIOUS CYCLE OF POVERTY AND INFECTIOUS DISEASE

The interrelationships between health, infectious diseases and poverty are dynamic and complex. Timely, targeted research will prevent these diseases from driving more people into poverty.

The vicious cycle formed by disease and poverty represents a fundamental public health problem, as poverty both increases vulnerability and exposure to disease and directly affects access to treatment and disease outcomes (*46*).

There is clear evidence that investments in controlling infectious and parasitic diseases can be highly effective in reducing the poverty of the poorest quintile of the population (*47*) – the so-called "bottom billion" (*11*). Medical and technical interventions to treat infectious diseases have made a significant difference in people's lives. However, many of the determinants of health lie outside the control of the health sector. Social, economic, political and environmental factors all influence risk, exposure and the effects of infectious disease (*46*). For example, the poorest populations have the least access to safe drinking water, decent sanitation and effective waste disposal. Accordingly, their exposures to associated infectious disease-causing agents are the highest.

> **"Many of the determinants of health lie outside the control of the health sector. Social, economic, political and environmental factors all influence risk, exposure and the effects of infectious disease."**

The environments in which poor people live are themselves often conducive to the emergence and spread of infectious diseases. Impoverished communities around the world typically live in close proximity to livestock and other animals. Zoonotic diseases (which can be passed between, or shared by, animals and humans) thrive in conditions of poverty. Yet while animals are a crucial link in the chain of infectious disease transmission, with around three quarters of the 1300 known infectious diseases of humans derived from animal sources (*48*), for many people they are also a critical resource for daily existence.

In many disease endemic countries, the internal political and economic situation is fragile and corruption is rife. External events, such as the global financial downturn, can compound an already difficult situation, affecting and disrupting the continuum of health interventions that may be available (see Chapter 3). Conflict, ecological and environmental challenges add further complexity, complicating longer-term planning (see Chapter 2).

Research can provide solutions to otherwise intractable problems by identifying risk factors for diseases and understanding of the complex interactions between them (see Table 1.2).

A full spectrum of research – looking across the biomedical to the social, cultural, political and environmental spheres – is needed to address the complex challenges of infectious diseases. Moreover, there is a need for researchers to interact and carry out multidisciplinary research so that, while new tools and strategies are developed, ways to deliver these to those in need are also created and improved.

TABLE 1.2. BREAKING THE LINK BETWEEN INFECTIOUS DISEASE AND POVERTY: SOME EXAMPLES OF THE ROLE OF RESEARCH

ISSUE	HOW RESEARCH CAN HELP
Infectious diseases are a proxy for poverty and disadvantage	Epidemiological research and analysis of surveillance data provides an insight into the risk factors for disease, enabling the development of targeted interventions and thus more effective use of resources (Chapters 2, 3).
Infectious diseases affect populations with low visibility and little political voice	Health services research can help to ensure that opportunities to "reach the hardest to reach" are maximized, drawing on the best available data and use of innovative technologies (Chapters 2, 3, 4).
Infectious diseases cause stigma and discrimination	Social science research can identify practical solutions that address stigmatization and marginalization of already disadvantaged communities, and find interventions which diminish stigma and promote reintegration into the community (Chapters 2, 3).
Infectious diseases impose a heavy health and economic burden	Bench research and research and development activity can identify, develop and test solutions to previously intractable problems (Chapter 4). Multidisciplinary research that considers the long-term effects of chronic conditions and the social, economic and cultural environment can offer a lifeline to help people and health services manage conditions more effectively (Chapters 2, 3).
Infectious diseases are low on research funders' agendas	Research studies can provide an insight into the research priorities of funding agencies, enabling the identification of funding gaps (Chapter 5).
Infectious diseases have greater impact where health systems are weak	Health systems research, specifically implementation research and research in the social sciences, can identify positive synergies and innovative mechanisms for improving the links between disease control systems and the wider health system (Chapter 3, 4).
Infectious diseases place a burden on caregivers and families	Social science research, health services research and multidisciplinary research can play a fundamental role in the empowerment of disadvantaged communities, families and individuals (Chapters 2, 3, 4).

2. FORGE AN ESCAPE FOR THE POOR AND VULNERABLE

Poor people living in the areas most affected by environmental factors are least able to respond to the challenges of environmental and climate change. Interactive, interdisciplinary research can identify ways to mitigate risk factors, establish the potential impact of an intervention and thus direct future interventions.

The environment is constantly changing. Already there have been dramatic changes in our climate, in our use of the physical environment and in the global ecology. Recently, the rate and pace of change has accelerated, magnifying both positive and negative effects of change and amplifying potential threats to human health.

Interrelationships between the environment, industrial and agricultural activities and the risks of infectious diseases are increasingly recognized. Air and water pollution, deforestation, habitat fragmentation, ecological disruption and changing agricultural practices can all have an impact on the incidence, prevalence and spread of infectious diseases. Environmental changes work in concert to increase the overall risk of infectious diseases and, through changes to the physical environment and the impact on animal reservoirs and vector control, further jeopardize the health of poorer populations (*49*).

> **Air and water pollution, deforestation, habitat fragmentation, ecological disruption and changing agricultural practices can all have an impact on the incidence, prevalence and spread of infectious diseases.**

Factors that heighten the risk of infectious disease transmission include close contact between humans, animals and insects/pathogens (*48*); human behaviour (*50*); weak institutions (*51*); low community cohesion (*50*); population growth and urban density (*52*); politically marginalized settlers (*50*); migration (*53*); environmental challenges such as earthquakes and climate change (*52*), and changing agricultural and land use practices (*52*). The interaction between these factors is complex. Using focused enquiry techniques, research can explore the dynamics of diseases and increase our understanding of factors that affect the spatial range and incidence of infectious diseases, such as links between the frequency and intensity of contact between humans and animal species. The environment and the associated implications of climate change need to be considered within policy development. Consider the example of the Three Gorges Dam in China (see Box 1.5).

This example vividly demonstrates the contribution that rigorous data modelling can make to large development projects. Risk assessment showed that constructing the dam would disrupt the ecology. Research helped to establish the level of risk associated with the environmental changes. By identifying and determining the social, ecological and health impacts, data modelling can provide a robust evidence base to establish the level of risk associated with a project, support the development of effective targeted risk management strategies and guide future interventions.

Identifying and managing risks such as those illustrated by the Three Gorges Dam project can be particularly important for poorer populations as they are less likely to be able to leave or otherwise alter their living conditions.

As Chapter 2 will describe, climate change may also have disease control consequences, as environmental changes can affect the

BOX 1.5. PUBLIC HEALTH AND THE THREE GORGES DAM IN CHINA

Built between 1994 and 2009, the Three Gorges Dam in China is the world's largest dam. Benefits cited for the dam include its hydroelectric generating capacity, flood protection on the historically dangerous Yangtze River and improved river navigation.

A review of the potential consequences of the Three Gorges Dam in 2008 highlighted risks of the spread of schistosomiasis to previously nonendemic areas, due to changed ecological conditions and delayed water transit time affecting the habitat of the intermediate host, Oncomelania snails.

A series of studies with rigorous data modelling were undertaken to better understand the factors affecting spatial distribution and seasonal habitat for onchocerciasis-transmitting snails, to identify active transmission sites and to forecast risk. In response to the research, ongoing surveillance using remote sensing data has been instigated to establish geographical distribution maps, analyse the influence of floods, assess the effects of returning wetlands to the reservoir and evaluate and monitor marshland changes due to the Three Gorges project.

Major conclusions to date include the need to deploy monitoring and intervention systems to provide successful prophylaxis of dam-associated schistosomiasis emergence. Further ecological simulations of the effects of the dam are also needed.

Source: *references (54, 55, 56).*

The Three Gorges Dam created a reservoir that reached its full height in 2010, having submerged 13 cities, 140 towns and 1350 villages. (L) A town and a mountain in the reservoir area of the Three Gorges Dam, with a bridge connecting the two mountain peaks. (R) An image created after modelling the areas that would be submerged following completion of dam construction. It shows most of the old town under water.

Photos: courtesy of Dr JG Guo.

ecology of animals that act as disease reservoirs. Control strategies need to be more complex, with an increasing need for collaboration and interaction between stakeholder groups working on both animal and human health and well-being. Climate change will also demand more interaction, particularly at country level, between researchers, service deliverers and policy-makers from various sectors (including health, environment, natural resources and livestock). This will enable disease control to be based on best possible evidence and also reflect good practice across different fields.

The research portfolio must be broad based. If we are to fully address the new complexities of infectious diseases, we need a new approach that goes beyond animal and human health – and acknowledges the interrelationships between biology, the environment and the social and cultural context.

3. TACKLE MULTIPLE PROBLEMS

Research will help understand both causes and consequences of polyparasitism, coinfection and comorbidities with NCDs on people, societies and systems. An integrated understanding of the complex relationships between infections, and infections and NCDs, underpins effective integrated health systems delivery and effective disease control programmes.

Investigation of the co-clustering of diseases often highlights unexpected biological, social or environmental drivers of disease. Research is needed to explore the complex relationships much more rigorously. Yet single disease control protocols often discourage this and comorbidities are not handled well with our existing research methods.

As an example, polyparasitism, or human infection with more than one parasite, is widespread (*12, 57, 58*), particularly in environments with predisposing risk factors such as poverty or lack of clean water and sanitation (see Box 1.6 for one example). According to a WHO report published in 2009, more than 70% of the 149 countries endemic for parasitic infections were endemic for two or more diseases; 28 countries were endemic for six or more diseases (*59*).

BOX 1.6. DISEASE CONSEQUENCES – MALARIA AND HELMINTHS

The geographical congruence between malaria and parasitic helminth infections such as hookworm and schistosomiasis is now well recognized (*60–62*). Each pathogen weakens the health of exposed populations – but these parasites have been shown to interact with each other (*63*).

Research to better understand the relationship between the malaria and helminth infections could inform:

- the way in which interventions are targeted (recognizing the role of the environment in relation to disease clusters);
- how investment is focused – such as whether combining disease control programmes (where appropriate) could improve the effectiveness of financial investment;
- the development of innovative therapeutic regimes that reflect a more holistic understanding of the consequences of polyparasitism.

While combining disease control programmes can potentially minimize costs and maximize prevention coverage (*64*), the effectiveness of such an approach is likely to depend on the degree of geographical overlap between diseases at the subnational level (*65*), and evidence on optimum control packages. Health services research can play a key role in such investigation (see Chapter 3).

The problem of comorbidity is not restricted to polyparasitism and coinfection. As mentioned earlier in relation to the MDGs infectious diseases coexist with, and may be exacerbated by, NCDs.

Infective agents may also predispose to, or trigger, some chronic NCDs including cervical, liver and stomach cancers (see Box 1.7), and possibly some types of diabetes (*66*).

BOX 1.7. LIVER FLUKES AND CANCER

Fish-borne liver fluke infections (that trigger liver and bile duct cancers) are important emerging public health problems in east and south-eastern Asia, where more than 600 million people are at risk of infection. Exponential growth of aquaculture in Asia (see Chapter 2) may be the most important risk factor for the emergence of liver fluke infections.

In Thai males, liver and bile duct cancer ranks fifth among the diseases of the country with the highest number of DALYs. Khon Kaen in north-eastern Thailand (where liver fluke is endemic) has reported the highest incidence of liver and bile duct cancer in the world. This would seem to indicate a link between the two conditions.

Research can unravel such complexities and tell us more about the relationship between liver fluke and bile duct cancer and between the environment, the animal reservoir and the incidence, prevalence and consequences of liver fluke infection.

Broader social factors (e.g. nutritional status and lifestyle factors such as smoking) can also affect how a disease progresses. For instance, studies have also shown that one fifth of the global TB burden may be linked to smoking (*67*). This is of concern, given that smoking rates are rising in many disease endemic countries. Research can provide more effective evidence of the link between smoking and TB.

The association between diabetes and TB is one example of this complexity (*68, 69*). It has been suggested that the long duration of diabetes, and associated depressed immunological function and poor glucose control, may increase the risk of TB (*70*). Insulin dependence, as a marker for severity of diabetes, has been found to predict increased TB risk (*71*). If the predicted rise in diabetes spurs a rise in TB prevalence, then the potential public health impact could be enormous (*66*).

> **"The problem of comorbidity is not restricted to polyparasitism and coinfection. Infectious diseases coexist with, and may be exacerbated by, NCDs."**

Both infectious diseases and NCDs can impose long-term disability (*33*) and stigmatization. This can have economic consequences both for the individual and (due to the need for health care resources) for the health system. These factors are likely to add to the strain on poorly resourced, fragile health systems.

Investigation of the complex interrelationships of coinfections and comorbidities will increase understanding of the risk factors and consequences of such diseases. This will provide evidence to inform future interventions.

4. COMMUTE THE LIFE SENTENCE

Many people must live with the long-term debilitating effects of past or current infection. Research can find ways to mitigate the consequences of chronic and persistent lifelong infection and its secondary complications and associated stigma.

Some infectious diseases cause both acute illness and chronic, long-term disability. The effects of chronic infection can be profound – for both the person infected, and his or her family, and the health system as a whole. Box 1.8 gives examples of this.

Chronic infectious diseases may also be a cause of stigmatization. This is particularly true where the individual is associated with some blame or personal responsibility, or in cases where diseases are believed to be untreatable or result in degenerative or disfiguring consequences. Fear of people who are different and the fear of the disease itself may coincide. Infected people become marginalized by such stigma – be it from the behaviour of others or their own perceptions. Levels of stigma may differ according to context (see Box 1.9) and that stigmatization may substantially increase the suffering of patients and their families, as well as making it more difficult to seek or obtain treatment. For example, sufferers from poorer backgrounds often delay seeking help (*75*) or stop treatment prematurely (*72*), resulting in disease progression to stages where treatment is more difficult or the symptoms become irreversible.

BOX 1.8. CONSEQUENCES OF CHRONIC INFECTION: CHAGAS DISEASE AND BURULI ULCER

Considered to be the parasitic disease with the greatest socioeconomic impact in Latin America (*72*), Chagas disease is estimated to affect 10 million people in 21 countries (*7*). More than one in four of those infected will suffer chronic effects, including irreversible cardiovascular, gastrointestinal and neurological problems.

Photo: MSF/ Juan Carlos Tomasi

Buruli ulcer is rarely fatal but, if untreated, the disease can cause severe long-term problems. These include functional disability such as restriction of joint movement and deformity. Most infected people live in isolated, poor rural communities and the costs of treatment can be devastating for the household; the disease can also be a major burden on health facilities.

- Estimates from Ghana show that the median annual total cost of Buruli ulcer to a household ranges from approximately US$ 76 to US$ 428 per patient (equivalent to as much as 16–89% of the average annual salary in the country) (*73*).
- A study in Cameroon, where hospital care for Buruli ulcer is free, showed that the true cost of the disease to the patient still exceeded 25% of annual earnings. This surpasses the threshold of 10%, the cost burden threshold generally deemed "catastrophic" to a household economy (*74*).

Such chronic burdens are often disregarded and underestimated (*13*). The costs to patients and their families, the impact on quality of life, and the socioeconomic consequences for individuals and the community are not adequately captured by indices that focus on mortality data rather than the consequences of chronic morbidity. Including such impacts into calculations of the cost effectiveness of interventions can make a difference to funding decisions and prioritization processes for health services (see Chapter 3).

Multidisciplinary research that considers the long-term effects of chronic conditions and the social, economic and cultural environment can help people and health services to manage such conditions more effectively, and identify practical solutions that address stigmatization and marginalization of already disadvantaged communities.

“The costs to patients and their families, the impact on quality of life, and the socioeconomic consequences for individuals and the community are not adequately captured by indices that focus on mortality data rather than the consequences of chronic morbidity.”

BOX 1.9. STIGMA AND LYMPHATIC FILARIASIS: COMPARISON OF THE DOMINICAN REPUBLIC AND GHANA

Globally, 120 million people suffer the consequences of lymphatic filariasis, including stigmatizing lymphoedema (or elephantiasis) of the leg.

Studies showed differences in how women from the Dominican Republic and from Ghana have experienced stigma associated with this condition (*76*). Antecedents, consequences, coping strategies and outcomes of the experiences varied between the two cultures, with people from the Dominican Republic faring better. In Ghana, poverty, poor access to health care, limited education and diminished social support challenged the coping strategies of many women and exacerbated negative consequences of lymphoedema related stigma.

Research could:

- identify effective interventions, educational strategies and policy changes that may be used to overcome stigma and enable these groups to access care;
- find interventions that diminish stigma and marginalization and promote rehabilitation and reintegration into the community.

5. BE PREPARED – FOREWARNED IS FOREARMED

Surveillance is essential at all levels to understand patterns of emergence, including the spread of drug and insecticide resistance. Mapping, monitoring and evaluation of these trends are critical. Access to such surveillance data allows us to anticipate and respond to emergent, re-emergent and drug-resistant diseases.

Surveillance is essential for identifying and controlling infectious diseases. It helps to detect emerging problems, identify human-animal disease "hotspots" (see Chapter 2), track any recrudescence after control activity and provide evidence on which to base policy decisions.

A good surveillance system is a cornerstone of an effective and sustainable disease control system. It is dependent on comprehensive health information systems, supported by readily available and appropriate diagnostic tools. Diseases may be undiagnosed or misdiagnosed because making a definitive diagnosis requires diagnostics that are unavailable and/or unaffordable in the settings in which the diseases occur. Clusters of cases and their true etiology therefore might not be recorded, especially if they occur in isolated areas in low and middle-income countries. Some cases may be wrongly attributed to NCDs (e.g. if symptoms are not those normally associated with an infectious agent). Hence the true burden of infectious disease is likely to be much higher than reported. Only system-wide research supported by effective surveillance can gauge the true extent of this problem.

Data for many infectious diseases are, at best, patchy. Despite efforts to improve disease surveillance and response, many countries still have difficulty in accurately identifying, diagnosing and reporting infectious diseases, particularly in remote areas. Lack of transport and communication infrastructures as well as capacity and capability gaps – such as a shortage of skilled healthcare workers and laboratory facilities to ensure accurate diagnosis – all compound the problem (*51*). However, greater connectivity in rural areas; communities' increasing involvement in data gathering; and technological improvements such as smartphones and tablets provide a new and affordable mechanism for extending and improving surveillance coverage in resource poor settings. Extending the reach of such new technologies across remote and impoverished communities is essential, if we are to address the current data challenges.

Effective surveillance relies on gathering information from a broad range of information sources including surveys, health service and disease control facilities, laboratories and registries. Studies such as the continuing Global Burden of Disease study[6] act as essential building blocks for surveillance, providing baseline information and giving an insight into the prevalence, incidence, mortality ratios and DALYs of several infectious diseases. However, local data-gathering systems are essential to ensure the robustness of country-level health information. Disease endemic countries need to invest in their own comprehensive health information and surveillance systems if they are to ensure that country-relevant data is captured and used to inform health policy and resource allocations.

Surveillance data is needed for baseline mapping of infectious diseases and for measuring the effectiveness of disease control programmes and interventions. Re-emergence of diseases (see Box 1.10 for some examples of emerging and re-emerging infectious diseases) or any development of resistance needs to be identified as early as possible.

6 http://www.who.int/topics/global_burden_of_disease/en/, accessed 13 February 2012.

BOX 1.10. EXAMPLES OF EMERGING AND RE-EMERGING INFECTIOUS DISEASES OF PUBLIC HEALTH IMPORTANCE

- Severe acute respiratory syndrome (SARS) due to SARS coronavirus
- Influenza due to H1N1 and H5N1 viruses
- Hepatitis B and C
- Ebola haemorrhagic fever
- Rift Valley fever
- Chikungunya infection due to Chikungunya virus
- Cholera
- Multidrug-resistant TB (MDR-TB)
- Viral encephalitis due to Hendra/Nipah viruses
- Hantavirus haemorrhagic fever and/or cardiopulmonary syndrome
- Lyme disease
- Diarrhoeal disease due to *Escherichia coli*
- Gastroenteritis due to norovirus
- Bubonic plague
- Legionella pneumonia
- Meningococcal meningitis.

Source: *courtesy of Annette Ives.*

BOX 1.11. MULTIDRUG-RESISTANT TUBERCULOSIS: WHY GOOD SURVEILLANCE IS CRITICAL

Each year, more than 400 000 people develop MDR-TB, which can spread from one person to another. MDR-TB emerges when there is mismanagement of drugs, underinvestment in quality TB control and poor patient compliance (many TB patients do not complete their full 6–9 month drug regimen). The TB bacillus develops resistance through incomplete, erratic or inadequate treatment. In some TB hotspots, up to 30% of patients are infected with drug-resistant strains.

Extensively drug-resistant TB (XDR-TB) is resistant to all of the most effective anti-TB drugs, and emerges through mismanagement of MDR-TB treatment. It can also be spread from one person to another. XDR-TB was highlighted as a global threat to public health in 2006, especially in high HIV-prevalence countries. If uncontrolled, it could spark an epidemic of untreatable TB that will jeopardize the major gains made in TB control.

How could research change this scenario?

Weaknesses in health information and surveillance systems are responsible for slow detection of MDR-TB. Technical challenges currently impede the diagnosis, treatment and prevention of TB. Rapid diagnosis and treatment could have a major impact on HIV-associated TB and drug-resistant TB. Key research priorities to address this include the following.

- Identifying feasible and optimal ways to undertake intensified case finding in communities.
- Developing rapid tests for easier diagnosis of MDR-TB and XDR-TB.
- Supporting the development of comprehensive health surveillance systems in communities to enable rapid detection of emergent, re-emergent and drug-resistant disease.
- Finding ways to better control TB in high-risk settings.
- Developing simple standardized treatment regimens for MDR-TB.
- Establishing rational re-treatment regimens for patients who fail or develop recurrent TB after first line treatment.

Source: *TB Alliance (http://www.tballiance.org/why/mdr-tb.php, accessed 17 February 2012); Stop TB Partnership (http://www.stoptb.org/, accessed 17 February 2012); TDR Disease-Specific Reference Group on Tuberculosis, Leprosy and Buruli Ulcer.*

The emergence of drug and insecticide resistance also emphasizes the need to routinely undertake surveillance to identify, isolate and prevent microbial and vector resistance as early as possible. Box 1.11 further outlines why surveillance is so important.

Drug resistance has been implicated in the spread of infectious diseases. Malaria drug resistance spreads rapidly and poses significant problems for the treatment of patients. Research plays a key role in mapping, measuring and charting the development of resistance to existing drug regimens. Through operational research, interventions can be targeted and proactive management strategies developed.

An effective response to vector-borne infectious diseases requires information on the levels of risk; distributions of parasites, vectors and reservoir species; and understanding of the social context. Surveillance can help provide this information. Box 1.12 illustrates how good surveillance has helped decrease disease incidence.

“Research plays a key role in mapping, measuring and charting the development of resistance to existing drug regimens. Through operational research, interventions can be targeted and proactive management strategies developed.”

Human health, veterinary, environmental and wildlife management expertise should be used jointly to develop a more effective surveillance system. Gathering and sharing data through such a system is vital if strategic responses at global, regional, national and local levels are to be sustained.

BOX 1.12. HALTING RIVER BLINDNESS

Between 1975 and 2002, 11 west African States, together with the World Bank, the Food and Agriculture Organization of the United Nations (FAO), United Nations Development Programme (UNDP) and the World Health Organization (WHO), embarked on one of the largest and most comprehensive vertical vector control operations against onchocerciasis in west Africa. An area of about 1 300 000 km², with more than 50 000 km of rivers, was covered by the operation.

The success of this intervention was due in large part to the enormous information infrastructure that had been created. This drew on hydrology/seasonal river flows, information on vector habitats, parasite mapping and information on population levels of infection and blindness.

This foundation of multidisciplinary knowledge undoubtedly played a key role in ensuring that an “escape route” was found from river blindness. The operation had a dramatic impact on the prevalence and transmission of infection. More than 40 million people in the areas concerned were freed from risk of infection and onchocercal eye lesions, while more than 1.5 million people were no longer infected. Another 600 000 cases were prevented and 16 million children living in the area (and born since the programme began) are free of onchocerciasis.

The socioeconomic impact has also been dramatic. Twenty-five million hectares of fertile land in the river valleys were made available for resettlement and agriculture, with an economic rate of return (ERR) of about 20%, resulting mainly from increased labour due to prevention of blindness and increased land utilization (*77*).

Maintaining such good surveillance is of utmost importance. While onchocerciasis is no longer a problem in some savannah areas of west Africa, transmission persists in other areas.

6. REACH THE HARDEST TO REACH

By identifying ways to strengthen health infrastructure and better deliver services in impoverished areas, we can reach disenfranchised populations who continue to struggle with the burden of poverty and disease. Health systems research can create positive synergies between disease control and wider health systems in poor regions.

Often, health services and disease control programmes struggle to reach the people who need their help the most. There are many reasons for this. Population coverage is a particular challenge for disease endemic countries, where fragile health systems often coincide with high disease incidence and prevalence rates, as well as with broader social, economic and environmental challenges such as a poor transport infrastructure.

Ideally, infectious disease control activities would be intimately interrelated with the health system (see Chapter 3). But in reality there is a gap (real or perceived) between disease control systems and health care delivery systems. Too often, disease control programmes are dissociated from the core provision of health services. This needs to change if we are to achieve long-term, sustainable control of infectious diseases of poverty: awareness of infectious disease and the programmes for its control must be seen as integral to health systems, particularly at the community level and in primary care. Health systems research can greatly improve the health system/disease control programme interface. It can identify ways to mainstream control programme activity (where appropriate) and to make more effective use of limited human and financial resources, including donor funding (*78, 79*). There may be a clear role to be played by communities themselves. Research on community-directed interventions shows that success can be substantially improved through community management.

As the story of Christophe (see Box 1.2) illustrated, people in under-resourced settings often experience difficulties in accessing appropriate, timely health care. Since we already know a lot about the factors that undermine access to health care, this information should be used to inform and improve health services. For example, pro-poor and pro-equity strategies need to consider not just income, but also systematic disparities in health status such as gender, health education and health literacy, all of which can be key determinants governing access to health.

7. PREVENT LOSS IN TRANSLATION

Progress along the route from basic research to clinical and public health practice is slow and patchy. Integrated multidisciplinary research programmes should aim to anticipate and avoid potholes along the route to introduction of more effective interventions.

The translation of research in the laboratory to the bedside, and of small-scale bedside research to the wider population, often receives low priority. At present much research is conducted in isolated "silos" and is not directed towards translation into effective interventions, policy and practice. A comprehensive research strategy is needed to maximize the impact of studies.

The example outlined in Box 1.13 shows how research evidence can have a dramatic impact if translated into evidence-based practice and policy. In this case, a coordinated and purposeful approach to tackling lymphatic filariasis, supported by intersectoral cooperation, paid a global health dividend. The robust partnerships that developed as a result of this intervention provide a firm foundation for future interventions.

> **At present much research is conducted in isolated "silos" and is not directed towards translation into effective interventions, policy and practice.**

Enabling the translation of research into evidence-based practice is critical to the achievement of a more coordinated and purposeful approach to health.

BOX 1.13. TRANSLATING RESEARCH INTO PRACTICE: CHINA'S SUCCESS LEADS TO GLOBAL PROGRAMME

The success of the Chinese lymphatic filariasis control programme during the 1960s and 1970s, using a single drug (diethylcarbamazine) and vector control, resulted in the elimination of transmission in a population of some 350 million people. This success led to the International Task Force for Disease Eradication recommending lymphatic filariasis as one of only six eradicable diseases.

TDR (The Special Programme for Research and Training in Tropical Diseases) supported research on drug combinations which, when given annually, reduced parasite levels in the blood to a level which would arrest transmission by mosquito vectors. These findings led to a World Health Assembly resolution recommending Member States to eliminate the disease as a public health problem.

In turn, these led to the donation of the drugs albendazole and ivermectin (by GlaxoSmithKline [GSK] and Merck & Co., Inc. respectively) and the launch of a global programme supported by an alliance of partners and known as the Global Alliance to Eliminate Lymphatic Filariasis (GAELF).

The strategy was based on two approaches: (i) mass distribution of the two drugs annually for at least five years and (ii) treatment of those with existing symptoms. The programme has expanded substantially since its launch in 2000, when only 2.9 million people were treated. In 2008, more than 500 million people benefited from annual treatments in 53 countries. In 2010, a further commitment to the donation of diethylcarbamazine was also made and the programme has been recognized to be the most rapidly advancing public health programme in history. It has resulted in some US$ 24 billion in savings and the cumulative number of treatments delivered at the end of 2008 was 2.8 billion. Using tools developed through operational research, intense evaluation is demonstrating impact on both prevalence and incidence of the disease.

Source: *references (80, 81).*

8. IDENTIFY SMALL CHANGES THAT CAN MAKE A BIG DIFFERENCE

Relatively low levels of investment in evidence-based interventions can have a big impact. Small modifications in where and how we deliver treatments and care can achieve dramatic improvements. Where effective research demonstrates positive effects from small modifications, this should be rapidly scaled-up in poor communities.

Research can make a profound difference to interventions and strategies by identifying and directly addressing the challenges to delivery faced within the field. For example, interventions can be tailored to specific audiences, and products can be modified to ensure that they are culturally acceptable and technologically adaptable to the field conditions within which they are to be used.

> **Educators, health promoters and decision-makers are more likely to achieve desired behavioural changes if community-based research is used to tailor health messages to specific populations and monitor their impact.**

By applying these changes systematically, enormous progress can be made against previously intractable conditions.

Interventions such as hand washing, water filters and bednets have been shown to have a significant impact on infectious disease control. However, often these interventions are not readily available or accessible to those communities and individuals in greatest need. Identified reasons for this include lack of compatibility with local lifestyles and cultural norms, and a lack of capacity and capability at district and sub-district level to deliver the effective intervention. Investment in research can do much more to ensure this "know–do" gap is bridged. For instance, research can help ensure that tools and strategies are locally relevant, particularly with regard to equity of access, field effectiveness, cost-effectiveness, community acceptance and uptake, sustainability and environmental challenges. Educators, health promoters and decision-makers are more likely to achieve desired behavioural changes if community-based research is used to tailor health messages to specific populations and monitor their impact (*50*).

9. STAY FOCUSED ON THE LIGHT AT THE END OF THE TUNNEL

Much has been achieved to date and even the most difficult situations are not irreversible. Significant progress will continue to be made if investment in coordinated research programmes is expanded and sustained.

Research has driven progress in many areas, providing new products to enable identification and control of infections and harnessing the capabilities of health systems and communities to support action and interventions to improve health. By highlighting up-to-date methodologies and new approaches, and drawing across a variety of disciplines, research provides solutions to improve the delivery of interventions and manage illness. Table 1.3 provides an insight into some of the ways in which research has made, and continues to make, a difference to disease identification, control and monitoring. Many other examples of success are cited throughout the rest of this report.

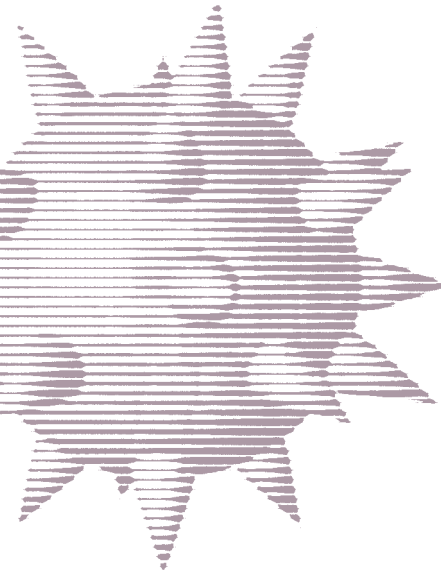
> **"Investment in research is about more than empirical scientific discovery and the creation of innovative products – it is about improving global health by discovering and advancing whatever methods work best."**

There has been a great deal of progress in combating infectious diseases of poverty. Some diseases such as smallpox have now been eradicated. Several other diseases are already targeted for elimination/eradication. Research has played, and will continue to play, a key role in achieving such goals.

Whilst very effective for some diseases, vaccines are not a panacea and should not be the only focus for research. While a worthy goal, disease eradication is rather easier said than done. New products are difficult to develop and may not provide effective solutions. A commitment to investment in research is about more than empirical scientific discovery and the creation of innovative products – it is about improving health by discovering and advancing whatever methods work best. Our existing evidence base shows that small changes can make a difference. However, implementation gaps need to be addressed as a priority.

TABLE 1.3. EXAMPLES OF RESEARCH SUCCESS

EXAMPLE	ROLE OF RESEARCH
Surveillance	Real time data and situational awareness, underpinned by broad use of data, are an integral part of the response to emerging threats (82). Systems that are making a difference to the identification, treatment and control of infectious diseases could not have been developed without significant research into developing tools and diagnostics to detect asymptomatic infections, and a rigorous approach to evaluation of the validity of the data produced.
Better use of resources/cross disciplinary work	Geographic information system (GIS) enabled the development of a spatial model of Loa loa risk in Cameroon. This information provided the baseline data for the development of an integrated approach to tackling *Loa loa* (see Chapter 2).
Community engagement in disease control programmes	Research has helped promote the use of community-based approaches to drug delivery and targeted use of community volunteers for multiple health intervention delivery. Studies have shown that involving communities in their own care can improve the enrolment of participants, which in turn improves the cost effectiveness of disease control programmes (*83*) (see Chapter 3).
Integration of new technologies such as mobile phones into disease control initiatives	Health services research has demonstrated that new, non-medical technologies can offer significant potential to improve disease control and treatment strategies. For example, a study that integrated the use of mobile phones and web-based technology into a routine malaria prevention and control programme on the Thai–Cambodian border showed improvements in the management of malaria cases among an underserved population, with case follow-up rates improving significantly. This study has now been expanded to cover a wider area (84) (see Chapters 2, 3, 4).
Drug development	Effective and affordable drugs to treat malaria in developing countries are still limited. Improvement has been achieved through the increasing development of artemisinin-based combination therapies (ACTs). Research is currently investigating the potential for the development of drug resistance (85) and will continue to play a key role in developing the next generation of artemisinin derivatives.



ACTION 10. ACT QUICKLY ON WHAT WE KNOW

Policy-makers and global funders need to have access to the right information at the right time to inform decisions that draw on the evidence of what works, and feed "best buys" into health policy, health budgets and the operations of health systems. Research data must therefore be rapidly translated into an effective tool for policy-makers.

More effective use of available tools and infrastructure will result in progress. But many opportunities to make a serious difference to global health equity in terms of infectious disease incidence, prevalence, morbidity and mortality are missed or only partially realized. One of the critical reasons for this, which we cannot afford to ignore, is the effectiveness of the link between research and policy.

If we are to effectively reduce the burden of the infectious diseases that plague impoverished communities, we need to understand how to ensure that the research and the research community are both informed by, and inform, activity across the broader social, economic and political landscape. A crucial factor to address is the fragility of the link between the research community and those making the policy decisions that translate research into action. At the political level there needs to be consistent reinforcement of the need to take actions, many of them relatively inexpensive, to implement evidence into practice.

Partnerships between the research community and others, including the private sector, have shown increasing interest in research on infectious diseases (*86*). Research that provides data and evidence needs to be readily available and accessible to support rational decision-making processes across both the political and the funding landscapes. Coordinated policy and planning enables more efficient and effective use of resources and fosters collaboration (*87*). Ensuring that this is based on the best available evidence, supported by robust cost-effectiveness analysis of available technologies and strategies, is essential to the development of effective health policy.

> **Good science is the basis of good public health, but the challenge we face is to translate the best science into public policy.**
>
> Gro Harlem Brundtland, former Director-General, WHO

Research can and should play a key role in informing the decision-making process (the "decision calculus") of policy-makers and global funders. In 2008 the Bamako Declaration established that all countries should have national research capacity so that they can answer nationally relevant questions. Ministries of health were called upon to dedicate 2% of their budgets to research (reinforcing a World Health Assembly resolution in 2008). Unfortunately, implementation of this has been inconsistent thus far (*88*). Encouraging and supporting local governments to make a political and financial commitment to the health of their own populations is crucial.

Available and emerging data from across the research spectrum need to feed into the policy arena to support "best buys" within health policy, health budgets and the operations of health and disease control systems. To do this, research to policy linkages are needed to support the decision-making processes of all relevant sectors.

Under the lens...

The burden of infectious diseases falls heavily on those who have the least ability to deal with it. The lens of poverty adopted in this report provides insights into the dynamics and context of infectious diseases and into the interactions between human health, animal health and the broader social, economic and political environment within which we live. Understanding the complex interplay of factors that affect our risk and exposure to these diseases is key to making progress in tackling them.

This chapter has set the scene and makes the case for research. The next chapters turn the lens on the role of the environment, health systems and innovation. Each of these chapters provides an insight into research evidence and the interface between infectious diseases and poverty, suggesting ways in which investment in research can make a difference to millions of lives. The fifth chapter describes the status of research funding, while the final chapter turns the lens to the macro challenges that will need to be addressed, outlining practical "options for action" that will go a long way towards addressing the challenges identified by the rest of the report.

This report provides a firm foundation for changes in the way that the global health community responds to the challenge presented by infectious diseases of poverty. The synthesis and discussion of the evidence it provides underlines the need for a robust and sustained commitment to tackling infectious diseases, and highlights the contribution this would make to social justice.

Infectious diseases are a pressing global problem, costing lives, reducing life expectancy, sapping economic growth, reducing educational opportunities and increasing the pressure on already fragile health systems. The search for solutions to this pressing public health challenge represents unfinished business of global relevance, work that the world can no longer afford to neglect. We need to invest in research, and the time to act is now.

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2 Environment, climate change, social factors and the implications for controlling infectious diseases of poverty

IN CHAPTER 2:

- Understanding the microbial world – the inescapable starting point
- Drug and insecticide resistance – magic bullets will not suffice
- Climate change, deforestation, urbanization, agriculture
- Hunger and malnutrition – getting the right food to the right table
- Migration and globalization – disease, a worldwide traveller
- Infectious diseases, the environment and poverty – a time bomb in the making?
- "One World, One Health"

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We cannot rely on discovering more "magic bullets" to meet the infectious disease challenges of the poorest billion. A new paradigm is needed that recognizes the fundamental influence of environmental and ecological systems (including climate change), as affected by humans, and integrates across the fields of environment, agriculture, nutrition and social conditions.

Human activities are generating an ever-accelerating wave of change in the natural environment, while new technologies and globalization continue to alter economic and social patterns across the planet. We already know that global climate change and degradation of air, land and water in many areas are capable of profoundly endangering human health. In light of this, it is imperative that the best scientific minds examine the potential of these momentous changes to exacerbate the spread of infectious diseases, so that the world's health systems are ready to respond.

The world's poorest billion people tend to live in ecologically and socially risky environments, which are also where the prevalence of infectious disease is highest. Worldwide, nearly 900 million people do not have access to an improved water source, while an estimated 2.5 billion people – half of all people in developing countries – lack access to adequate sanitation (*1*, *2*). Experience shows that the poor are more vulnerable than anyone when natural disasters strike. They are least able to advocate for sustainable ecological initiatives and will suffer most as the deleterious effects of environmental and climate change increase. And yet the world's poorest billion are responsible for just 3% of the global carbon footprint (*3*, *4*).

The impetus to act is at once moral, scientific and practical. For development to be sustainable, inclusive and effective in lifting people out of poverty, we need to find ways to address these inequities – particularly the links between environmental conditions and the infectious diseases that destroy so many lives and communities. Research can play a key role by informing the global community on the specific effects of climate change and other environmental drivers on infectious diseases and human health – helping us to anticipate what will happen in the decades to come. Such research may point to strategies for overcoming or at least mitigating

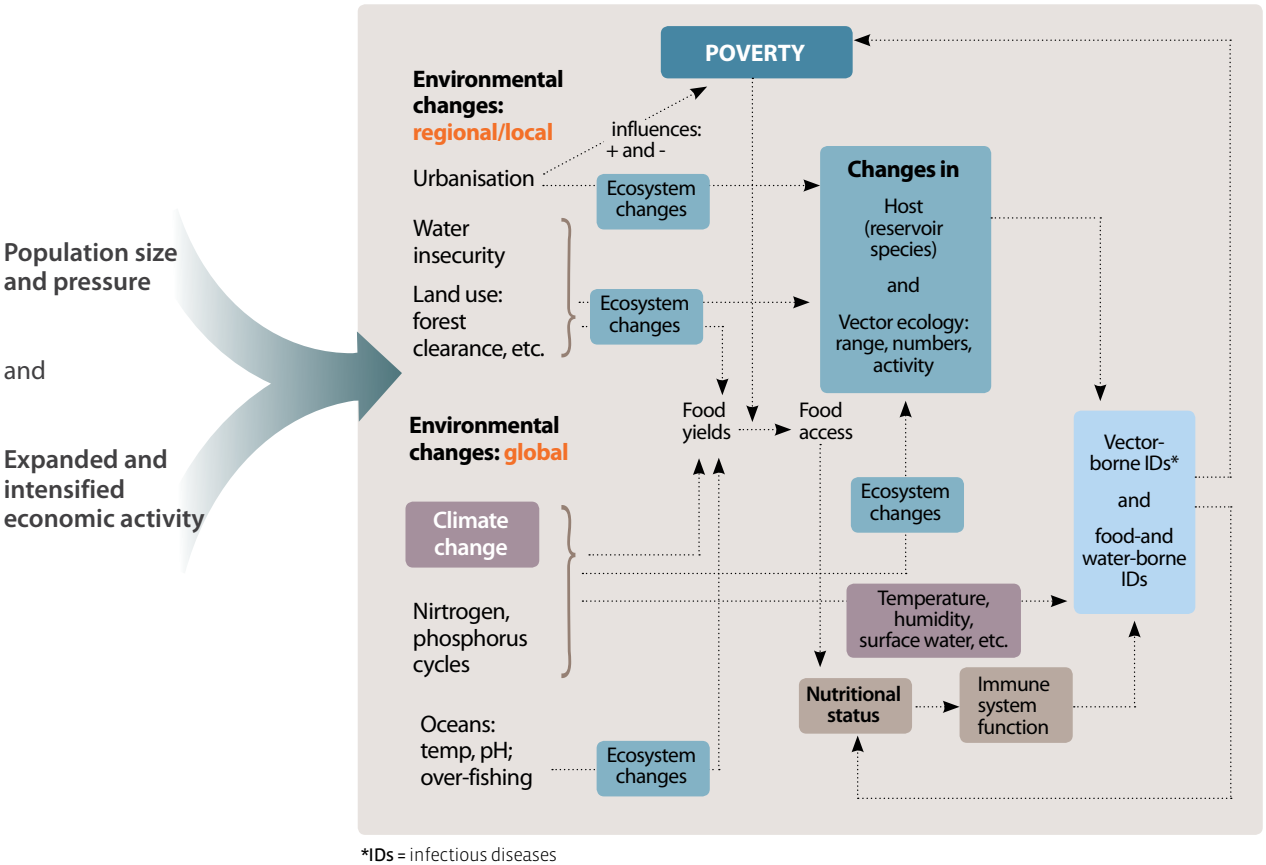

FIG. 2.1. Environmental and social drivers of the infectious disease burden – an interwoven and complex web.
Source: *courtesy of Anthony McMichael.*

the effects of the infectious diseases arising as a result of environmental change. What is really needed is a new systems-based framework, drawing on interdisciplinary thinking and concepts that recognize the broader ecological dimension of infectious disease.

This chapter lays the foundation for a broadened paradigm of infectious disease research. We begin by analysing the core environmental and social drivers of infectious disease: drug and insecticide resistance, climate change, deforestation, urbanization, agriculture, hunger, conflict, migration and globalization. These drivers have complex links to infectious diseases of poverty (see Fig. 2.1) and need to be addressed within an integrative ecological framework, building on the definition of "One World, One Health" that is historically associated with the complex interrelationship between human health, animal health and the environment (5). To this nexus we add the eco-social determinants of health, recognizing that the infectious disease burden in human and animal populations is substantially influenced by changes in environmental and social conditions. To conclude, we list key questions for future research on links between the environment and infectious diseases.

Understanding the microbial world – the inescapable starting point

The impact of human activities on the environment is unparalleled (*6*). Every hour of the day, human activities clear another 1500 hectares of forests, release 4 million tons of the main greenhouse gas, carbon dioxide, into the atmosphere and cause the extinction of three species – a rate at least 1000 times greater than the historical norm (*7*).

These and other environmental changes are affecting the microbial world, resulting in new challenges for controlling infectious diseases. They influence the emergence of new diseases and further the persistence of older, well-established infectious diseases of poverty – including "neglected diseases" (8) such as filariasis, soil-transmitted helminthiasis, onchocerciasis and schistosomiasis, which together have a burden as large as that of tuberculosis and malaria combined. In 2008, nearly 70% of the 8.8 million deaths in children aged under five were caused by infectious diseases (*9*).

Most of today's common infectious diseases entered human populations from animal or (less often) soil and water sources during the past eight millennia. The species barrier was crossed during repeated contact through activities such as land clearing, animal herding and domestication. Village life (which often featured exposure to rodents and other pests, including vectors), urbanization and increases in inter-group and inter-societal contacts via trade, conflict and warfare have enabled species jumps – zoonoses – and the spread of infectious diseases amongst human populations (*12*). In a recent analysis of 335 episodes of human infectious disease emergence from 1940 to 2004, researchers noted that 60% were zoonotic and that 72% of these originated in wild animals (*13*).

Human infectious diseases can be broadly grouped into four categories:

1. Diseases caused by infectious agents ***newly recognized*** as human pathogens that have probably long existed. These include Ebola in Africa and Nipah in south Asia.

2. Diseases that appear to be ***genuinely new,*** such as severe acute respiratory syndrome (SARS), bovine spongiform encephalopathy (BSE) and legionellosis.

3. Diseases that have ***re-emerged,*** such as malaria, tuberculosis (TB), dengue, Chikungunya, West Nile fever, Crimean-Congo haemorrhagic fever and Lyme disease. These maladies have spread beyond their usual geographic confines or have reappeared where once thought controlled. This may be due to the evolution of antimicrobial resistance by pathogens or due to insecticidal resistance by vectors, human migration, HIV/AIDS and changes in transmission strategies (*12*).

4. Diseases caused by infectious agents that are ***changing their modes of transmission,*** such as Chagas disease, which has recently been recognized to have significant oral transmission (*13, 14*), and Nipah virus infection, where there is airborne transmission of the virus between pigs and to their handlers (see Box 2.1).

RESEARCH QUESTION:

We need to better understand the "eco-social" factors which facilitate resistance. What strategies – biological, chemical, genetic, cultural and social – exist to better control pathogens and vectors?

BOX 2.1. CHANGING MODES OF INFECTIOUS DISEASE TRANSMISSION IN AN EVOLVING MICROBIAL WORLD

Though not responsible for a heavy burden of disease, Nipah virus is of scientific interest in that it illustrates how complex ecological factors – including deforestation, intensive agriculture, and possibly climate change – have affected its transmission. This paramyxovirus was isolated in Malaysia in 1997 after the deaths of 105 humans who had been in close contact with domestic pigs (*15*). Increased deforestation and the intrusion of small-scale human livestock operations into forest areas appear to be cofactors for the emergence of the virus. The pigs probably acquired the virus through direct contact with the faeces or saliva of bats eating fruit around the piggery. The pigs then developed a respiratory form of the disease and passed the virus on to their human handlers, who surprisingly did not develop respiratory symptoms but instead died of encephalitis. It was later recognized that Nipah virus also occurs in Bangladesh and West Bengal, India, and is also thought to be transmitted to humans directly by bats and indirectly via date or palm sap (*16*).

DRUG AND INSECTICIDE RESISTANCE – MAGIC BULLETS WILL NOT SUFFICE

Most responses to infectious diseases of poverty have emphasized interventions requiring economic development – better housing, sanitation, public hygiene – alongside improved detection and drugs, insecticides and vaccines. Too often, biotechnological initiatives have not been accompanied by commensurate efforts to achieve environmental and social innovations that can ensure effective implementation. Regrettably, many health workers and poorly informed populations have used drugs and insecticides too readily, thus accelerating the evolution of drug resistance in many microbes and vectors. There have been recent reports suggesting that the parasite responsible for the most severe form of malaria (Plasmodium falciparum) has evolved resistance to artemisinin (*17*). It is also likely that the use of single insecticide-treated bednets will stimulate pyrethroid resistance in mosquitoes, as happened previously when bednets were treated with dichlorodiphenyltrichloroethane (DDT) (*18, 19*).

The response called for is two-fold. First, we cannot rely primarily on discovering more "magic bullets". Rather, we need a new paradigm that integrates diverse fields – a paradigm that recognizes the fundamental centrality of environmental systems and processes, including climate change, to infectious diseases of poverty. Second, we need a more anticipatory approach in our decision-making for infectious diseases of poverty, one that accommodates the complexity and uncertainty inherent in a changing microbial world.

CLIMATE CHANGE – NOT ENTIRELY TO BLAME

The Earth's atmosphere has been getting considerably warmer over the past two centuries. During the last century the global temperature rose by 0.8 °C (*20*). Since entering the industrial age around the mid 18th century, we have produced a vast output of greenhouse gas emissions that now far exceed the planet's capacity to absorb them. Most of the global temperature rise measured since 1950 is attributed to human activity (*20*).

However, climate change entails more than just warming. It includes atmospheric alteration which is driving significant changes in the Earth's weather system, including shifts in rainfall patterns, seasonality and increasingly frequent and severe weather events.

The incidence of extreme weather events is increasing, and climate change is increasingly recognized as a contributory factor. Sixty years ago, there were an average of two weather-related disasters per year; by 2007, this rate had risen to slightly more than six per year. Today, nearly 70% of these events occur in regions of Asia, the Pacific, Africa and the Middle East, where the largest populations of the poor and vulnerable reside (*21*).

These changes affect human health in multiple and complex ways. For example, devastating floods in Pakistan in August 2010 displaced 22 million people. In the same month a prolonged and record-breaking heatwave in Russia, associated with countless fires, killed thousands of people. It also led to a spike in the world wheat price, which in turn contributed to a rise in global food prices and thereby an increase in malnutrition and disease. On another front, global warming is causing a rise in sea levels and increasing the acidity of the oceans as carbon dioxide is absorbed. These and other climate change-related phenomena, collectively and individually, influence the ecology and the life cycles, behaviours and survival of species everywhere.

The manifestations of climate change also influence infectious disease patterns. For instance, warmer weather permits vector survival at higher elevations, spreading malaria beyond its historical geographic range, as has been documented in eastern (highland) Kenya (*22,23*). Climate modelling predicts that further warming may make more areas suitable for malaria transmission. Fig. 2.2 presents data from Zimbabwe examining the geographical distribution of malaria over time. Sixteen climate projections were completed, and in the absence of constraints on malaria transmission imposed by human activity, in all scenarios, changes in temperature and precipitation were shown to alter the geographical distribution of malaria (*24*).

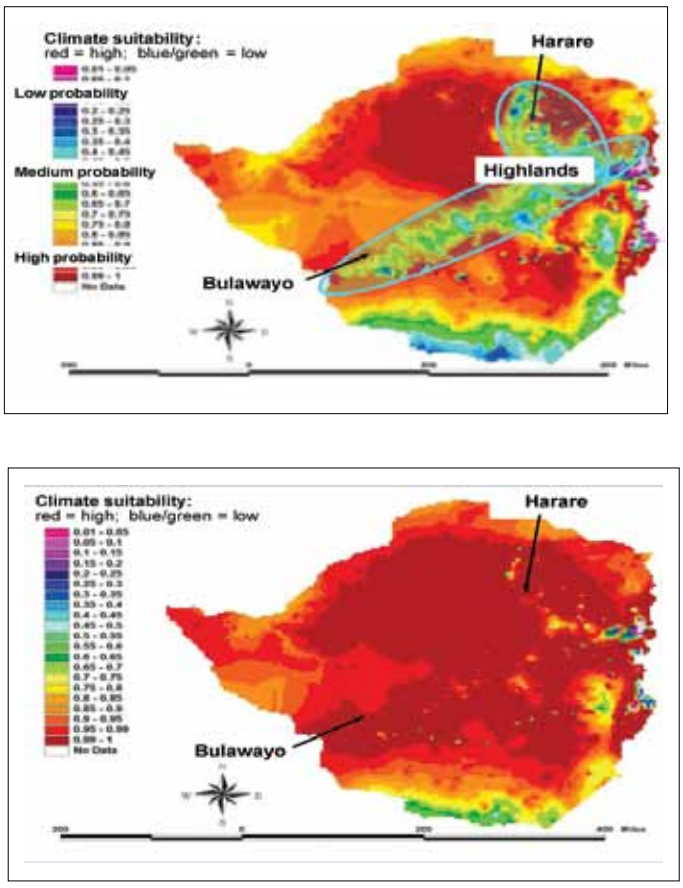

FIG. 2.2. Climate change and malaria: potential transmission in Zimbabwe. *Climate modelling predicts that further warming may make more areas suitable for malaria transmission (see lower image for 2050 projection compared to upper baseline image).*
Source: *reference (24).*

Previously unsuitable areas – such as the central plateau where the majority of the country's population is concentrated – were projected to become suitable for transmission. According to these projections, by 2050, most of Zimbabwe could have a suitable climate for stable malaria transmission (*24*).

Some aspects of climate change may actually benefit health in some areas. For example, warmer average temperatures and hotter extremes may reduce vector populations when conditions are too hot for vector reproduction. Heavier rainfall may wash away mosquito eggs and larvae (*21*). It should be remembered that heavier rains, especially those that lead to flooding, often aggravate malnutrition, diarrhoea and diseases such as cholera.

RESEARCH QUESTION:

What is the most effective way to use existing, orphaned and potential datasets (e.g. epidemiological, social and climatic) to analyse and forecast infectious disease outbreaks?

Overall, however, current evidence suggests that climate change is increasing the global burden of infectious diseases (*25,26*). This is happening in complex ways and in combination with other eco-social changes involving things such as migration, poverty and land use change. In addition, climate is likely to be contributing to the emergence of diseases in regions previously unaffected (including at higher altitudes) and to their persistence and changed seasonality in endemic areas. As described above, extreme weather events affect the incidence and prevalence of many infectious diseases, including cholera and other diarrhoeal diseases. Flood-associated outbreaks of leptospirosis have been reported in countries as diverse as India, Argentina, Australia, Brazil and Italy (*27*).

The precise causal relationship of climate change to infectious diseases, especially those that are vector-borne, remains uncertain. One way to reduce this uncertainty is to establish and support data "observatories", especially in low-income settings. A good location for an observatory would be in a transitional zone between areas either free of, or having low prevalence of, diseases thought to be climate sensitive, and those that have a high prevalence of such diseases. Candidates include the highlands of east Africa and Papua New Guinea. Other good locations are in the slums of the world's megacities. These observatories would gather and monitor social, health and environmental indicators, including those relevant to climate. However, care must be taken not to waste precious funds on indiscriminate data collection. It may also be prudent to build on existing "orphaned" data sets – that is, time series data collected in the past that may have been abandoned due to a lack of funds or for other reasons. To help accomplish this, an inventory of existing and incomplete datasets would be useful.

DEFORESTATION – CUTTING THE BRANCH WE SIT ON

The relentless growth of the human population during the past half-century has stimulated city-building, forest-clearing and the expansion and intensification of agriculture. Collectively, these have dramatically altered the global landscape. While they have brought numerous health benefits for the population at large, many critical "regulating" ecosystem services (*28*) have been damaged, including carbon sequestration, nutrient cycling, the regulation of floods and loss of important natural buffers such as mangroves and wetlands.

Deforestation and other forms of landscape transformation have increased the risk of infectious diseases in several other ways. Pathways include more frequent direct and indirect human contact with rodents, primates, bats and birds, thereby increasing the risk of old and new zoonoses. In the Brazilian Amazon region, 186 different arboviruses have been isolated, of which 32 are known to be zoonotic (*29*). The loss and displace-

ment of predators and competitors can alter the population density of both reservoirs and vectors in complex ways. For example, the extinction of the passenger pigeon, once the most common bird in North America, is thought to have increased the rodent population because acorns, formerly consumed by these birds, became more available for rodents to thrive on. In turn, this increased the habitat and population of Lyme disease-transmitting ticks because mice are one of the principal reservoirs for Lyme disease spirochetes (*30*).

Deforestation can also alter the distribution and population size of vectorial sub-species, many of which have differing capacities to transmit pathogens. The resultant change in vectorial biodiversity can thus alter human and animal epidemiology. This has occurred with onchocerciasis, a disease where it has been shown that transmission has been altered by changes in the density of the different sub-species populations of the blackfly *Simulium damnosum* (*33, 34*). Similarly, forest clearing in Peru has been shown to increase the rate at which *Anopheles darlingi* mosquitoes, the major vector of *Plasmodium falciparum* (one of the malaria parasites), feed on human blood (*33*). In Mexico, genetic changes in mosquito vector populations linked to deforestation affected the transmission of Venezuelan equine encephalitis virus, which resulted in epidemics in animal hosts (*34*). Other examples of human infectious diseases that have increased in prevalence following alterations in biodiversity include hantaviruses, schistosomiasis, West Nile fever and Chagas disease.

Finally, loss of biodiversity is destroying a vast "library" of potentially valuable species – those that could potentially have medicinal, nutritional or ecological value, for example. Artemesinin, ivermectin and quinine, three drugs crucial to infectious disease management, are derived from plant species. Some of this library has been catalogued through countless generations of indigenous experience; the rapid loss of indigenous languages, knowledge and cultures risks eroding it (*35*).

URBANIZATION – IS WEALTHIER ALWAYS HEALTHIER?

The world's population is quickly becoming urbanized as growing numbers of people migrate to the cities. Today, around 3.5 billion people – about half the world's population – live in urban areas; by 2050, this figure may exceed 6 billion (*36*). New cities are forming while many old ones are expanding. In 1975, only three of the world's cities – New York, Tokyo and Mexico City – had populations exceeding 10 million. Today there are 21 such megacities and by 2025 this number will likely grow to 29. The majority of them will be in Asia, followed by Latin America and Africa *(37*).

Careful and far-sighted urban planning can enhance environmental conditions and health. But all too often urban growth is rapid and unplanned, thereby worsening the environment and generating crowding, poor sanitation and water and air pollution (see Box 2.2). These conditions, in turn, increase the risk of exposure to waterborne and respiratory infections, occupational hazards, heatwaves, pollutants and chemical wastes.

BOX 2.2. THE EFFECT OF URBANIZATION ON LAKE TAI, CHINA

Lake Tai (or the Grand Lake) is the third largest lake in China. In May 2007, human activity and pollution produced high levels of cyanobacteria (blue-green) algae that rendered the lake's water unfit for human consumption. This affected 30 million people in the city of Wuxi and its region. Nearly 60% of the water in China's seven main rivers has been judged unsafe for human consumption, harming public health and endangering social and economic development (*38*). Amid all of this, the price of bottled water has risen, further harming the poor.

The cyanobacteria that rendered the water of Lake Tai unsuitable for human consumption.
Photo: courtesy of C Bradshaw

Increased urbanization has been accompanied by rising urban poverty. In 2000, an estimated 128 million poor households were in urban areas; that number is expected to reach 380–455 million by 2020 (*39*). The urban poor are often homeless or survive in illegal, temporary and flimsy shanties. They are also at greater risk of substance abuse, undertaking sex work and suffering violence. Such activities present many challenges to the management and spread of diseases, including diarrhoea, respiratory illnesses, dengue fever, kala-azar, leptospirosis, TB and HIV/AIDS.

Vulnerable urban subpopulations, such as migrants, typically struggle to access health and human services (*40*). The successful implementation of infectious disease control in these settings thus requires addressing the physical and social determinants of transmission: poverty, exploitation and overcrowding. Research is needed to develop effective strategies that control the risk of infectious disease and improve social well-being and quality of life for the poor.

RESEARCH QUESTION:

How can infectious disease control campaigns be incorporated into broader policies to improve the wellbeing of the urban poor?

AGRICULTURE – ALSO SOWING SEEDS OF SICKNESS

The production of a sufficient amount of food for the global population is absolutely essential for human health and livelihood. The management of the agriculture-climate-health nexus is critical, as good nutrition boosts immunity and reduces infectious disease susceptibility. In this respect, agricultural innovations – such as improvements in farming methods, crop varieties and livestock management – can benefit human health by expanding production of safe, nutritious and culturally appropriate food. Improvements in irrigation techniques and waste treatment, food biofortification (see Box 2.3), inoculation of animals and targeted insecticide spraying offer ways in which agriculture can reduce infectious disease prevalence in humans and animals (*41*).

BOX 2.3. BIOFORTIFICATION – ITS IMPACT ON HEALTH

Biofortification is the enriching of food crops (in situ) with essential micronutrients, such as vitamin A, zinc, folate and iron (*42*). Consumption of these nutrient-rich foods can lower vulnerability to infectious and non-communicable diseases (NCDs) and improve the physical and cognitive growth of children and adolescents (*43*). These efforts are consistent with the underlying aims of several of the Millennium Development Goals.

As with deforestation and urbanization, however, agricultural activities can also harm both health and the environment. Agriculture accounts for about 20% of global greenhouse gas emissions, especially through land clearing, livestock rearing and rice cultivation – thereby contributing to climate change and its deleterious effects on human health.

Intensive agricultural techniques can unexpectedly trigger infectious diseases. For instance, large-scale crop farming has led to a rise in the incidence of malaria (as a result of both irrigation and changes in forests and forest species) and of Japanese encephalitis (also associated with irrigation). Large-scale palm oil *(Elaeis guineensis)* plantations in Colombia and Venezuela have provided excellent habitats for Chagas vectors although, as yet, the effect on human health has not been evaluated (*44*). On the other hand, the increased wealth earned from cash crops can, if well managed, reduce infectious diseases. This has been documented in some locations for malaria and it is plausible that palm oil production in Colombia could produce the same effect.

Some agricultural activities can also result in overworking of the soil, contamination

of the food chain with harmful pesticides and unwanted elements (such as arsenic and cadmium) and pollution of ground and surface water. The growing diversion of food crops for biofuels is harming both biodiversity – as is happening in south-east Asia – and human nutrition. In 2011, the global food price index was at a new record high, likely due in part to extreme weather events, rising energy prices and the diversion of food crops to fuel crops.

The raising of animals for meat and of crops for feed (which has increased as growing numbers and increased incomes of consumers in urban areas fuel the demand for higher-value products) is also problematic. As mentioned above, livestock production produces large quantities of greenhouse gases, including methane, carbon dioxide and nitrous oxide (*45*). Intensive farming releases many nutrients, especially in manure, that harm local and even regional ecological systems. Riverine and coastal eutrophication leads to harmful algal blooms and several oceanic "dead zones" that depress marine productivity and thus (again) threaten nutrition (*46*).

Changes in climate and patterns of land use have also influenced the susceptibility of non-human species to infectious diseases. This in turn affects human health and well-being. For the many infectious diseases affecting animals and plants that are not known to infect humans, the resulting loss of livestock, livelihoods, income and sources of food directly affects the social and economic determinants of human health (*47*). For example, foot and mouth disease, which is a very rare cause of human sickness and does not directly kill many animals, has resulted in losses to livestock farmers via trade restrictions and large-scale slaughter of healthy animals to curb the spread of infection (*47*). The fungus *Phytophthora infestans*, cause of the Irish famine in the 1840s, still remains the most significant threat to potato crops (*48*) and the fungus has recently reappeared as a risk to the global wheat crop (*49*).

Some modern agricultural practices also bring humans and animals into closer contact than ever before, facilitating the spread and emergence of zoonoses. In both the field and around and about the home, the risk of disease being transmitted to humans via contamination of food; direct skin contact with vectors; or contact with aerosolized animal droppings and urine has risen to new levels. Already, in Latin America, several arenaviruses (e.g. Machupo, Junin and Guanarito) have spread as humans and infected rodents have come into closer contact with each other in farming areas. Intensive animal farming may also alter viral evolution, as it enables viral mixing and the emergence of new strains, some of which may be more lethal for animals and humans.

As large numbers of agricultural workers migrate to pursue work opportunities, infectious diseases are carried into periurban environments where they can infect a greater number of people (see Box 2.4). Finally, the overuse of antibiotics, especially as growth promoters in animal rearing, can also lead to multiple antibiotic resistance in human pathogens such as salmonella (*50*).

BOX 2.4. AGRICULTURE AND KALA-AZAR IN NORTH-EAST BRAZIL

In the semi-arid regions of north-east Brazil, periods of drought are associated with outbreaks of kala-azar. Small landholders are driven by food shortages to the cities to search for government assistance (*51*). This increases the incidence of this sandfly-transmitted disease in periurban areas and strains local health systems. Climate models forecast that in the next 25–35 years aridity in this part of Brazil will intensify, with increased average temperatures and less rain (*52*). These climatic changes will increase food insecurity and consequent migration – conditions conducive to kala-azar persistence and its possible emergence elsewhere in Brazil (*52*).

HUNGER AND MALNUTRITION – GETTING THE RIGHT FOOD TO THE RIGHT TABLE

For decades, the world has produced enough food to end global hunger and achieve the first MDG. However, the persistent maldistribution of food entitlement (*53*) means that this goal remains out of sight. While migration in search of greater food security usually reflects an acute shortage of locally available food, diverse sociopolitical and cultural factors –including poverty, corruption, high food prices, food waste and ineffectual food storage and distribution mechanisms – also contribute. In fact, from 2007 to 2009 food insecurity was responsible for a 200 million increase in the number of people considered undernourished. Despite there being enough food available to feed everyone (*55*), today more than 1 billion people lack adequate nutrition (*54*). Natural disasters, poor agricultural infrastructure and over-exploitation of natural resources – all linked to global ecological challenges – are among the key causes of hunger and malnutrition.

Lack of food, malnutrition and poor hygiene interact to compromise immunity and increase disease vulnerability (56). Multiple infections or poly-parasitism are common, especially in children. A combination of malnutrition, diarrhoeal diseases, malabsorption and parasitic infections in the early years of life can have long-term negative health effects, including impaired physical and cognitive growth. For example, the average diarrhoea burden in malnourished children in the first two years of life is estimated to lead to a 17% loss in work productivity in later life due to impaired fitness and a loss of nearly 10 IQ points. Progress at school, physical health, and economic and social prospects are all diminished by this. Even the absorption of drugs (needed to combat diseases such as AIDS, TB and malaria, which often coexist with malnutrition and diarrhoea) is impaired (*58*).

It is predicted that climate change will exacerbate malnutrition, especially in low-income countries, by depressing agricultural productivity in many low-latitude countries. There are multiple pathways to this projected outcome, including heat stress, intensified rainfall events and more severe droughts. These threats will be increasingly amplified by sea level rises, particularly in highly productive river deltas such as the Mekong and the Nile (*59*). We need better data to more accurately predict the effect of climate change on food production, as well as its potential for exacerbating food shortages, malnutrition and vulnerability to infectious diseases – and the long-term effect on people and development.

RESEARCH QUESTION:

To what extent and in what ways will climate change worsen malnutrition, thus increasing infectious disease susceptibility? What strategies exist to control these risks?

CONFLICT – ANOTHER MAN-MADE DISASTER, AMPLIFYING INFECTIOUS DISEASE

Shortages of resources such as food, water or oil can interact with divergent claims over access, rights and entitlements to create political instability and, in some cases, outright warfare. The resulting conflicts can amplify existing environmental crises, further undermining the social fabric of communities. There are numerous political "hotspots" where climate change has, or will, amplify existing tensions and conflict. Further, these tensions often cause significant rates of migration and internal displacement while placing additional pressure on the resources of those nations where people go to seek asylum and refuge. Conflict also increases the prevalence of infectious diseases and reduces the availability of health services and their capacity to cope in crisis zones.

In Sudan, conflict has been linked to desertification and shortages of water, food and oil.

It has led thousands of people to leave their homes and seek refuge, often in settings with a higher burden of infectious disease, resource shortages and the other challenges of complex emergencies (*60*). Epidemics of leishmaniasis (visceral and cutaneous), dracunculiasis and African trypanosomiasis have intensified as a result, spreading to neighbouring countries including the Democratic Republic of the Congo (*8*).

Similar situations have been observed in other areas of unrest. Examples include outbreaks of malaria in Pakistan, Afghanistan (see Box 2.5), Tajikistan and Cambodia (*8*). Moreover, evidence from refugee and emergency camps in Africa, Asia and Latin America consistently reveal poor sanitation, disruption of food and water supplies, unhygienic living conditions, substandard housing and poor health care. These can nurture epidemics including cholera, dysentery, diarrhoeal disease and malaria, while concomitantly increasing hunger and malnutrition.

BOX 2.5. MALARIA AND CONFLICT IN AFGHANISTAN

Recent conflict and population displacement in Afghanistan have been implicated in the introduction of malaria into the Bamian valley in the central highlands – at an altitude of 2250–2400 metres, the area used to be malaria free. Researchers found that of 215 peripheral blood smears analysed, 63 were confirmed to show infection by a malarial parasite (90% *P. falciparum* and the remainder *P. vivax*). Mortality rates were high as the area has poor health infrastructure and services (*60*). The fact that the local community had reduced natural immunity to malaria may also have contributed to the high mortality rate.

Conflict also harms health infrastructure and capacity. Many health personnel flee conflict zones, leaving people to manage with fewer resources under greater stress. Relief teams working in conflict and disaster zones may overlook infectious diseases such as Chagas disease, sleeping sickness, dracunculiasis and Buruli ulcer, even though conflict and trauma create heightened vulnerability to infectious diseases (*61*).

MIGRATION AND GLOBALIZATION – DISEASE, A WORLDWIDE TRAVELLER

In a globalized world, migration offers both the possibility of improved socioeconomic opportunities and also the spread of infectious diseases to non-endemic areas, facilitated by increased travel by air, rail, road and even ship. Growing trade volumes also facilitate the spread of disease. A case of "airport malaria" – whereby mosquitoes infected in a malaria-endemic country are inadvertently transported to a non-endemic region – occurred recently in France when a food parcel imported from Cameroon contained mosquitoes that bit and infected the recipient (*62*). On a larger scale, human migration has spread Chagas disease (with its prominent chronic component) from Latin America to countries outside the region. This places an additional pressure on health systems, including those with little experience of such diseases (*63*).

The mass gathering of peoples from different parts of the world for religious, sporting and cultural events also presents challenges to the control and global spread of infectious diseases. For example: Hajj, the annual pilgrimage to Mecca in Saudi Arabia, attracts 1.6 million foreign visitors from 160 countries every year (*64*), making it one of the largest temporary mass migrations today. Documented infectious diseases associated with the Hajj include meningococcal meningitis, gastroenteritis, hepatitis A, B and C, various respiratory tract infections and, most recently, H1N1 influenza (*65*). Lowering the spread of these diseases and other environmental and public health hazards requires coordination and planning from all government sectors of the host country, often years in advance. This includes development of quarantine facilities, vaccine requirements and screening procedures at entry, as well as the upgrade of health services to deal with

additional demand – initiatives which are essential for effective health system functioning and response to infectious disease.

The movement of humans, animals, plants and foods all contribute to "pathogen pollution"; that is, the introduction of a (potentially) pathogenic parasite into a new or native species, population and environment (*66*). A number of parasites have "travelled" to other parts of the world with their human and animal hosts. *Taenia solium* (pork tapeworm) endemic in Latin America, most of Asia, eastern Europe and large parts of Africa, has also recently been found in North America and Europe as a result of migration, tourism and the global sale of pigs and pork products (*67*).

A worldwide trade in wild game and exotic species parallels the global trade of domesticated animals. Nearly 500 million kilograms of meat from free-ranging animal species are consumed in the tropics alone, more than six times the sustainable rate (*68*). The hunting, consumption and sometimes farming of exotic animals, including bats, civet cats, primates and raccoon dogs, is intensifying the likelihood of new infections emerging and being spread effectively via migration and globalization (also see Box 2.6).

BOX 2.6. SARS, WILD GAME AND GLOBALIZATION

SARS emerged in humans in Guangdong province, southern China, in late 2002. Once SARS reached Hong Kong, a global travel and trade hub, the virus spread rapidly to North America, Europe and the rest of Asia, causing nearly 8000 cases worldwide in 2003 (*69*). It appears to have been spread to humans via the consumption of Himalayan palm civets and raccoon dogs, both of which are intensively farmed in China and sold as delicacies in restaurants. The first person to meet the case definition was a chef. It is now thought that Chinese horseshoe bats are the original host, with civets and raccoons forming secondary viral hosts (*70, 71*).

RESEARCH QUESTION:

What strategies can reduce the adverse impact of migration in the globalization of infectious diseases?

Risks also arise from the transport of pathogens (including fungal spores) in fresh produce, plants, livestock and products that use wood, nuts, fibres and roots, as well as certain medicines. In 2011, a rare strain of *Escherichia coli* bacteria, linked to the consumption of contaminated foods, caused a large number of cases of bloody diarrhoea and haemolytic uraemic syndrome in Germany, which then spread to France, Sweden and other parts of Europe (*72*).

The increased global circulation of blood and blood products, human tissues and organs, also contributes to pathogen pollution. Further, when pathogens cross borders they rarely do so alone; poly-parasitism is an important issue, and reflects the interconnectedness and clustering of biological, social and environmental risks in the emergence and spread of infectious diseases.

Infectious diseases, the environment and poverty – a time bomb in the making?

Today, over one-quarter of the world's population, approximately 1.75 billion people, experience multidimensional poverty (*73*). They have poorer health, inferior education and lower living standards than other humans. The poor tend to live in ecologically and socially risky environments characterized by inadequate sanitation; unsafe and irregular supplies of drinking water; absent or intermittent electricity; and use of dirty cooking fuels such as dung, wood and coal. Not surprisingly, the prevalence of infectious diseases is high in these conditions (*73*). Even in wealthy nations there are many vulnerable groups: elderly people, children, and the rural and urban poor (*74*).

Gender is a major determinant of the distribution of infectious disease, including the risk of transmission, health-seeking behaviour and patterns of care. For example, in southern Ghana, women who are engaged in fishing and trapping of shrimps in the mangrove swamps have greater exposure to the mosquitoes that transmit filariasis, contributing to the higher prevalence of lymphoedema in women in this region (*75*). Water contact is linked with the different social roles and practices of men, women, boys and girls in particular locations and this affects the spread and control of schistosomiasis (*76*). In many cultures in disease endemic countries, girls have less access to food and medical care. Many girls and women also experience a disproportionate risk of HIV/AIDS. Less well understood are the links between gender and other social and economic variables such as age, ethnicity and socioeconomic status and further research is needed into these areas (*77*).

The causal relationship between infectious diseases and poverty is often two-way, as outlined in Chapter 1. Infectious diseases affect the poor disproportionately, especially children and women, while chronic or recurrent infectious disease can create or exacerbate poverty. Illness may lead to loss of livelihood and the treatment itself may prove economically disastrous. In some cases the poor have their funds wasted by medical treatment that is of marginal benefit, or even fraudulent (*78*). Whole families can sometimes be impoverished as a result of disease.

Infectious diseases affecting livestock pose additional threats to community well-being and health through lost income, status, livelihood and food. The poorest one-tenth of the world's population (around 700 million people) is predominantly made up of subsistence farmers, many of whom are livestock-dependent (*79*).

High levels of national capacity and wealth certainly impede the diffusion and persistence of infectious diseases, but they cannot entirely prevent their spread, the best strategy for reducing risks in wealthier societies would be to improve health in disease endemic countries. It is also the most equitable course of action. WHO's Commission on Social Determinants of Health has persuasively argued that there is an urgent need to close the gap in health inequities and tackle social injustices (*80*). The socio-ecological drivers we have discussed in this chapter reflect the material and ecological conditions faced by households and policy-makers in disease endemic countries.

How populations are fed, cities built, conflicts resolved and globalization managed profoundly influence the prevalence of infectious disease. This link ought to be a prominent part of the global development discussion. Policy and planning decisions should reflect the need to avoid the harm of adverse environmental change, including that which is caused by the spread of infectious diseases. We need to plan for more integrated, far-sighted and collaborative ways for the world to develop, while at the same time working to reduce the risk and impact of infectious diseases.

Approaches for future research – three tracks to explore

The unprecedented scale and intensity of human activity in the world today, and particularly its environmental effects, presents us with an array of research challenges. Basic research remains essential, but it needs a rich superstructure of more integrated interdisciplinary and systems-based research. The biggest challenge is how best to apply this enlarged and more complex conceptual frame and the attendant analytic strategies and methods to our research.

Research within this context is unlikely to yield much in the way of categorical "yes-or-no" answers – and that has implications for decision-making under conditions of uncertainty and unpredictability. We argue that there are three essential approaches:

1. to better understand the microbial world;

2. to expand and better utilize existing data sets and resources: and
3. to work towards a unified agenda.

It is imperative that future researchers integrate these concepts into their programmes if their work is to have a real hope of controlling infectious diseases of poverty in the long term. As advances are made in science and technology, people (especially in disease endemic countries) are going to be increasingly vital to managing their local environments and reducing the effects of disease. Communities must be involved in the implementation of research interventions designed to minimize the disruptive effects of environmental change.

BETTER UNDERSTANDING OF THE MICROBIAL WORLD

The relationship between the ecology of microbes and the broader environment needs further study aimed at gaining important insights into the biology of microbes and their potential evolutionary adaptations. There may be various natural barriers to the spread of some infectious diseases, but the functions, vulnerabilities and strengths of these barriers are not well understood. For example, why has yellow fever spread from Africa to the Americas but not to Asia? Why are trachoma and rheumatic fevers less prevalent now than 40 years ago, despite having received little to no attention? What are the macro-ecological factors that facilitate the spread of dengue from Indonesia to Saudi Arabia? If these natural barriers and salutogenic (health-promoting) forces can be identified, then efforts can be concentrated on maintaining and enhancing them. Conversely, if there are particular ecological vulnerabilities to disease, preventative efforts such as targeted insecticide spraying can be strengthened and health systems better prepared to respond to an increased number of cases.

However, microbes are highly diverse in their evolutionary pathways and lifecycles, and in their pathogenic adaptations that facilitate spread and persistence in human populations. There is much still to be learnt about the factors influencing the passage from animal to human species; how drivers such as deforestation, urbanization, agricultural practices and migration influence these ecological relationships; and the characteristics of the pathogen that make for "emergence" and for easy and rapid disease transmission. Recent research efforts based on epidemiological, ecological, microbiological, biogeographic and human demographic information have sought to forecast situations of high risk of infectious disease emergence, but this work is nascent and much more investment is needed in this area (*81*).

> **"Invest in research which investigates the natural barriers and facilitators of the emergence, spread and persistence of infectious diseases in order to better control them."**

EXPAND AND BETTER UTILIZE EXISTING DATA AND RESOURCES

GIS and bioclimatic monitoring offer ways to measure, anticipate and plan for infectious disease outbreaks (see Box 2.7). Satellite-derived datasets have been used to predict the risks posed by malaria, Rift Valley fever, visceral leishmaniasis and tick-borne encephalitis (*82*). However, the full potential for infectious disease control from these datasets is yet to be used. Existing datasets such as HealthMapper, the Global Health Atlas (both WHO) and the TREES Project (Tropical Ecosystem Environment Observation by Satellites) from the European Commission offer useful tools to improve infectious disease management and control. Such technologies and systems may also be used to improve infrastructure and capacity in disease endemic countries.

BOX 2.7. GIS, *LOA LOA* AND MINIMIZING ADVERSE REACTIONS TO IVERMECTIN IN CAMEROON

In 2004, an experience in Cameroon demonstrated the public health value of GIS as a means of reducing the risk of severe, sometimes fatal, reactions to ivermectin (the drug used in mass community-directed treatment of onchocerciasis).

It was known that individuals with high *Loa loa* microfilarial counts were at greater risk of dying from ivermectin treatment (*83*). Because this parasite is co-endemic with the onchocerciasis transmitting nematode *Onchocerca volvulus* in many parts of central Africa, it was recognized that mapping *Loa loa* distribution would identify areas where the greatest risk of severe adverse ivermectin reactions was highest. A spatial model of *Loa loa* risk was therefore developed, integrating prevalence with geospatial data for altitude, forest cover and soil type. This information was incorporated into the African Programme for Onchocerciasis Control (APOC) planning for community-directed ivermectin treatment (*84*). This was then refined by WHO/TDR studies that developed a field applicable, community-based rapid assessment procedure – RAPLOA – based on community recognition of ocular Loa infections (*85*).

Mobile phone technology also offers new ways of implementing telemedicine and disease surveillance. Prototypes with phone-mounted light microscopes have been used to detect *P. falciparum*-infected and sickle red blood cells, and *M. tuberculosis*-infected sputum samples (*87*). While such technology is still under development – and must be affordable, durable and usable to have wide reach – it illustrates an exciting possibility.

> **Use and expand existing datasets and new technologies to map disease prevalence and to identify areas for intervention and control.**

"ONE WORLD, ONE HEALTH"

The need for intersectoral collaboration is now urgent. Funding priority should be given to research that adopts inter-disciplinary approaches; encourages collaboration between government ministries and agencies; and better incorporates ecology into disciplines – including public health, medicine, social sciences, veterinary sciences and agriculture. The health sector is increasingly struggling to cope with the consequences of poor management of climate change and environmental damage, yet there are many intervention points that governments can use to prevent the loss of human life and livelihood. It is only through closer collaboration between government, private sector, civil society and communities – in areas such as agriculture, technology, education, social welfare, transport and health – that the complex socio-ecological drivers which contribute to ill-health can be mitigated.

The "One World, One Health" model offers such an integrated approach. As contact between humans and animals becomes more frequent, there are more opportunities for infectious agents to cross the species barrier. Domesticated species (especially pigs) can serve as viral mixers, combining and recombining influenza viruses of human, porcine and possibly avian origin (*87, 88*).

It is critical that research findings, clinical experience and learning from both human and veterinary domains be connected.

Areas needing research include effective ways to build capacity among human and veterinary pathologists; integration of disease-surveillance, shared animal-human epidemiological studies; and best ways to develop health services able to deal with animal and human health (*89*). The socio-economic impact of zoonotic diseases on livestock production and the consequences that control of such disease (such as the condemnation of carcasses) have for the livestock trade need to be studied, as does how zoonotic diseases impact on wildlife populations and biodiversity. How social variables (gender, ethnicity, culture) influence human-animal interactions, the transmission of disease, cultural aetiologies of disease and patterns of health-seeking, as well as the social and mental health consequences of disability caused by infectious disease (e.g. social stigma, fear), are also areas needing further inquiry.

> **"Stronger collaboration between government ministries and agencies is needed to fund interdisciplinary approaches to research on human-animal health."**

Collaborative approaches work. Rinderpest was a disease that once devastated livestock and wildlife and destroyed rural livelihoods and food supplies. This was eradicated from cattle through vaccination and surveillance efforts under The Global Rinderpest Eradication Programme (GREP), spearheaded by the Food and Agriculture Organization and with support from the World Organisation for Animal Health, the African Union, the South Asian Association for Regional Cooperation and other donor agencies (*90*). During the 2009 H1N1 influenza pandemic, good research and rapidly shared information led to clear clinical protocols and appropriate vaccines, which in turn enabled effective containment (*91*).

Communities also have an important role to play in preventing the spread of infectious diseases of poverty. In the Democratic Republic of the Congo, the Wildlife Conservation Society has established a network of hunters and other local people to report sightings of dead primates showing signs of Ebola. Researchers then test the faeces of the reported animals to see if they are infected. In Ebola "hotspots," researchers also monitor great ape health, collect diagnostic samples and teach Ebola prevention awareness in at-risk communities. Local people are provided with information on how to prevent contamination and minimize the spread of the virus. In these parts of central Africa it is the Wildlife Conservation Society field veterinarians who deliver education and information to communities about Ebola and other zoonotic diseases (*5, 92, 93*).

If we are to achieve a more unified agenda, investment is required in human capital and knowledge systems. Interdisciplinary research and action are only possible when there is a common meeting ground. The education sector, especially universities, has a role to play in building capacity and fostering interdisciplinary learning in a new generation of scientists and policy-makers. This is part of shifting the paradigm of how research is conceptualized and practised, through encouraging interdisciplinary work.

Conclusion: a big picture requiring intelligent investment and interaction

Increasing recognition of the interplay between demographic, social and environmental factors in infectious disease occurrence is leading to a more integrative, ecological, approach to studying, understanding, preventing and responding to infectious disease risks and outbreaks. This has important consequences for the repertoire of required research – topics, methods and interpretation – and for the social application of research findings.

A tantalizing inverse law often seems to apply to the conduct of research – the larger the frame of the research question and the more complex its constituents, the less precise and certain is the research result. Yet that result will often help us to understand the upstream determinants of vulnerability, risks, behaviours and exposure patterns that influence the probabilities of infection occurring or persisting.

It is becoming increasingly apparent that large and growing forces impede the control and eradication of infectious diseases. These dimensions of "causation" must be more purposefully studied and better understood, otherwise we face the continuing prospect – already clearly evident in the generally slow and partial achievement of many of the United Nations' MDGs – of making welcome downstream advances in local disease control and treatment, but failing to address simultaneously the larger-framed upstream loci of intervention. In general, those larger-framed interventions will provide the key to finding *sustainable* solutions – solutions that entail wiser management of the natural environment (and its multiple microbial sources); wiser and fairer commercial practices; and social policies that reduce poverty, disadvantage and inequity.

Sustainable solutions to the specific causalities of the infectious diseases of poverty will also come from interdisciplinary research that considers the upstream "big picture".

"Sustainable solutions to the specific causalities of the infectious diseases of poverty will also come from interdisciplinary research."

A continued research focus on the downstream effects of these diseases, resulting in more effective therapies, may not be enough to break the cycle in which it appears the affected populations are now trapped.

Ultimately we must learn how to think more widely and in a more socially and ecologically sophisticated manner about how we undertake human activities: how we produce our food; undertake travel and trade; encroach upon and manage the natural environment; construct our cities; and interact with each other and other forms of life.

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3 Health systems research and infectious diseases of poverty: from the margins to the mainstream

IN CHAPTER 3:

- Understanding the role of health systems research
- Leadership and governance – getting a grip on things
- Financing – the right level at the right time and place
- Human resources for health – caring comes from people
- Medicines and technology – an essential combination
- Health information and health infrastructure – good data clear the path
- From dependence to ownership

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Successful control of infectious diseases of poverty requires a positive interrelation between programmes for disease control and the rest of the health system. Research can help to develop a better understanding of the relationships between disease control interventions and health system components, other sectors and the broader contexts of living in poor communities. We explore this relationship in this chapter and outline how research can help.

In an ideal world, wherever he or she lives, every individual should have access to quality health care whenever they need it. The goal of all health systems is to attain this ideal of universal coverage by providing primary health care services that are accessible, equitable and responsive to the needs of their target communities. While many country health systems struggle to attain universal coverage, low-income countries face particularly complex challenges. Health systems research has great potential to address health systems strengthening for effective infectious disease control.

Poor countries of Africa, Asia and Latin America carry the greatest global burden of disease and their population health needs exceed the capacity of health services and providers. Prevalence rates of infectious diseases of poverty are high; multiple conditions co-exist in the same geographical location; and large numbers of individuals live with multiple infectious diseases, often of chronic duration (*1, 2*). Poverty and wider socioeconomic and sociopolitical factors increase the disease burden of these countries. Prevalence rates of infectious diseases of poverty and neglected tropical diseases (NTDs) are highest in countries that have political instability, authoritarian rule, suppression of human rights and conflict (*1*). Global economic forces and donor activities have been shown to challenge the ability of weak governments to invest in health systems and quality health care for their populations in a way that reflects national priorities.

In the 1980s, structural adjustment policies imposed on African, Asian and Latin American countries by the International Monetary Fund (IMF) and the World Bank led to economic reforms that had a negative impact on public institutions, including health systems (*3*). Following the establishment of the Millennium Development Goals (MDGs) in 2000, increased resources for infectious disease control have become available through innovative channels of development assistance termed Global Health Initiatives (*4*). The better known of these include the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), GAVI Alliance, UNITAID and the African Programme for Onchocerciasis Control (APOC). Global Health Initiatives have contributed to the creation of complex health systems, with an increasing number of actors entering the field of infectious disease control and implementing diverse health systems strategies through vertical, often fragmented, programmes that conflict within countries.

“Global Health Initiatives have contributed to the creation of complex health systems, with an increasing number of actors entering the field of infectious disease control and implementing diverse health systems strategies through vertical, often fragmented, programmes that conflict within countries.”

There is a consensus that strong, well-integrated and effective health systems are essential to reducing the disease burden and to achieving the health MDGs. Strong health systems typically consist of the seven building blocks shown in Fig. 3.1: service delivery; governance structures; financing mechanisms; human resources; medicines and technology supply systems; health information systems; and participatory community mechanisms (people). Ideally, these seven components must exist and work in concert to produce quality (accessible, equitable, responsive) health care.

Health research and policies are needed to strengthen health systems serving the poor and to integrate disease control programmes in a sustainable way. Health systems research has been defined as:

> *“the production of knowledge and applications to improve how societies organize themselves to achieve health goals, including how they plan, manage and finance activities to improve health, as well as the roles, perspectives and interests of different actors in this effort”* (*7*).

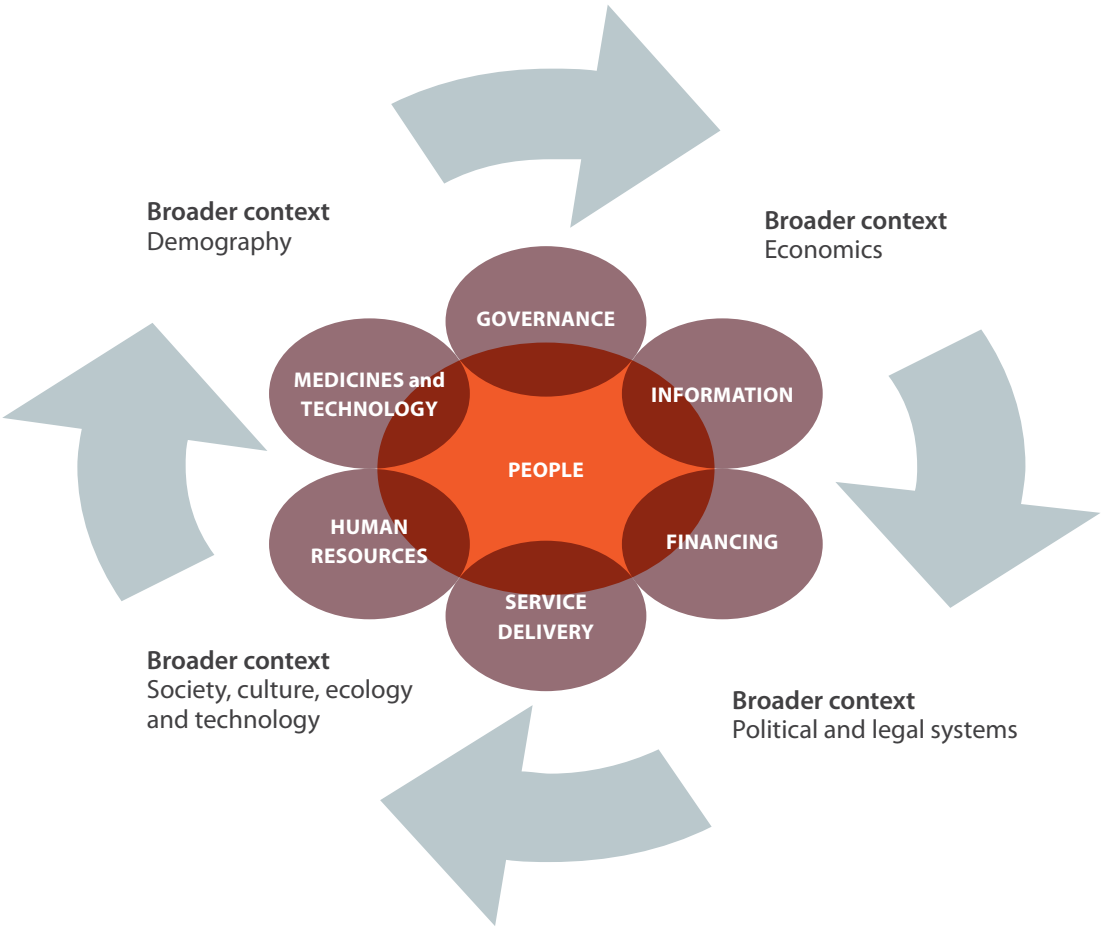

Fig. 3.1. **Interrelations of health system components through people and the broader context**

Source: *References (5, 6).*

Health systems research is concerned with health policies, organizations and programmes on which health ministers, policy-makers and service managers draw to make critical decisions about organizing and changing health systems (*8*). The field therefore focuses on how research can better examine the interrelationship between health systems and disease control programmes in order to improve health service delivery (*7*). This interrelationship is addressed by focusing on the demand side and the supply side of health systems. The demand side refers to population health needs: here, health systems research addresses the relationship between health systems and communities or health service users. The supply side refers to health services and other structures, such as those provided by modern health teams, traditional healers, community delivery mechanisms and patient groups. In this case, health systems research examines the broader socioeconomic and political context in which health systems are situated through its focus on the roles, perspectives and interests of the diverse actors engaged in health systems development and strengthening at local, national and international levels.

This chapter examines how health systems research sheds light on the complex relationship between infectious disease control programmes and health systems and offers opportunities for strengthening health systems to improve healthcare for the global poor.

In the first section of this chapter we provide a review of health systems research insights that help our understanding of the complex way in which health systems and disease control programmes (particularly those

funded by Global Health Initiatives) intersect in the delivery of health care. We focus on the seven health system components and, for each, explore this relationship by asking a number of questions: What is the ideal structure and goal for the health system component? What are the existing challenges and problems with respect to the building block? How might the challenges and problems be addressed? How can health systems research help this process?

In the second section, we address future approaches for health systems research by proposing three cross-cutting issues that need to inform how positive synergies between health system components and infectious disease control programmes are developed: (i) advocacy for values; (ii) systemic approaches; and (iii) capacity strengthening in health systems research. We conclude by offering a synthesis of the key research questions that must guide health systems research approaches towards strengthening the relationship between health systems and infectious disease control programmes for universal coverage.

> **"The bulk of Global Health Initiative investments and activities focus on the big three diseases: HIV/AIDS, TB and malaria. There are limited to no investments in improving access to treatment of other infectious diseases of poverty. The focus on equity often reflects the priorities of Global Health Initiatives and not the priorities of countries."**

Understanding the relationship between health systems and disease control programmes and the role of health systems research

In this section, we present an overview of health systems research insights on the seven building blocks and identify one key research question for each block. Some building blocks have received more attention than others, therefore the scope of available information and the implications for further research vary. We conclude this section by summarizing what existing research on the health systems components means for the future conceptual and methodological development of health systems research, particularly in terms of addressing the mutual interrelationship between infectious diseases and poverty in low-income countries.

SERVICE DELIVERY – FINDING THE RIGHT MIX

The main goal of health systems is to provide health services that are accessible, equitable and responsive to the needs of their target communities. This goal can be achieved when all the other health systems components work in concert at optimal levels. As we will see in the following sections, many low-income countries lack appropriate infrastructure; the right mix of health workers; and the systems to make medicines and medical technologies available at point of community need. As a result, service delivery is severely compromised. The challenges that service delivery face and the strategies to address them must therefore be understood within the context of the challenges faced by other health systems components, as well as of the support they can lend for infectious diseases control.

It is useful to outline important successes and challenges in efforts to improve service delivery in low-income countries as a backdrop for the discussions that follow. Health sector reforms instituted by some governments in the 1990s led to improvements in health

CASE STUDY 3.1

Integration of lymphatic filariasis through decentralization and primary health care reform

Integration of the lymphatic filariasis programme in the Dominican Republic has improved both the programme and primary health care. Geographicalal coverage of mass drug administration increased and the number of municipalities achieving the target coverage rate of 80% rose by 21%. Benefits for primary health care included improved information systems and strengthened relationships between health services and the community. Best practices documented were: professional development of disease-specific programme staff as their roles changed; strengthening of specific weaknesses in the general health system; active engagement of senior management at an early stage; and continual evaluation of the impact of integration.
Source: Reference (9).

CASE STUDY 3.2

The Colombian health sector reform

The Colombian health sector reform implemented in the early 1990s has had some positive impacts on disease control and, more generally, on health equity. However, problems have also arisen due to rapid implementation and the nature of some reform features.

In the case of malaria, research showed positive signs including: the strengthening of central control staff when transferred from the Ministry of Health to the National Institute of Health; improved opportunities for planning initiatives and intersectoral cooperation; and the reduction of malaria mortality (due to diagnosis and treatment being integrated into general health services). On the negative side, the reform did not solve the shortcomings of the old vertical control system, such as the negative aspects of trade union activity. Meanwhile, some positive aspects of the old system – such as capacity building, operational planning and supervision – were lost through the decentralization of scarce resources to the provincial level (***10***).

In the case of TB, the Colombian reform also led to a weakening of the national programme's capacity for case detection and control, leading to a decrease in critical indicators (***11***). It has been argued, based on the evidence, that the reform's reliance on private for profit providers and insurers led to a loss in the capacity to target public goods for TB control (***12***).

service delivery and other health system components (Case study 3.1) (*9*). In other countries results have been more mixed. For instance Colombia's health sector reform recorded positive impacts on disease control and equity but led to a weakened national programme for TB case detection and control (Case study 3.2) (*10–12*).

Since 2000, improvements in service delivery have occurred through Global Health Initiative investments (*4*). An increased access to HIV/AIDS services and insecticide-treated bednets has been reported in some African countries. There have been various efforts to integrate health interventions, the two main approaches being integration of (i) HIV and TB control; and (ii) onchocerciasis control with malaria case management, insecticide-treated bednet distribution, Vitamin A distribution and monitoring of directly observed treatment for TB. In the Democratic Republic of the Congo and in Zambia, the extension of TB services to scale up HIV/AIDS care led to increased service coverage and access to HIV/AIDS care for individuals with co-infections. In African countries where multiple health interventions were incorporated into community-directed interventions for onchocerciasis, treatment coverage with ivermectin was high and good results were obtained for coverage of additional interventions.

Service delivery in terms of equity has also improved in some countries. Strategies – such as provision of free access to care and outreach programmes – have been established to benefit the poorest, most marginalized and stigmatized groups in poor countries (such as commercial sex workers and men who have sex with men) (*13*). The quality of services has improved through a number of strategies – including the development of standardized guidelines of care (for example for HIV/AIDS) and global procurement systems that led to universal standards of care. Service delivery strengthening has led to improved health outcomes and to positive ripple effects in other areas, such as higher demand for a wider array of health services. Other examples are significant correlation between HIV intervention and improved family planning and antenatal care services in Rwanda. In Haiti, HIV intervention has improved a range of services including family planning; vaccination; case detection and cure of TB; and health promotion. In Botswana and Uganda reduced disease-related disability and mortality has meant household support of infants has improved. In some instances the reduced infectious disease burden has made resources available to tackle other essential services, such as infrastructure, laboratory support and health worker training. For example, in Mexico the programme to scale up immune-preventable disease control towards universal coverage invested in the establishment of regional surveillance laboratories designed to support other, lower priority, disease control programmes (*14*).

Despite these service delivery improvements major challenges remain. The bulk of Global Health Initiative investments and activities focus on the "big three" diseases: HIV/AIDS, TB and malaria. There are limited to no investments in improving access to treatment of other infectious diseases of poverty. The focus on equity often reflects the priorities of Global Health Initiatives and not the priorities of countries.

For example, Global Health Initiatives often disburse HIV or TB funding to countries with a low burden of these conditions, or neglect marginalized communities such as urban slum communities. Finally, standardized care guidelines often have an imperative to meet numerical targets and local health providers' quest to meet these goals can sometimes undermine quality of care.

LEADERSHIP AND GOVERNANCE – GETTING A GRIP ON THINGS

Leadership and governance are central to the development and strengthening of all the health systems components. The United Nations Development Programme (UNDP) has defined governance as "the exercise of political, economic and administrative authority to manage a nation's affairs" (*15*). Governance for the health sector has been defined as the effort to rationalize "the role of government (reducing its dominance and sharing roles with non-state actors); empowering citizens, civil society, and the private sector to assume new health sector roles and responsibilities; and creating synergies between government and these actors" (*16*). Several indicators have been developed to evaluate the quality of governance. These include effectiveness in the delivery of quality public services; regulatory quality in relation to private sector development; voice and accountability of citizens and civil society; the control of corruption; and the maintenance of political stability. Many low and middle-income countries score poorly on some or all of these indicators.

Global Health Initiatives have created a new challenge for health leadership and governance in terms of the way their priorities sometimes intersect unfavourably with the priorities of governments. Therefore, a recurrent and urgent research issue concerns the need to understand the changing relationship between Global Health Initiatives and governments and how this shapes the future development of health systems. It is generally recognized that political leaders and health policy-makers lack the power to set national health agendas. This lack of power is strongly associated with the power of development partners and international funders to shape global and local priorities. Research suggests that Global Health Initiatives distort recipient countries' national policies and priorities, by forcing governments to focus on global priorities and distracting them from coordinating efforts to strengthen health systems.

"It is generally recognized that political leaders and health policy-makers lack the power to set national health agendas. This lack of power is strongly associated with the power of development partners and international funders to shape global and local priorities."

This leads to fragmented planning, management, and monitoring and evaluation systems. For example, a campaign in Mali to treat the five most neglected tropical diseases led to disruption of basic health services as staff were diverted from their routine duties to run, report on and evaluate the campaign (Case study 3.3) (*17*).

International initiatives – such as the 2005 Paris Declaration on Aid Effectiveness, the 2007 International Health Partnership and the 2008 Accra Agenda for Action – have called for the strengthening of country ownership of health aid, whereby governments are self-empowered to exercise effective leadership over policy development, strategy, coordination, implementation and evaluation.

CASE STUDY 3.3

Health system impact of the Neglected Tropical Disease Control Initiative

In 2007, an integrated control programme was initiated in 24 districts across 3 regions in Mali. Funded by the United States Agency for International Development (USAID) through two international nongovernmental organizations (NGOs) – the International Trachoma Initiative and Helen Keller International – the programme involved mass drug administration for the five most neglected tropical diseases (lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminths and trachoma). The programme yielded both positive and negative results across the six health systems building blocks outlined in Fig. 3.1. However, overall effects undermined health systems performance. At point of delivery, campaign-related workload severely interfered with routine care, which was cut down or totally interrupted during the campaign. Importantly, only 2 out of 16 health centres with better-qualified, stable and motivated workforces were able to keep routine services running and to use the campaign as an opportunity for quality improvement. Staff income was significantly improved by allowances, but sustainability beyond the funded programme was questionable. Parallel systems established for drug supply and evaluation demanded extra efforts, thereby burdening local health systems. The campaign budget barely financed institutional strengthening and the mediating role of the international agencies involved undercut the decision-making processes of the Ministry of Health. Pressures to absorb donated drugs and reach short-term coverage results helped distract energies from other priorities. The programme evaluators underscored a common argument that "positive effects of GHIs are more likely to occur when the health system is robust" (*17*).

It is worth noting that the economic fortunes of some emerging economies have improved over the last decade. Of the ten fastest growing economies in the last decade, six were in sub-Saharan Africa (Angola, Chad, Ethiopia, Mozambique, Nigeria, Rwanda); three were in Asia (Cambodia, China, Myanmar); and one in eastern Europe (Kazakhstan). This is likely to impact on governance and aid effectiveness. The private sector plays a significant role in strengthening the macro-economy of African countries (*18*). It has invested around US$ 11.5 billion (an average of 3% of Africa's gross domestic product) in the region and is driving the expansion of technology access. This has implications for wider social determinants on health (e.g. job creation, trade, communication, access to knowledge) and on health systems strengthening (through inter-sectoral collaboration e.g. on information technology (IT) and health information systems, production of health products and improved access to medicines).

RESEARCH QUESTION:

How do we develop research frameworks to assess the reciprocal impact of global initiatives and national health systems and intersectoral governance on infectious disease control?

Diaspora communities have played an important role in the macro-economic success stories of Africa and Asia. In the 2000s, the brain drain of the 1980s and 1990s was transformed into a more nuanced transnational phenomenon termed "brain circulation" as diasporan African and Asian professionals returned to influential positions in the public and private sector in their home regions and countries. This has contributed to the growth of the private sector, particularly in areas such as information and health technology. In Ghana, innovation for the production of health products (generic medicines, antiretrovirals, herbal medicines) is spearheaded by diasporan groups with access to international networks and financing (*19*). It is important to factor these trends into discussions of the current and future nature of the relationship between Global Health Initiatives and governments, particularly in the areas of governance and financing. Because leadership and governance issues permeate the development and strengthening of all the health systems components, we go into further detail in the following sections.

FINANCING – THE RIGHT LEVEL AT THE RIGHT TIME AND PLACE

Financing involves mobilizing, pooling and allocating money to sustain health delivery programmes and to cover the health needs of the people (*20*). Health systems research has focused on three aspects of financing in relation to infectious disease control: (i) the amount and effectiveness of global funding and its relationship to national funding; (ii) the coordination of funding by health systems across diverse priorities and programmes, and (iii) the extent to which financing lowers financial barriers to health service users and protects them from ill-conceived and impoverishing expenditures.

Substantial financial investments have been made in health systems strengthening and disease control programmes in low and middle-income countries. Estimates of global funding needs to meet the MDGs from 2009 to 2015 diverge widely (ranging from US$ 111 billion to US$ 251 billion) – demonstrating a limited knowledge of what would be the most rational strategies for service delivery and capacity strengthening, always a key problem in global funding.

One particularly worrying example of this problem is a skewed approach to funding the control of prevalent diseases. Currently there are over 100 Global Health Initiatives focusing on at least 26 disease areas (*4*). However, focus has usually been on single diseases, with HIV/AIDS attracting the majority of funding over the last 20 years. In 2007, out of approximately US$ 14.5 billion of development assistance for health (for which

project-level information was available) US$ 5.1 billion was allocated to HIV/AIDS. This compared with US$ 0.7 billion for TB, US$ 0.8 billion for malaria and US$ 0.9 billion for health sector support (*21*). Research has pointed to a discrepancy between global and national priorities, with the dominant focus on HIV/AIDS being more the product of donor values and interest, rather than of national health needs. For example, actual funding for HIV/AIDS increased more than twelvefold between 1992 and 2005, yet during the same period adult prevalence of HIV rose approximately fourfold. The case has been made for a more equitable channelling of resources for infectious disease control (*22*). This can be done by moving beyond the over-focus on the "big three" diseases, to tackling the diseases of the majority of the poor which represent "low-hanging fruit" that can be addressed through available preventive interventions.

A second problem with global funding is the challenge of determining whether and when funding should focus on short, medium or long-term goals (*23*). On one hand, short-term Global Health Investment funding cycles have been criticized for inducing vertical demand-side programmes that seek fast disease control and elimination targets, fragmenting health system governance in the process. On the other hand, horizontal, supply-side programmes funded by governments have also proven inadequate to provide quality and effective disease control. A middle ground, termed the "diagonal approach", has been proposed to scale up disease control in ways that strengthen the capacity of the wider health system (*14, 23, 24*). As discussed above concerning governance, evidence suggests that the diagonal approach can protect critical vertical programmes from redistributive claims by other programmes. At the same time, the diagonal approach can enhance local and country ownership and align the goals and policies of local, national and global actors (*23, 24*). A critical challenge for health systems research is to examine and establish when global finance should be planned for the short to medium term to achieve urgent disease control or elimination targets (for instance, within the context of civil war and population displacement), and when funding is planned for the long term to help strengthen health systems as a whole.

Health systems in most low-income countries find it difficult to coordinate funding from the many sources that have now become available (*4, 23*). Their budgeting procedures are not suited to identifying disease control programme funding gaps. There is also limited or no capacity to track how money is spent or to link financial inputs to health-related outputs. Responses to these difficulties now include the adoption of sector-wide approaches (SWAps) and/or general budget support (GBS) which have helped some countries to coordinate the flow of resource between donors and government agencies (*25, 26*). SWAps involve donors pooling their funds based on strategic health sector plans jointly developed with the health ministries, to be disbursed against specific expenses such as salaries or infrastructure development. GBS involves channelling donor funds to the ministry of finance in the host country, rather than directly to the ministry of health. Some countries have introduced pay-for-performance schemes in order to provide incentives for health workers and health service users that extend access to essential services (*27*). The potential and limitations of these innovative tools need to be researched to ensure they complement non-financial incentives.

Over 100 million people are pushed into poverty every year due to health care expenses. The poorest people experience the most ruinous costs of health care. As much as 60% of total health spending in low-income countries is estimated to come from out-of-pocket expenditure (the comparable figure in high-income countries is 20%) (*4*). Poor people need to pay for this out-of-pocket expenditure from their meagre income or by selling personal possessions and borrowing money. This deepens financial and social insecurity and emphasizes the urgent need for social health insurance and other financial protection interventions for the poor. The ideal route to providing quality health care in an equitable, efficient and

sustainable manner is probably through a mix of financing sources, taxation and, to a much lesser extent, out-of-pocket expenditure (*28*). Poor countries have typically faced enormous obstacles in offering this mix of financial interventions to their citizens. Social insurance schemes are based on strong equity principles, but their success depends on how they identify and target vulnerable social groups; how they structure the range of services and diseases covered by the scheme; and how they develop cost containment mechanisms while protecting the poor (*29, 30*).

Locally based community health insurance schemes have provided financial security for primary health care and basic hospital care in some poor African and Asian countries although, so far, there has been modest capacity for collecting revenue, pooling resources and purchasing services through these schemes. However, such schemes have been found effective in modifying the demand for, and the supply of, health care in the community (*31*) and thus could play an as yet unexplored role for disease control. Microfinance schemes have proven particularly effective in supporting health provision. Research suggests that microfinance schemes improve knowledge and facilitate positive health behavioural change in both maternal and child health and infectious disease programmes (*32–40*). Careful design, implementation and evaluation of intersectoral programmes are required to link microfinance and health as an innovative response to the ongoing challenges of poverty, social exclusion and chronic disease (*32, 34*).

Global Health Initiatives have increased public financing and may have contributed to reduce out-of-pocket expenditures for specific diseases such as HIV/AIDS. However, they have not yet invested systematically in the development (or extension) of pre-payment or insurance mechanisms.

RESEARCH QUESTION:

What is the best mix of infectious disease control funding mechanisms to strengthen health system financing, and in what contexts?

HUMAN RESOURCES FOR HEALTH – CARING COMES FROM PEOPLE

The health workforce, or human resources for health (HRH), encompasses a broad range of actors, including public and private-sector doctors, nurses and midwives, as well as informal health providers such as "family caregivers, patient-provider partners, part-time workers (especially women), health volunteers and community workers" (*41*). However, health systems research has focused largely on workers formally employed by public health sectors. Research consistently shows that low-income countries face some major HRH constraints (*4, 42–46*). There is shortage, attrition and maldistribution of health workers. Attitudinal factors such as a lack of motivation have also been highlighted. The importance of research on human resource problems is critical not only to improve health system effectiveness, but also to implement health research findings in general:

> *"Health service providers are the personification of a system's core values – they heal and care for people, ease pain and suffering, prevent disease and mitigate risk – the human link that connects knowledge to health action. At the heart of each and every health system, the workforce is central to advancing health."* (*41*)

Including doctors, nurses and midwives, 23 health workers per 10 000 people has been set as the minimum number required to achieve 80% coverage for measles immunization or for deliveries by skilled birth attendants. Most low-income countries have a shortage of health workers according to this criterion. In 2006, WHO reported a worldwide shortage of almost 4.3 million doctors, midwives, nurses and support work-

ers (*41*). Of the 57 low-income countries that faced severe shortages (averaging 2 or fewer health workers per 10 000 people), 37 were in Africa. HRH shortage has been attributed to limited capacity for training health workers in low-income countries. For example, some African countries lack the capacity to train doctors locally, leading to necessary (but financially crippling) investment in expensive foreign training. HRH shortage has also been attributed to poor forecasting of health workforce needs. This problem is linked to weak health information systems. Without adequate information on the prevalence and impact of diseases, health ministries are unable to develop and strengthen health systems capacities to meet future needs.

Attrition has already been addressed when discussing brain drain as a governance issue. The loss of personnel from disease endemic countries to wealthier countries undermines the capacity of their health systems to provide comprehensive services, thus increasing the necessity to implement vertical approaches for specific diseases (*45–48*). In some countries, attrition also occurs when health workers take up administrative work or work outside the health sector within the country (*46, 49, 50*). In parts of Africa high mortality among health sector workers, due to diseases such as AIDS, compounds attrition. Forty-three percent of health worker deaths in Ethiopia, Kenya, Malawi, Mozambique and Zimbabwe are known or suspected to have been caused by HIV/AIDS, while over one third of deaths are known or suspected to have been caused by TB (*4*).

The effectiveness of disease control programmes is also affected by the skewed distribution of health workers across geographical location, professional category and gender (*42, 50, 51*). Often, health workers prefer to work in urban rather than rural areas, and in more affluent, urban areas rather than poor areas such as slums (*51*). A lack of adequate amenities in rural areas (such as quality housing and good schools) and lack of security in urban slums and other poor areas have been highlighted as key factors in health workers' reluctance to work in these poorer areas.

In the 1990s, health sector reforms included capacity building interventions for HRH. Some countries invested in training health workers, increasing salaries and providing relocation incentives to address the maldistribution problem. Results have been mixed. For example, Ghana developed a health human resource policy in 2002 to address its health worker crisis. A "deprived-area incentive" initiative failed to get workers to move from urban areas due to lack of infrastructure and amenities for families of health workers. Task-shifting has been also tried as a solution to the maldistribution problem. This involves transferring responsibilities from highly trained health workers to community health workers (CHWs) in order to increase access to disease control services. BRAC, an NGO, provides a good case on how its 70 000 CHWs in Bangladesh continue to work and are connected to a functioning health system (see Case study 3.4) (*52–54*).

Over the last decade Global Health Initiatives have made investments in HRH, with mixed outcomes (*4*). These investments have included funding salary increases and offering relocation and other incentives to address the problem of attrition and maldistribution, with the focus primarily on the delivery of disease programmes. However, in some countries, Global Health Initiative interventions have not been enough to prevent attrition within the public sector or to improve health outcomes through provision of health services.

RESEARCH QUESTION:

How do we determine the optimal balance between health workforce options and requirements to attain disease control targets in the context of broader health systems strengthening?

CASE STUDY 3.4

Sustaining the work of community health workers

Two major challenges faced by community health worker (CHW) programmes are: (i) building incentive mechanisms; and (ii) connecting CHWs to a functioning health system. In Bangladesh, BRAC has introduced innovative systems to address these challenges and has trained over 70 000 CHWs with a considerably high continuation rate. BRAC CHWs are recruited from among its microfinance beneficiaries and so have access to small loans for income earning activities. Moreover, they are allowed to sell essential drugs with a mark-up. They are also trained to provide directly observed treatment for TB through which they earn an income by identifying patients and by ensuring treatment completion. The CHWs are linked to the health services BRAC runs in the villages and are supervised in the field by CHWs who attend a monthly refresher training course. Apart from treating common illnesses, the BRAC CHWs are trained to treat pneumonia and provide appropriate services in maternal, newborn and child health programmes.

The BRAC programme has been replicated in other countries including Afghanistan and Uganda. Health systems research has played an important role in the development and scaling-up of such programmes – studies identified issues with programme implementation relating to incentives, supervision, drop-out, training retention, equity focus and roles in society. A recent study compared the implementation of the BRAC model in Bangladesh, Afghanistan and Uganda and reported on what works in different settings and how programmes in each country evolved according to local realities.

Source: *References (52–54).*

MEDICINES AND TECHNOLOGY – AN ESSENTIAL COMBINATION

Sick people need not only medicines to treat their conditions but also medical technologies that help with diagnosis and treatment. However, in many poor countries the procurement and distribution systems for medicines and medical technologies and equipment are weak, erratic and dysfunctional (*55*). Health workers may also lack relevant training in basic pharmacology (such as dosage and administration of medicines) and in the use of available technologies. In some countries, a combination of weaknesses in the supply chain and a lack of training has reportedly led to delays in drug administration or dose reductions for malaria, causing subsequent shortfalls in the agreed Abuja Declaration and Roll Back Malaria (RBM) targets (Fig. 3.2) (*56*).

The problems with procurement and distribution are compounded by the production, supply and inadvertent use of counterfeit medicines (*57*). It is estimated that about 15% of drugs sold worldwide are fake (*58*) and, in some parts of Africa (such as Nigeria and the United Republic of Tanzania), up to 30% of drugs on sale can be fake (*58*). These problems obviously affect the quality and effectiveness of disease control programmes – particularly as traditional medicines are popular and often cheaper sources of treatment for a broad range of conditions (especially in rural areas underserved by formal health services in Africa, Asia and Latin America).

RESEARCH QUESTION:

How can we improve access and appropriate use of quality medical technologies for infectious disease control?

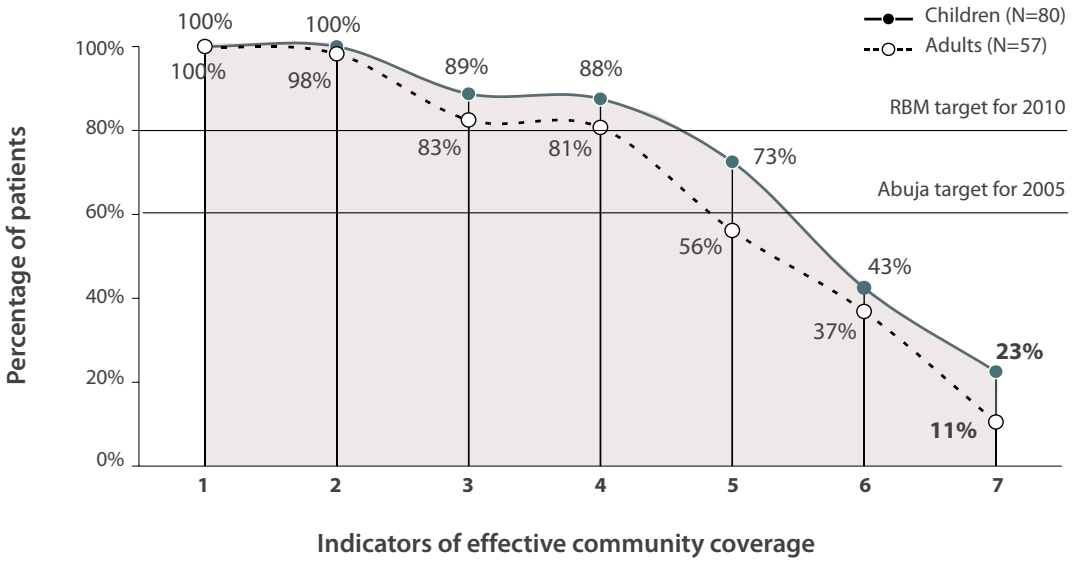

Fig. 3.2. Estimated effective coverage of fever treatment model based on patients' or caretakers' accounts. *Percentages are proportions of the study sample with a reported recent fever. 1 = episode treated; 2 = drug administered; 3 = antimalarial administered; 4 = recommended antimalarial given; 5 = recommended antimalarial on same or next day. 6 = recommended antimalarial on same/next day, in correct dose; 7 = recommended antimalarial on same/next day, correct dosage, appropriate considering reported symptoms.*

Source: *Reference (**56**).*

HEALTH INFORMATION AND HEALTH INFRASTRUCTURE – GOOD DATA CLEAR THE PATH

Health systems need information on trends in incidence and prevalence of health risks, diseases and fatalities and on the availability and utilization of resources so that the structure, scope and delivery of health services can be planned. They also need monitoring and evaluation data on health outcomes and service outputs. In addition, health systems need appropriate facilities, technologies and equipment to function effectively. However, facilities in low-income countries are often run-down, over-crowded and ill-equipped. This undermines both quality of care and the occupational health of health workers. For example, in sub-Saharan Africa "50% of sites dedicated to the provision of antiretroviral treatment do not have basic infrastructure and supplies, such as soap, running water, gloves and post-exposure prophylaxis for HIV prevention" (*4*).

Research from Uganda, Rwanda, Mozambique, Mexico and the United Republic of Tanzania on the strengthening of institutional data collection provides important models for developing robust health information systems (*59–64*). Some countries have already started experimenting with wider use of electronic information technologies, which has led to improved provider-patient interactions (e.g. in Rwanda, Zambia); the ability to track pharmaceutical and other essential supplies (thereby reducing stock-outs); and increased information sharing between different stakeholders (*4*).

Global Health Initiatives have invested in improving the availability and accuracy of data on specific diseases. Such investments strengthen monitoring and evaluation and improve access to information for users, programmers and implementers. Countries such as Burkina Faso, Nigeria, and Indonesia have yielded important results. For example, The US President's Emergency Fund for AIDS Relief (PEPFAR) investment in household surveys of seroprevalence led to a global downward adjustment in the total number of HIV/AIDS infections. Global Health Initiative investments in health information

systems have also produced negative outcomes. They often establish parallel systems that duplicate national surveillance efforts and they limit their focus to the "big three diseases", prioritizing national surveillance at the expense of surveillance systems for primary prevention at community levels.

RESEARCH QUESTION:

How can stand-alone disease control ***information systems be integrated*** *into existing national health information systems and into general health decision-making processes?*

COMMUNITIES AND HEALTH SYSTEMS – PEOPLE MAKE THE DIFFERENCE

Communities are beneficiaries of health care in their various capacities as patients, consumers, financiers and citizens entitled to health care. Communities interact with health care through their health seeking, caregiving and health promoting behaviours (*4*). Community beliefs, knowledge, norms and capacity for collective action are therefore recognized as part of an active and dynamic component of working health systems (*1, 4, 65*). The need to prioritize community ownership and participation in decision-making has been underscored by researchers and policy-makers because of the unique human resource challenges faced by disease endemic countries.

Research suggests that the relationship between Global Health Initiatives and communities has had positive effects on governance through increasing the participation of communities (Case study 3.5 & Case study 3.6), traditional healers and medicine sellers (Case study 3.7) and community health workers (Case study 3.4) in the planning, implementation and evaluation of community-based interventions (*66–77*). Community-based dengue control activities suggest that behaviour change is only temporary when prevention tools are deployed "top-down", without the active involvement of communities. Insights from community participation interventions in onchocerciasis control suggest that, while the acts of volunteering and participation are important, community knowledge and decision-making are the central factors underpinning successful interventions. Cultural factors and gender also

CASE STUDY 3.5

Lessons from the community-directed treatment with ivermectin strategy in west Africa

The African Programme for Onchocerciasis Control (APOC) uses community-directed treatment with ivermectin (CDTI) as the sole strategy for onchocerciasis control. Based on a successful programme implemented in 11 west African countries – Benin, Burkina Faso, Côte d'Ivoire, Ghana, Guinea, Guinea-Bissau, Mali, Niger, Senegal, Sierra Leone and Togo – in the 1980s and 1990s, the strategy relies on active structural community participation (*66, 67*). Communities are empowered to decide on how, when and by whom ivermectin treatment should be administered; communities also monitor the CDTI process.

In rural areas of sub-Saharan Africa, the CDTI strategy is proving to be very successful for onchocerciasis control. Over the years, over 56.7 million people living in 16 African countries have received regular ivermectin treatment (68), and more than 700 000 community drug distributors and 60 000 health staff have been trained. They are also available for other interventions, such as providing insecticide-treated nets for malaria at a relatively low cost.

The CDTI process has underscored the importance of harnessing local support in delivering disease interventions, and has also emphasized the importance of community decision-making in participatory health projects.

CASE STUDY 3.6

Case studies in community integration of dengue control

In Honduras, neighbourhood health committees took on the task of controlling the breeding of mosquitoes at both community and household level (*69*). As a result, neighbourhoods showed significantly reduced numbers of mosquito breeding in containers in comparison to the control areas. Control of Aedes aegypti breeding in Viet Nam also adopted a community approach with health agents, school children and community members involved in delivery of biological control agents to prioritized breeding locations. Over three years there were reduced numbers of the vector in most communities under study and actual elimination in a few. Returning to the study site some years after the project concluded, the researchers found that some communities had maintained their role in vector control to prevent dengue (*70*). In Cuba, a community participation strategy was designed to supplement routine vector control activities. In selected communities local stakeholders formed steering committees and coordinated the work of grassroots working groups that focused on behaviour change related to local water storage containers. The community intervention reduced levels of Aedes infestation by as much as 50% to 75% compared to the control (*71*).

Research on dengue control has identified models for successful community participation (*72, 73*). Top-down deployment of technical tools without active involvement of the community has a temporary effect and does not lead to the behavioural changes necessary for sustainable *A. aegypti* control (*74*). However, based on published studies, the evidence that community-based dengue control programmes alone and in combination with other control activities can enhance the effectiveness of dengue control programmes is weak (*75*). A multilevel approach is clearly needed and a framework has been proposed for evaluating the sustainability of community-based dengue control projects (*76*).

play critical roles in the success or failure of community participation programmes given the disabling and stigmatizing nature of infectious diseases of poverty (*78*).

Research to identify the role of cultural systems for disease control is critical for developing health systems solutions and strengthening the role of communities in the implementation of solutions (*6*). While onchocerciasis control in Africa has been a marked success, particularly in terms of widening access to other health services, success elsewhere has been variable. In India, for example, community-directed treatment for lymphatic filariasis has not worked because community members from different caste systems are unable to come together for mass drug administration (*79*). The success or failure of HIV interventions often depends on the moral values that different cultures place on gender, sex and sexuality and associated stigma (*80*).

RESEARCH QUESTION:

How do we develop research frameworks to assess the interaction between Global Health Initiative-targeted services and non Global Health Initiative-targeted services so that overall service delivery is improved?

INFECTIOUS DISEASES, POVERTY, HEALTH SYSTEMS AND HEALTH SYSTEMS RESEARCH – BRINGING IT ALL TOGETHER

Research has revealed that the control of infectious diseases of poverty is more complex than previously thought. For instance, the epidemiology of infectious disease is changing with the emergence of new infectious diseases and re-emergence of old infectious diseases while the biological, ecological and social determinants of infectious diseases need to be understood and addressed.

CASE STUDY 3.7

Strengthening the capacity of medicine sellers

Medicine sellers have played an important role in facilitating access to essential medicines in sub-Saharan Africa. Training and capacity building has strengthened their effectiveness to induce appropriate demand, enhance quality assurance and operate within an enabling environment. Successful capacity strengthening interventions were shown to be acceptable and to increase rates of appropriate treatment. Their features included a comprehensive situation analysis of the legal and market environment; buy-in from medicine sellers, community members and government; use of a combination of approaches; and maintenance of training and supervision *(77)*.

Health systems are also complex, context-specific and dynamic; operating within three interdependent sets of relationships (see Fig. 3.1) (*4–6*). First, the relationships between the seven building blocks are interdependent – changes in any one building block affects the others. For example, weak health governance and financing systems in many poor countries have led to extensive health systems weaknesses ranging from poor training and retention of health workers to an erratic supply of medicines to communities in need.

Second, relationships between health systems and the communities they serve are also interdependent (*5, 6*). Diseases infect and affect individuals, households and communities differently. Understanding how different social and interest groups within disease endemic communities respond to general and individual risk, or to their disease experiences, is therefore essential for understanding how they demand, access and use health services. Often, poor communities possess the capacity and will to engage in the solutions to their health care problems. Thus community ownership, participation and decision-making must constitute an active and dynamic component of working health systems (*1, 4, 65*).

Finally, relationships between health systems and broader country contexts are interdependent. A useful definition of the broader country context is the "demographic, economic, political, legal, ecological, socio-cultural (including historical legacies) and technological factors in the environment" (*6*). The success or failure of health systems and health interventions depend on these complex and dynamic contextual factors. Sectors and public institutions that deal with the wider social determinants of health – such as finance, education and labour – can enhance or undermine the capabilities of health systems. Conflict or ecological disasters can derail national governance and public services for decades and create long-term challenges for health services. In other contexts they can create opportunities for the development and sustainability of required health interventions. Global policies, such as economic reform and food and agricultural policies, can support fragile or struggling states; but they can also undermine governance and priority setting with implications for health, the wider socioeconomic determinants of health and health systems capabilities.

The complex nature of infectious diseases of poverty and health systems demand multidisciplinary research approaches. Health systems research has different frameworks for addressing health systems strengthening; for instance implementation research and operational research. While this offers a multidisciplinary approach to conduct health systems research, there is a need for an overarching framework that coherently integrates concepts and methods. Furthermore, as health systems research is predominantly carried out by institutions in high-income countries, divergent value systems create a power imbalance within the health systems research community (similar to the power imbalance between Global Health Initiatives and governments of developing countries) (*81*). The research challenge is to

develop integrated approaches for health systems strengthening that actively draw on equitable partnerships between high and low-income research communities.

Developing the interface between health system components and infectious disease control programmes – the missing link

Successful control of infectious diseases of poverty requires a positive interrelation between disease control programmes and the rest of the health system. Such a relationship can be built on the basis of values, approaches and health systems strengthening (see Fig. 3.3). Health systems research can contribute to the setting of priorities and to the identification of solutions for these three areas.

BROAD HEALTH SYSTEM VALUES

Each health system is driven by a range of stakeholders with varied interests, values and power status in relation to socially defined health problems, priorities and solutions. There are at least three areas which need to be in broad agreement if an effective interrelationship between infectious diseases of poverty and health systems is to be attained: (i) the right to health and equity through universal coverage; (ii) community involvement; and (iii) sustainability.

Given that infectious diseases of poverty disproportionately affect the poor, health systems and disease control programmes need to operate with the shared value of equity, where the critical needs of the poor are addressed first (*82*). There must also be an understanding that communities are both beneficiaries and deliverers of health care, so that community beliefs, knowledge, values,

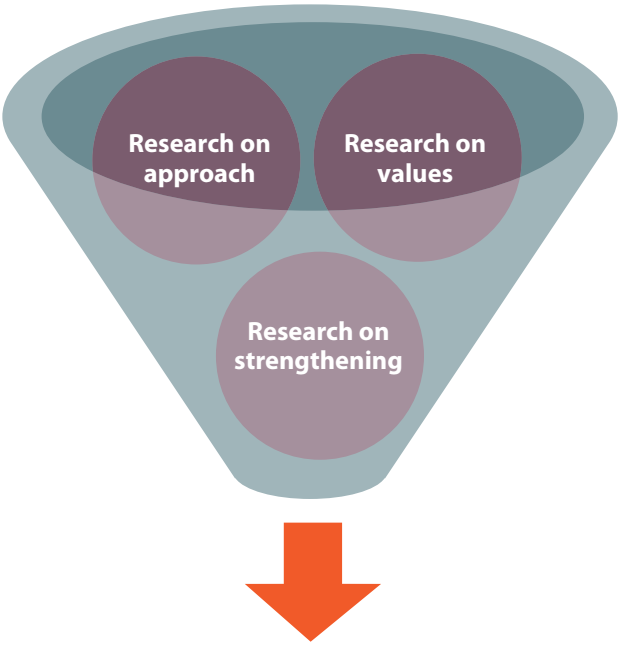

Fig. 3.3. **Researching values, approaches and health systems strengthening to improve the interrelationship between disease control and health systems**

Source: *Courtesy of Charles Collins*

norms and capacities are integral to health systems and health service delivery. Meanwhile, sustainability should deliver a balanced approach to meeting short, medium and long-term needs of health systems and the people they serve.

Research needs to focus on leadership strategies and on the development of mechanisms to share these common values across diverse actors. It needs to become outcome-oriented so that a positive interrelationship is developed between interventions for infectious diseases of poverty and the rest of the health system.

DEVELOPING SYSTEMIC APPROACHES

In theory, infectious disease programmes and interventions are part of the overall health system operating within a given country. In practice, they often operate in parallel to, and even at cross-purposes with, the health system. The governance of this relationship needs to be strengthened through specific approaches that allow policy-makers to interpret the manner in which disease control interventions can be best incorporated into country health systems, to implement governance solutions and to monitor their success. Such approaches must rely on systems thinking. By placing the interdependency of the components of the health system at the forefront of analysis, systems thinking leads to a fuller understanding of how changes in one component can lead to intended and unintended effects in other components, or in the system as a whole; and of how these processes can be modelled and evaluated. A key research concern here is the ability to work through the impact of changes as they are designed and implemented; for example, understanding the impact of decentralization on disease control interventions (Case study 3.2), or how the introduction of pay-for-performance schemes impacts on the rest of the health system.

Systems thinking also aids analysis of the interdependent relationships between health systems and the communities they serve, as well as between health systems and the broader country context. A wide range of stakeholders at local, national and global levels play a role in the development and evolution of health systems. Changes in health systems affect the interests and actions of these stakeholders, therefore any interventions and changes require the collaboration of, and work with, these stakeholders. Research needs to address how stakeholder analysis can be developed in such a way as to develop positive relations between infectious diseases of poverty interventions and the rest of the health system.

“Research needs to focus on leadership strategies and on the development of mechanisms to share these common values across diverse actors... so that a positive interrelationship is developed between interventions for infectious diseases of poverty and the rest of the health system.”

The wider social determinants of health are as important as the direct causes of disease and illness. Hence, there is an important relationship between health systems and other sectors (such as nutrition, sanitation, education, labour). Research has to examine those aspects in the environment that have a significant impact on the health system (and vice versa) in order to develop robust and sustainable intersectoral collaboration. Likewise, health systems are in a dynamic interaction with their environment. The changing epidemiology of disease; governance and political systems; culture; and globalization forces can impact on the structure and functions of health systems. Research on how health systems interact with the wider social system and institutions is therefore critical.

Scaling-up has been defined as the deliberate effort to increase the impact of health innovations successfully tested in pilot or experimental projects, in order to benefit more people and foster the development of sustainable policies and programmes (*83*). The importance of scaling-up rests on the depth and breadth of the challenges facing disease control and the need to improve the quality of disease control and expand its coverage (*84*). To scale up a programme, decisions have to be made about different degrees of health system integration, such as how to deal with human resource scarcity; how interventions can be expanded through public–private relations; and how advocacy can be incorporated into community participation and ownership or buy-in by international donors. The process can be accelerated through approaches that consider how programme development, monitoring and evaluation interface with the broader health system. A good example of this approach is the Oral Therapy Extension Programme (OTEP) carried out in Bangladesh in the 1980s (Case study 3.8) (*85*).

Health franchising is an example of scaling-up through systemic integration of interventions within an unstructured private sector. Franchising "incorporates into one system all of the interventions that have been shown to have some effect individually, for example training, performance-based incentives, accreditation and certification, vouchers or other external payment schemes, ongoing support relationships and monitoring" (*86*). Franchising can provide an attractive addition to the available tools for leveraging existing human resources. Successful health franchising programmes on family planning in Africa and Asia, and on voluntary counselling and testing for HIV in Africa, suggest that health franchising can ensure that diverse groups of practitioners in the private sector increase their quality to an agreed public standard through improving drug supplies and providing training and support (*87*).

Research into the scaling-up of successful interventions should address bottlenecks from the health systems strengthening perspective: the characteristics of the health system, particularly the strength of primary health care, will have an important effect on how the scaling-up is done. Some basic questions must guide the development of research. What is the opportunity cost of scaling-up a specific innovation on other forms of health care and disease control? How does it relate to equity and efficiency? What are the contextual determinants for success? What information is available to assess scaling-up strategies? (*84, 87, 88*).

CASE STUDY 3.8

Scaling-up of oral therapy extension in Bangladesh

OTEP was implemented during the 1980s to reduce dehydration and death from diarrhoea. Thirteen million rural households were reached to demonstrate to mothers how a simple solution of a fistful of molasses (local brown sugar), a pinch of salt and a half litre of water can be mixed at home and used to treat diarrhoea. A year-long pilot programme was implemented to test and develop a home-based sugar salt solution. Once the intervention components were standardized through the pilot, OTEP was launched in 1980 and continued for ten years in three phases. Each scaling-up phase was analysed and modified based on evaluative research.

The studies provided answers to a number of problems – including improving the retention, reinforcement and use of ORT – oral rehydration therapy – and increased the accuracy of the home-based formula. Regular impact assessments of the programme were also conducted at different phases. This case illustrates how research can play a strategic and useful role in programme development and its scaling-up.

Source: *reference (**85**).*

STRENGTHENING RESEARCH CAPACITY FOR A POSITIVE INTERRELATION BETWEEN DISEASE CONTROL PROGRAMMES AND THE REST OF THE HEALTH SYSTEM

Health systems research has great potential to address health systems strengthening for infectious diseases control. However, this field of research has a number of challenges and limitations.

- As a new and growing field, health systems research receives significantly less funding than other areas of health research. It was estimated that, around 2002, national health systems in low and middle-income countries devoted only some 0.007% of total health expenditure to this research (*89*).
- Despite a growing interest and focus on health systems strengthening in poor countries, health systems research has been confined largely to research institutions and activities based in high-income countries; few developing countries have the capacity required (*90*).
- Health systems research draws heavily on diverse frameworks and disciplines to address context-specific problems. This challenges the growth of a well-structured body of theory and therefore often is not prioritized for funding. Finally, health systems research has focused mostly on a limited number of building blocks, namely financing, human resources for health and medicines and technology. These challenges should be addressed as integral components of health systems strengthening.

The Bamako Call to Action on Research for Health paid particular attention to implementing research on promising innovative tools and strategies as a way of ensuring rapid adoption and scaling-up as well as broader health systems strengthening (*91*). Implementation research aims to develop the critical evidence base that makes the case for the effective, sustained and embedded adoption of interventions by health systems and communities. It deals with the knowledge gap between efficacy, effectiveness and current practice to produce the greatest gains in disease control (*92*). Implementation research asks: "What is happening in the design, implementation, administration, operation, services and outcomes of social programmes? Is it what is expected or desired? And why is it happening as it is?" (*93*). In this way the research can provide evidence to support close engagement with policy-makers and public providers as well as with civil society organizations engaged in service delivery. Implementation research for infectious diseases of poverty is a rapidly growing field, although it lacks adequate definitions and an understanding of its strategic value by researchers, donors and governments (*94*).

> **"Research needs to focus on developing tools for systemic analysis to be used by diverse actors. The objective is to develop a better understanding of the relationships between disease control interventions and health system components, between health systems and other sectors and, finally, between health systems and broader developing country contexts. Depending on the context and resources, a health system impact analysis (HSIA) can be done every time a new infectious disease of poverty is introduced."**

Knowledge translation platforms are being encouraged at country and regional levels to strengthen health systems through the judicious use of evidence (Case study 3.9) (*95*).

The Canadian Institutes of Health Research define knowledge translation as "…a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically-sound application of knowledge, through sustainable partnerships to improve the health of citizens, provide more effective

CASE STUDY 3.9

Strengthening knowledge translation for malaria scaling-up

The Evidence-Informed Policy Network (EVIPNet) team in Burkina Faso focused on strengthening its capacity for knowledge translation and research use. A workshop was aimed at producing a research brief for policy-makers and engaging in a deliberative dialogue, both targeting access to artemisinin-based combination therapies (ACTs) for uncomplicated malaria. The process aimed to reach consensus to:

- engage the private sector in adhering to national guidelines about subsidized drugs in all settings;
- motivate and retain community health workers involved in the home management of malaria;
- ban monotherapies after ensuring that ACT is fully deployed across the country and that pharmacies are informed about the policy.

The knowledge translation process was also helpful to reach agreement across stakeholders participating in the proposal tendered to Round 7 of the Global Fund for HIV/AIDS, TB and Malaria (Global Fund). The implementation of the project was therefore able to make an early start with the implementation of the CHW option, through a pilot in three districts of the country, aiming for full-scale implementation for Round 8. An implementation research protocol (mostly a rapid ethnographic assessment) applied to each participating district helps to monitor and evaluate the advantages, disadvantages, costs, barriers and facilitators in the execution of the policy option at the very specific district level. The other two options proposed in the policy brief are also being implemented through additional activities.

Source: *Reference (**95**)*.

health services and products and strengthen the health care system" (*96*). Knowledge translation platforms are required to bridge the know-do gap (between knowledge and practice) by setting priorities and by disseminating knowledge that enhances the interfaces between country health systems and policy-making contexts. This is achieved by involving policy-makers as active players in order to make evidence systematic. Policy-maker involvement in knowledge translation and demand for research evidence is now being promoted by global initiatives such as EVIPNet, as well as regional and country initiatives (*97–99*).

Conclusions – from dependence to ownership

Low and middle-income countries are characterized by complex disease burdens, fragile political systems, national poverty and an unfavourable international economic context. This mix of problems has led to governments of low-income countries becoming overdependent on development partners, donors and philanthropic organizations. In turn, ideological battles have ensued within this complex group of stakeholders on issues concerning the developmental and health needs of poor countries and poor people, and the inability of health systems to control infectious diseases of poverty. Health sector reforms in the 1990s yielded mixed results for infectious disease control in a number of countries. Global Health Initiatives have provided a significant amount of funding for the development of disease control programmes since 2000. However, their bias towards the "big three diseases" – HIV/AIDS, malaria and TB – has left other infectious diseases of poverty and emerging public health challenges underfunded, under-researched, and poorly controlled and treated. Furthermore, like the health sector reforms, Global Health Initiatives have yielded mixed results in terms of the impact of disease control programmes on health systems strengthening.

Much of the complexity underlying the relationship between health systems and the control of infectious diseases of poverty in endemic countries can be explained by

health systems research. It can become a powerful ally by acting as a foundation for capacity strengthening and integration during the design, implementation and scaling-up of disease control programme innovations. Research has demonstrated how care and control programmes for major diseases such as TB have become integrated successfully into health systems, and how they have helped to innovate systems through complementary and mutually reinforcing efforts. Research has also demonstrated the importance of ensuring minimum primary health care capacity if global health initiatives are to have a positive impact, as well as the critical role that communities can play for integration and scaling-up of disease programmes.

Health systems research capacity needs to be strengthened through institutional development, training, project funding and publications to enable countries to identify optimum solutions that systematically address health system bottlenecks. Low-income countries must own their health systems research agendas and the gap between these research communities in high-income and low/middle-income countries needs to be bridged. Some existing approaches within health systems research, such as operational and implementation research, can yield great benefits by exploring the success of capacity strengthening, integration and scaling-up strategies at local, national and regional levels. Implementation research is particularly important now that a host of product development partnerships are developing a rich pipeline of innovations. However, conceptual and methodological challenges need to be addressed in order to achieve successful scaling-up of interventions.

“Committed future investments in health systems research are essential if the field is to move fully and convincingly from the margins to the mainstream of intellectual efforts to attain universal coverage for health through robust health systems.”

Further research on the demands of health systems and the effects of community delivery approaches is needed to strengthen scaling-up, as well as health systems in general.

There is undoubtedly a growing global interest in health systems research. Health research funding bodies (such as USAID and the National Institutes of Health) have made recent investments in implementation research platforms and translational research, suggesting that health systems research has increased in credibility. This is important. Committed future investments in health systems research are essential if the field is to move fully and convincingly from the margins to the mainstream of intellectual efforts to attain universal coverage for health through robust health systems.

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4 Innovation and new technologies to tackle infectious diseases of poverty

IN CHAPTER 4:

- Global initiatives to encourage innovation
- Funding for innovation – food for brains
- Priority setting for health R&D – where to start?
- Policy environments in developing countries
- Social innovations – science on its own is not enough
- Building capacity – incubating entrepreneurship
- Ethics, innovation and infectious disease
- Innovating for "One World, One Health"

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The traditional approach to tackling infectious diseases of poverty has been a disease-centred one but now, to benefit effectively from innovative products and use the tools needed to beat such diseases, the approach must be people-centred. In this chapter we explore how this might be achieved.

In a little over a century, knowledge in the fields of microbiology and parasitology, immunology and genetics, public health and medicine has increased exponentially. In combination with economic developments, this has resulted in many positive changes in human health: reductions in infant mortality, improved life expectancy, the near eradication of certain infectious diseases and the effective treatment of others. More recently, major advances in new fields and technologies, including genomics, proteomics, high-throughput screening, robotics, imaging and geographical information systems (GIS) have revolutionized drug discovery and the surveillance, prevention, treatment and control of new and emerging infectious diseases (*1–3*).

However, getting the right tools to those who need them most is not easy. Although government agencies and research institutes, private organizations, public–private partnerships (PPPs) and community-based organizations have all worked to reduce the burden of infectious diseases, the challenges persist. Life-saving innovations, including very simple yet effective interventions, still remain out of the reach of many. Many infectious diseases are still under-researched and poorly understood, and the innovations to address them are of limited commercial interest.

To reduce the burden of infectious disease and broker greater global equity, we need new levels of global commitment and new models of collaboration among stakeholders to bring about innovative solutions and to translate these solutions into effective programmes in settings where the needs are greatest. The challenge is more than the pursuit of technological marvels and "magic bullets". It is about fostering a "culture of innovation".

Innovation is about stimulating the search for novel discoveries; the development of technologies and tools for health interventions; understanding the specific social contexts in which interventions will be delivered; and strong engagement with communities to ensure maximum and sustainable implementation and uptake (*4*). Innovation is not just about doing things differently but also about doing things in a more sustainable, effective, safe and equitable manner.

In this chapter, we take a systems-based approach to innovation. We start by discussing how to create an environment of innovation in low and middle-income countries (LMICs), then examine how to foster innovative collaborations and product development for infectious diseases, the social innovations necessary for the uptake and delivery of health interventions, and how to build capacity in research and training in these countries.

Understanding the health innovation system – navigating unchartered waters

Health innovation systems acknowledge the interrelationship between education, research and development (R&D), manufacture, domestic and export markets, intellectual property and regulatory policies (*5*). These different components must be linked so that overall national and regional systems work efficiently and swiftly to respond to country and global health needs. Research plays a central role in an innovation system, from the inception of ideas to new ways of translation, policy design and regulation (*6, 7*).

For high-income countries, health innovation systems include actors from multiple sectors and disciplines. Conventionally, training and basic research are funded by the public sector through universities and government research institutions. Translational research and product development such as prototype productions or small-scale production are conducted by pharmaceutical or other companies or, depending on the national system, government institutions. In low-income countries, however, the health innovation system is often rudimentary and fragmented. The public sector provides most, if not all, funding and infrastructure for research. Although research is conducted in academic institutions, often there is little applicability to local health problems, due to the lack of capacity to conduct translational

research and limited manufacturing capacity. LMICs with some industry and manufacturing experience are usually limited to manufacturing low-technology products, or higher-technology products only under technology transfer agreements, rather than producing "home-grown" innovation for local health needs. The absence of private sector institutions engaging in health innovation also reflects limited expertise in product development, in regulatory and intellectual property management. This is partly due to the consistent drift of scientists to higher-income country research institutions, and partly due to lack of access to domestic and global markets. These factors represent major barriers to establishing and strengthening national innovation systems in LMICs. The various steps in the innovation value chain remain disconnected, impeding the progress of innovation in these countries.

Thus, unlike high-income countries, most LMICs have only a few areas of research and very limited development capacity. Resources in most other areas of innovations (e.g. intellectual property management and regulation, production and operation standards, and other social research) are also very limited. These scattered clusters of R&D-linked activities need to be connected in order to transform ideas and commitments towards innovative solutions (see Fig. 4.1).

Richard Mahoney and Carlos Morel argue that innovation disparity has created three kinds of "health failures" (*4*).

- **Science failures:** This refers to a lack of knowledge and tools to address health problems. For example, there are still no effective vaccines or drugs for infectious diseases such as dengue, tuberculosis (TB), malaria and trypanosomiasis.

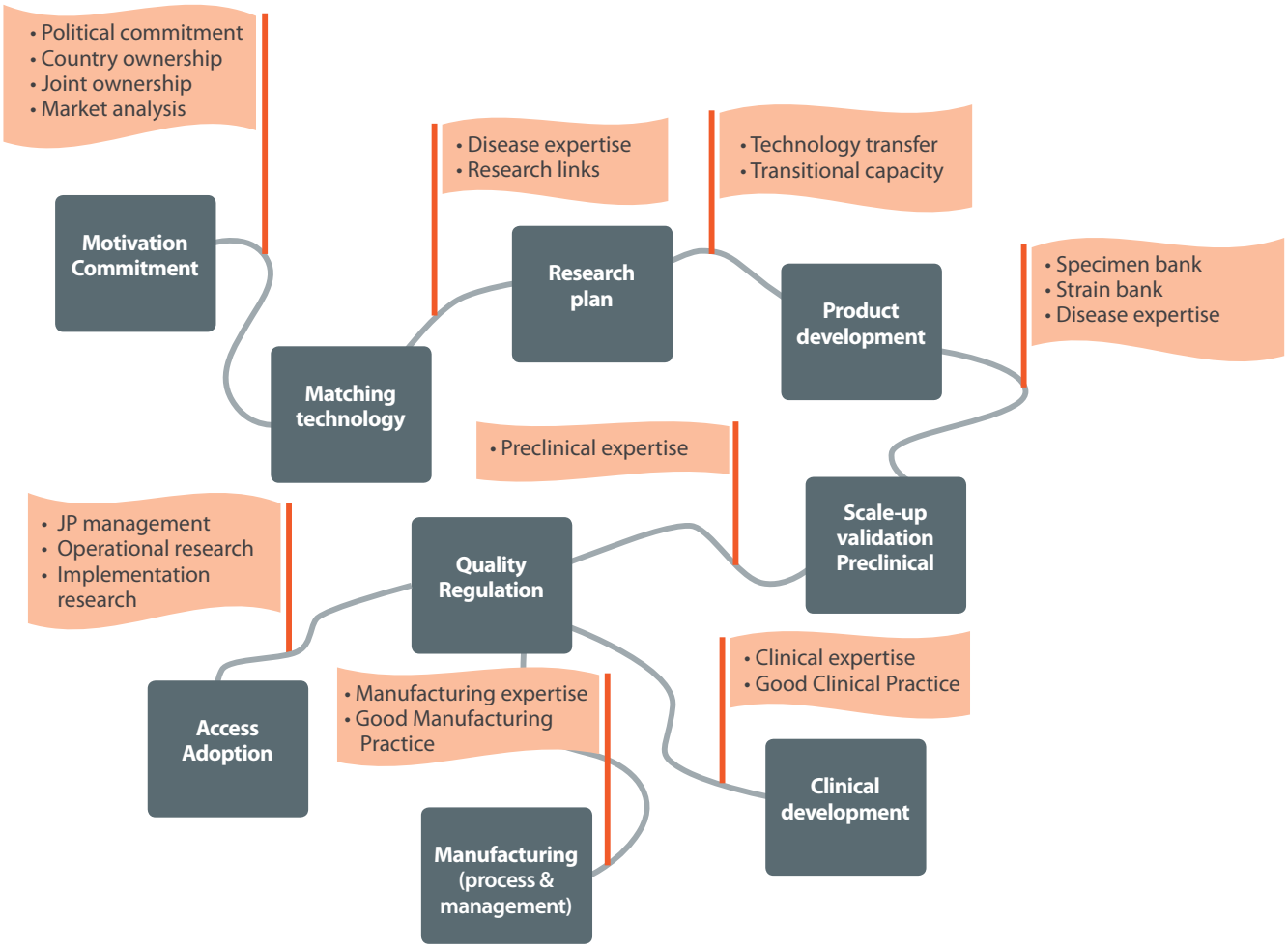

Fig. 4.1. Disconnected value chain within the low and middle-income country health innovation system

- **Market failures:** These happen when stock-outs occur due to high demand or when the purchase costs of drugs, vaccines and health interventions prevent the poor from accessing them. Often the new drugs and diagnostics are very expensive to develop and/or require sophisticated technical and health infrastructure for optimal use.
- **Public health failures:** This refers to the lack of good governance, transparency, effective delivery systems and a clear articulation of health priorities and values. Political and economic instability, cultural and religious barriers and shifts in government priorities can block the uptake and implementation of health innovations.

To overcome these failures and to maximize the potential for innovation, stronger partnerships are needed between countries, through global health initiatives and between the private sector and civil society. The World Health Assembly has called for the global control or elimination of neglected diseases of poverty as a major public health problem by 2020 (*8, 9*). An innovative and systems-based approach can help realize this goal (see Case study 4.1 below). New thinking on innovation, access to medicines, and developing capacity in health innovation will allow the stronger translation of basic research, support product development and strengthen and sustain community uptake.

New thinking on innovation, access to medicines, and developing capacity in health innovation will allow the stronger translation of basic research, support product development and strengthen and sustain community uptake.

Global initiatives to encourage innovation – turbo-charging

We are in the "era of partnerships" (*4*). Over the last two decades, product development partnerships involving the public and private sector have been formed to tackle diseases such as HIV, malaria, TB and, to a lesser extent, other infectious diseases. These partnerships include the International AIDS Vaccine Initiative (IAVI), International Partnership for Microbicides (IPM), Medicines for Malaria Venture (MMV), The Global Alliance for TB Drug Development (TB Alliance), Aeras Global TB Vaccine Foundation, Human Hookworm Vaccine Initiative (HHVI), Foundation for Innovative New Diagnostics (FIND), Drugs for Neglected Diseases initiative (DNDi) and OneWorld Health. The partnerships comprise multilateral agencies, foundations, donor countries and LMIC governments.

CASE STUDY 4.1

Can some infectious diseases be made history?

Many water-borne and vector-borne infectious diseases, such as guinea worm, schistosomiasis, lymphatic filariasis and onchocerciasis, could be controlled effectively by 2015, the target date for reaching the Millennium Development Goals (MDGs) (*10*). Donations of safe and effective drugs from pharmaceutical companies; adequate funds from foundations and bilateral donors to deliver these donated drugs; effective global health partnerships; effective systems of delivery; and good governance can help make these diseases history. For example, donated generic formulations of praziquantel from MedPharm and other groups were used in the Schistosomiasis Control Initiative and by African ministries to reduce the burden of urinary and intestinal schistosomiasis in school children in a number of African countries (*10–12*). The mass distribution of albendazole and mebendazole has lowered the disease burden of soil-transmitted helminths and consequently improved school performance in children (*13*). Dracunculiasis is poised to be eradicated (*14*).

To encourage product development by the private sector in LMICs, many high-income country governments offer incentives such as R&D grants, tax credits and priority regulatory review for orphan drugs. Orphan drugs are those developed for rare diseases that may be used to treat more prevalent conditions. For example, the drug compound cethromycin has been given orphan drug status and is being investigated as a prophylaxis against community-acquired pneumonia and the anthrax virus (*15*).

Initiatives such as advance market commitments, fast-track regulatory approval vouchers and humanitarian licensing practices have also been proposed to encourage product development. Funding agencies and private foundations now offer grants and prizes for innovative ideas and products. For example, The Bill & Melinda Gates Foundation's Grand Challenges in Global Health programme targets 14 major global health challenges, with the aim of engaging creative minds across scientific disciplines to work on solutions that could lead to breakthrough advances in health. The resulting research outcomes could potentially have highly beneficial effects on the treatment and spread of infectious diseases.

Innovative mechanisms to finance the creation and delivery of new drugs for infectious diseases are also being developed. For example, GAVI Alliance offers advance market commitment to expedite the introduction of new vaccines by providing guarantees of the quantity and the purchase price of a vaccine once it enters the market.

RESEARCH QUESTION:

What are the most effective global partnership models to encourage innovation for the poor while minimizing the risks associated with innovation?

> **We should identify the most effective partnerships to encourage health innovation for the poor as there are still few initiatives to develop and strengthen such partnerships in poor countries.**

The global health community needs to observe closely the impact of these partnerships and incentives on developing country innovation systems. Numerous partnerships and initiatives are being orchestrated but we know little of how these initiatives interact and overlap, the unwanted side-effects created, or how negative reactions are managed. To date, we have still not identified the most effective partnerships to encourage health innovation for the poor and there are few initiatives to develop or strengthen such partnerships in poor countries.

Funding for innovation – food for brains

The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPOA), published by WHO in 2008, called for the need to promote new thinking on innovation and access to medicines and to develop capacity in relation to health innovation as an essential response to public health needs. The GSPOA specifically drew attention to the need to invest in science and technology research and capacity, local production of pharmaceuticals, clinical trials, regulation, intellectual property and traditional medicine (*16*). This requires commitment and know-how from stakeholders in high-income countries, as well as stronger commitment from stakeholders in LMICs. But what role should LMICs take in funding these types of health innovation? As discussed later in Chapter 5, most of these countries allocate relatively low percentages of their gross expenditure to R&D for health (*5*, *17*).

To date, bilateral funding from high-income countries to low-income countries remains the main mechanism for improving access to health products for the poor. The US President's Emergency Plan for AIDS Relief (PEPFAR) and the President's Malaria Initiatives are two of the largest bilateral aid initiatives presently available.

Funds are also available through public–private schemes. For example, UNITAID – supported by a tax on airline tickets, by 29 individual countries and the Bill & Melinda Gates Foundation – functions as a central procurement agency for drugs to treat HIV infection, TB and malaria in LMICs. The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) also provides financial aid to deliver treatment and prevention products for these highly prevalent infections. While most of these funds derive from government donations, UNITAID, Global Fund and partners have also implemented several initiatives to raise social awareness of these diseases and to solicit additional monies from private philanthropists: an example is the (RED)™ campaign and the Dow Jones Global Fund 50 Index (*18*). Though these schemes focus on the "big three" (HIV/AIDS, TB and malaria) infectious diseases, they illustrate what could be possible if similar approaches were applied to other infectious diseases of poverty.

"While...partnerships capture the imagination of donors and foundations, they do not necessarily address core health concerns in LMICs. Further, the initiatives do not always clarify the responsibilities of these countries or facilitate the development of their innovation capacities."

The GAVI Alliance, MMV, DNDi and similar initiatives also have a significant portion (25.6%) of the total global funding for neglected diseases and have been successful in establishing a solid pipeline of more than 140 products (*19*). While these partnerships capture the imagination of donors and foundations, they do not necessarily address core health concerns in LMICs. Further, the initiatives do not always clarify the responsibilities of LMICs, facilitate the development of their innovation capacities, or address the need for sustainability in health R&D in disease endemic countries.

CASE STUDY 4.2

Lessons from Cuba

Cuba is a positive example of how initial public investments in pharmaceutical research and production capacity can be leveraged into developing country collaborations, the export of novel health products and the creation of a global health success story. Cuba's state-run pharmaceutical industry was established in 1972 to import pharmaceuticals and export traditional medicines cited on the WHO Model List of Essential Medicines. By 1993, Cuba had reduced the importation of finished medicines and instead was producing its own pharmaceutical products. This included over 1000 biologic and diagnostic products, as well as 162 non-prescription and generic drugs. Strong and enduring collaborations between national scientific and public health institutions led to the development and production of 11 vaccines, including the Cuban meningococcal BC vaccine, Haemophilus influenza type B vaccine, immunodiagnostics systems and more than 40 therapeutic products including monoclonal antibodies and recombinant proteins and drugs for HIV/AIDS. While Cuba imports most of its raw pharmaceutical materials from countries such as China, it exports not only pharmaceuticals but also health education, health promotion and methods of product delivery to low-resource settings in Africa, Asia and Latin America (*20–22*).

RESEARCH QUESTION:

How can global funding be used to build mechanisms for innovation and health R&D in the lowest income countries?

Despite the work of organizations including WHO/TDR, product-focused initiatives remain concentrated in developed nations and LMICs have not been able to take full advantage of them. In instances when agencies designate funds for in-country operational research, technical expertise and technology is often lacking and so funds are quickly diverted. Investment in product-focused research needs to be matched with investment in health systems, good governance and other structures to create and strengthen the innovation systems in LMICs (see Case study 4.2 opposite).

Priority setting for health R&D – where to start?

To invest effectively and strategically in R&D, funding agencies need to move away from disease-specific approaches, and think more broadly and systemically. The development of tools for disease prevention and control must take into account the changing global health context including the epidemiology and economics of disease, the increasing impact of climate change, and demographic changes including migration on disease distribution (see Chapter 2). Changing health systems and structures, and the values that underpin these, need to be accommodated (Chapter 3).

As noted above, considerable political and funding support has been directed to HIV/AIDs, TB and malaria, but little attention has been paid to other "neglected" infectious diseases, despite the fact that infections such as intestinal helminths and schistosomiasis are frequently co-endemic with malaria and HIV/AIDS (*23, 24*). Delivering rapid-impact drug packages could have important preventive and collateral effects, including reducing disabilities, improving well-being and, in some instances, disrupting disease transmission (*25*). Such a single dose of combination drugs not only addresses the need to treat common coinfections, but also saves time and reduces the direct and indirect costs for both health provider and consumer. Women – who are most often the community health providers as well as the ones responsible for household health care needs – are especially advantaged by this approach. Priority needs to be given to develop tools which are effective and affordable, have high benefit–cost ratio, are sustainable and carry low risks. They need also to be culturally appropriate and acceptable.

RESEARCH QUESTION:

What are the most effective ways to implement the criteria for innovation (effectiveness, affordability, acceptability and sustainability) in national and global innovation systems?

LMICs must be involved in setting and implementing the agenda for action in the response to, and control of, infectious diseases. The governments of some developing countries have already become important contributors of financial and technical resources in the global health landscape. For example, Bangladesh, India and Nepal have a formal agreement that promotes the successful implementation of proven cost-effective interventions/tools such as rK39 and miltefosine for diagnosis and treatment of patients with visceral leishmaniasis in the Indian subcontinent (*26, 27*). Other initiatives, including The India-Brazil-South Africa Dialogue Forum (*28*) and China-Africa Development Fund, aim at building local infrastructure for development and manufacture in LMICs *(29)*.

CASE STUDY 4.3

India, trade-related aspects of intellectual property rights (TRIPS) and the Patents Act

In India, the original Patents Act (1970) restricted patents on food, chemicals and drugs and discouraged the presence of multinational drug companies. This allowed local companies to build expertise in generic drug manufacturing and to sell drugs at low cost (*37*). On joining the World Trade Organization in 1995, India was required to comply with TRIPs. This could have reduced India's generic drug manufacturing capacity and the availability of affordable essential medicines (*38, 39*). However, TRIPs was implemented judiciously and the Patents (Amendment) Act (2005) contained stringent intellectual property measures, opposition measures for challenging frivolous patents, limited patentability exceptions and detailed criteria for provisions relating to compulsory licensing and parallel importation (*37*). These legislative measures helped Indian companies to expand into foreign markets in the United States of America and Europe, and to offer the United States of America's Food and Drug Administration approved facilities for drug R&D, including clinical trials, in India (*37*).

Policy environments in developing countries – more than scaffolding required

Effective policy design and implementation are pivotal to supporting innovation and nurturing local industry (*30–32*). Countries such as Brazil, China, India and South Africa illustrate how national innovation policies and investment in science and technology infrastructure have resulted in improvements in public health. Different approaches have been followed: Brazil passed the Law on Innovation which strongly encouraged PPPs (*33*); China prioritized biopharmaceuticals and the modernization of traditional Chinese medicines (*34*); and South Africa created Biotechnology Regional Innovation Centres to identify and develop commercial opportunities in biotech (*35, 36*) (for India see Case study 4.3).

Although very different in culture, governance and policy, these innovative developing countries have commonalities that are pivotal to nurturing innovation. Foremost, they are relatively stable countries which have benefited economically from globalization. They have created local private sectors in health R&D, provided incentives for PPPs and encouraged technology transfers. They have designed innovative intellectual property management strategies through humanitarian licensing agreements, which have allowed for the manufacture of licensed products to promote the access of health technology in other developing countries.

Market and profit-driven private sectors in these countries service large domestic and international markets. Investments continue into science and technology infrastructure to resolve local problems. The potential of large populations as talent pools for professionals and entrepreneurs is increasingly being realized. By generating an environment that enables private initiatives to thrive, many developing countries (including China, India, Republic of Korea and Taiwan) have been able to maintain their talent pool, while also attracting returnees from the United States of America and the European Union who have much needed managerial experience, technical expertise and access to a global business network (*30–32*).

Investing in health R&D has provided social and economic returns, through direct-cost saving from using locally produced technologies and revenue generated from exporting products and services (*31, 32*). One indicator for the return on this R&D investment is the number of American pharmaceutical patents measured against gross domestic product per capita. India (3rd), China (4th), Brazil (12th) and South Africa (14th) are among the world's top ranking for this indicator (*5*). Argentina, Indonesia, Malaysia, Mexico and Thailand are in the top 25 (*40*).

Other LMICs are seeking to emulate these approaches. Because they lack the capacity to innovate in all aspects of health, smaller countries have sought to invest strategically in particular areas. For example, Guinea-Bissau has started to formulate a national health research policy and build a functional system for health research; Mauritius has opted to build on its capacity for clinical trials; and Tunisia has identified particular aspects of pharmaceutical innovation to increase its capacity to produce essential medicines locally (*41*).

Established innovative developing countries such as Brazil, China, India and South Africa are well positioned to help other LMICs to innovate strategically. They share a similar burden of disease and have first-hand knowledge of the devastating effects of infectious diseases. Already these nations play a strong role in supporting global health research and innovation via their financial commitments, product, technology, and knowledge transfers. For example, Brazil's Ministry of Health provides technical assistance on HIV/AIDS prevention and care to 11 African countries and has signed an agreement to help Mozambique manufacture antiretroviral drugs (*7*). The Oswaldo Cruz Foundation (Fiocruz), the premier publicly funded science and technology health institution in Rio de Janeiro, is helping to set up schools of public health in Angola and Mozambique (*7*). These efforts need to be scaled-up, better integrated with other capacity building initiatives and more effectively globalized to assist smaller LMICs to create similar innovative environments.

RESEARCH QUESTION:

What policies, scientific and financial links should innovative developing countries mobilize in order to support health innovation systems in other LMICs?

Public–private product development partnerships – the fast-track alliance

Innovations in research management and financing have led to the formation of PPPs and product development partnerships (PDPs). The aim is to accelerate R&D, infusing business philosophies with values of social justice and equity to improve implementation and access to existing technology. PDPs can establish mechanisms to redistribute funds and pool expertise and, importantly, to share benefits and risks of investments in health R&D.

An increasing number of products are being developed and marketed by emerging economies with sustainable research and manufacturing capacity such as China, Brazil and India. Today, nearly 62 products (vaccines, diagnostics and drugs) are being developed by 78 companies in developing countries (*42*). These include innovative processes for manufacturing local versions of the recombinant hepatitis B vaccine in Cuba, India and the Republic of Korea; Brazil's efforts to produce low-cost generic antiretrovirals for HIV/AIDS in order to provide free access to life-saving drugs; and the development of the antimalarial arteether (a synthetic version of artemisinin) by India's Central Drug Research Institute (*40*).

Pharmaceutical companies and global health programmes have also partnered with local research institutes to develop and manufacture new products. For example, arteether was transferred to Themis Chemicals Ltd. for commercial manufacture and distribution and is now sold in 48 countries (*40*); Fiocruz/Bio-Manguinhos and the Butantan Institute in Brazil have partnered with the HHVI, while Ranbaxy Laboratories Ltd. and Bharat Biotech International Ltd. in India are linked with the PATH Malaria Vaccine Initiative (*40, 43*). Such partnerships go beyond drug development and include drug manufacture – China is currently the leading global producer of penicillin, the Serum Institute of India Ltd. leads the production of the diphtheria-pertussis-tetanus

vaccine, and over 60% of the United Nations Children's Fund's (UNICEF's) vaccine requirements are met by Brazil, Cuba, India and Indonesia (*31, 40*).

The successes of public–private PDPs highlight the need to expand the scale and scope of activities. Until now, the focus typically has been on delivering a product or service for a particular disease within a specific timeline of five to ten years. The expectation of such short-term returns on investment has excluded LMIC partners with incipient research capacity but less experience with product development. This approach has also excluded embryonic technologies which require investment in R&D beyond the ten-year mark. To ensure long-term sustainable global health innovation systems it is important that LMICs with developing capacities be given more active roles in public–private PDPs. Innovation must include long-term capacity building as well as capitalizing on quick short-term gains.

Few PPPs and PDPs concentrate on the delivery and uptake of products or on strengthening local capacity for R&D. Innovations and partnerships to address these aspects of the system are important to ensure that innovations reach those who need them most. For example, PATH, an international non-profit organization, aims to advance relevant and appropriate health technology, strengthen health systems and encourage positive health behaviours in low-resource settings (*44*). The European and Developing Countries Clinical Trials Partnership (EDCTP) comprises 14 European Union Member States, Norway, Switzerland and 47 sub-Saharan African countries[1]. It was established to accelerate the development of new pharmaceutical products through multicentre projects by combining clinical trials with capacity building and strengthening of regional partnerships (*45*). More initiatives like these are required.

1 For more information see (http://www.edctp.org/, accessed 1 March 2012)

RESEARCH QUESTION:

How can public–private partnerships be expanded and scaled-up to include not only PDPs, but also the development of more basic research in the laboratory and the delivery of sustainable innovative products into the field?

Social innovations – science on its own is not enough

Initiatives to strengthen health innovation systems must account for the complex challenges of health infrastructure, economics, social and cultural factors that inhibit people from accessing new and life-saving innovations. Innovation must include R&D and delivery. It is crucial to understand local contexts, engage communities and incorporate the wisdoms of local knowledge.

Partnerships between private, civic and public sectors should be strengthened to enhance access to essential drugs. Already, a number of partnerships have proven that success is possible. For example, in partnership with WHO, Merck & Co. and the Global Alliance to Eliminate Lymphatic Filariasis (GAELF), GlaxoSmithKline donated albendazole to mass-drug administration regimens of diethylcarbamazine or ivermectin. This has resulted in the near elimination of lymphatic filariasis in Egypt, Samoa, and Zanzibar in the United Republic of Tanzania (*46–48*). Pfizer worked through the International Trachoma Initiative to donate azithromycin and as a result, trachoma has virtually disappeared as a public health problem in Morocco (*49, 50*). Since the 1980s, Merck & Co. has donated over 300 million treatments of ivermectin for the control of onchocerciasis via the Mectizan® Donation Program in Africa and Latin America. This partnership has been running for 25 years and has proven so successful that it has been hailed as one of the greatest medical achievements of the 20th century (*51–53*).

OVERCOMING SOCIAL AND CULTURAL BARRIERS – GETTING COMMUNITIES INVOLVED

To expand access to health innovation, we must also factor in social and cultural barriers to prevention and care. These are associated with social norms, sex and gender biases, stigma and taboo behaviours. Too often interventions and innovations are not taken up because local communities are not consulted. The story of polio teaches us important lessons: the failure to obtain informed consent from parents of vaccinated children, combined with lack of clear communication about the limitations of the oral polio vaccine and the outcomes of vaccine-induced harm, have seen polio eradication campaigns beset by rumours, low attendance and active community resistance (*54, 55*). Instead of being eradicated years ago, poliomyelitis continues to affect people in LMICs. Similar themes have recurred in relation to other infectious diseases such as leprosy, leishmaniasis, Buruli ulcer, severe acute respiratory syndrome (SARS) and schistosomiasis (*53*).

RESEARCH QUESTION:

What strategies and social entrepreneurship models are available for local communities to innovate in the prevention, control and treatment of infectious diseases?

> **"We need to find new ways of engaging communities so that initiatives are sustainable in the long term and not simply imported interventions, the effects of which will fade once the programme has ceased."**

Stigma often disproportionately affects women, resulting in delayed diagnosis; non-adherence to treatment; and greater psychological, social and emotional distress because of abuse, abandonment, divorce and other relationship problems (*56, 57*). In Ghana less than one quarter of people with schistosomiasis-related symptoms seek medical treatments through the health system (*58, 59*).

CASE STUDY 4.4

The community-directed treatment approach

The community-directed treatment (CDT) approach has been implemented across 50 000 communities in Africa and is one of the most successful innovations in creating community ownership and building programme sustainability. Communities in meso or hyper-endemic infectious disease areas identify amongst themselves those who will be responsible for community-directed drug distributions, organizing distribution according to their own cultural norms and organizational structures. This approach builds programme sustainability, community ownership and empowerment. Cost-savings are made by health departments as staff do not have to be sent into the field to supervise distribution (*60*). CDT has been successfully implemented across 19 countries involved in the African Programme for Onchocerciasis Control (*61*). It has also been used in the control of lymphatic filariasis in Ghana (*62*); to distribute Vitamin A and iron supplements to nomadic pastoralists in western Kenya (*63*), and to teach Ethiopian mothers how to recognize and quickly treat children showing symptoms of malaria.

To overcome such barriers, we need to find innovative methods to translate and customize health interventions and products to local settings. In other words, we need to find new ways of engaging communities so that these initiatives are sustainable in the long term and not simply imported interventions, the effects of which will fade once the programme has ceased (see Case study 4.4).

Building capacity – incubating entrepreneurship

Capacity building is crucial if developing countries are to become active participants in innovation and research. Considerable efforts have already been made. WHO/TDR, the Wellcome Trust, Fogarty International Center, Japan Society for the Promotion of Science and the Academy of Sciences for the Developing World are among the agencies that have made substantial investments in human capital development in LMICs through scholarships and research training, institutional support and research project support.

Capacity building through the creation of centres of excellence has been successful in helping poorer countries to conduct high-quality research and produce new graduates, but the impacts are often localized to one or a few academic institutions. Despite active research programmes in infectious diseases, academic centres of excellence in most LMICs have been underrepresented in the various PPPs and PDPs whose initiatives drive the development of new health products. Rather than shaping the local culture of innovation, these centres of excellence can bias the national science and technology landscape as they have competitive advantage over local institutions for the limited human and financial resources for R&D. These centres are also more likely to have research collaborations with developed-country partners than in-country or regional partners. These partnerships are usually the results of engagement between individual researchers of similar research interests and technical expertise, which may not be conducive for interdisciplinary research towards innovative solutions. The performance of these centres must be continually monitored and evaluated to ensure their capacity in research innovation.

> **“Without individuals with “technopreneurship” or private sector experience to support local academic scientists, R&D spin-off projects may suffer from a higher than necessary attrition rate and lower returns on investments.”**

Many developing countries have also experienced a profound loss of human resources, not only in the R&D sectors but also across disciplines relevant to population health and disease control and in the health services system. Generations of young scientists, medical and public health professionals have been sent abroad for training. Often they continue to work overseas – in facilities with resources that cannot be matched in their poorer home countries. Talented individuals who have returned tend to be concentrated in the few centres of excellence where the research environment is most conducive for career development, or are diverted into senior administrative and management positions. They are liable to be cut off from the rest of the health infrastructure in these countries, so there is a need to better connect individuals at these centres with the rest of the health infrastructure in LMICs.

Areas of research such as the social sciences, epidemiology, and health systems research require significant local involvement in capacity training (see for example Case study 4.5). This is because the effective implementation and adoption of health solutions require understanding of local contexts and the participation of the local partners.

CASE STUDY 4.5

Consortium for Advanced Research Training in Africa (CARTA)

CARTA (64) is an innovative capacity-building initiative in public health and the social sciences. It aims to train African researchers at their own universities, while building a critical mass to sustain Africa's strongest and most talented researchers. CARTA involves nine academic and four research institutions from west, east, central and southern Africa, to provide doctoral training in population and public health and strengthen research infrastructure and multidisciplinary research capacity. CARTA Fellows enrol in a PhD degree programme in a member university and are supervised by African researchers. They participate in extended residential seminars at key points during their doctorates, facilitated by senior staff from both African participant universities and research institutes, and select "northern" partners including WHO/TDR. These seminars offer training in research methods, disciplines and theories relevant to population health; and generic teaching, research management and grants skills. Training opportunities are also provided for their supervisors to gain new and upgrade existing skills, and to take advantage of expanding research networks. The African-led nature of CARTA ensures sustainable, measurable changes in research capacity, output and translation of population and public health.

Innovative ways of capacity building need to be expanded, along with enabling environments to retain the talent pools. Interactive video and online training modules can be incorporated in training programmes and made accessible to researchers across countries through knowledge-sharing platforms such as the WHO/TDR TropIKA.net portal (*65*).

Mechanisms to promote R&D spin-offs from academic institutions in developing countries also require personnel with research management skills. Without individuals with "technopreneurship" or private sector experience to support local academic scientists, R&D spin-off projects may suffer from a higher than necessary attrition rate and lower returns on investments.

RESEARCH QUESTION:

What is the most effective way to link the local milieu of innovation in the public and private sectors in LMICs with international partners?

Ethics, innovation and infectious disease

Science cannot be an end in itself; it needs to be framed by moral and ethical imperatives. Innovation must start with the premise that the ultimate aim is to reduce health inequities.

Rapid shifts in technology and policy can have detrimental effects on human health, cultures and the environment. Critical reflection is needed on how new science influences the biosphere; how medical interventions affect the quality and dignity of human life; and how discrepancies in power and knowledge may be used to subjugate others (*66*). On one hand, the pharmaceutical industry has become a close partner with public health initiatives, particularly in dispersing essential drugs and medicines to LMICs. On the other hand, vulnerable people continue to be recruited into clinical trials, in environments that are poorly regulated, where ethics and the rule of law are not easily enforced (*67*). The enthusiasm of some LMICs to establish themselves as hubs for clinical trials and drug development needs to be tempered with concerns over their regulatory capacity to cope with the influx of trials, limited ethical oversight and the impact of poorly designed and implemented trials on human subjects.

> **The enthusiasm of some LMICs to establish themselves as hubs for clinical trials and drug development needs to be tempered with concerns over their regulatory capacity to cope with the influx of trials, limited ethical oversight and the impact of poorly designed and implemented trials on human subjects.**

Further, the pursuit of innovation cannot displace the need to address weak infrastructure and inequities. Nor should the pursuit of the "new" and relatively untested replace what has been shown to work. Occasionally, new practices have been employed, without evidence to prove their efficacy. This poses risks to patient safety and quality of care. In other cases, what has been proven to work is not disseminated throughout health systems (*68*). Sound science requires continuous evaluation and assessment to determine a rigorous evidence-base and the feasibility and transferability of an initiative (*69*). Too often, innovation has concentrated on expensive and complex technological interventions, difficult to implement in developing country settings and available only to a privileged few. Understanding of the local context is critical, especially in impoverished communities; companies must consider how power and conflict affect the health of the most vulnerable. Ultimately innovation is not just doing things differently but doing things more safely, more effectively and more equitably. This might mean starting in settings in which poor people are already engaged. This is likely to include informal, unregulated providers; local associations such as citizen groups; and engagement with local governance where structures and accountability mechanisms are not always transparent (*17*). A democratic and grass-roots approach is essential but raises challenges such as managing competing interests, waning commitment and mitigating the unforeseen effects of the innovation itself (*68*).

A three-step approach to future research

To alleviate the effects of infectious diseases, especially on our poorest and most vulnerable, we need to engage with all aspects of the innovation system. Different sectors and systems for innovation need to integrate with one another to address the dynamic interaction of social, ecological and biological factors that influence the prevalence of infectious disease. Only by doing so can the development and delivery of relevant, appropriate and effective innovation and technologies be accelerated. We argue that there are three essential approaches:

1. to develop more open models of sharing new knowledge and products
2. to highlight the importance of innovation by engaging key players in global networks
3. to work towards a "one world–one research" community agenda.

> **Ultimately innovation is not just doing things differently but doing things more safely, more effectively and more equitably.**

NEW MODELS OF SHARING AND DELIVERY – THINKING OUT OF THE BOX

Research is needed to determine the best models for sharing of knowledge and delivery of new innovations. Drug and product development are long and expensive processes – relying solely on philanthropic donations to support these endeavours is not sustainable. There have been calls for an open-access approach to innovation and drug development (*70*), i.e. closer interactions between academia, biotechnology and the pharmaceutical industry to improve productivity through pre-competitive collaboration (*71*). Open-access models already exist. GlaxoSmithKline established the Tres Cantos Open Lab Foundation in Spain, focusing on TB, malaria and trypanosomiasis. Scientists from around the world can come together to collaborate and share intellectual property in relation to these infectious diseases. GlaxoSmithKline has also made 13 500 malaria compounds from its private library publicly and freely available in the hope that new medicines for malaria can be developed. A similar initiative is underway in Singapore at the Novartis Institute for Tropical Diseases, with special emphasis on dengue, TB and malaria.

These efforts need to be scaled-up. Existing financial constraints can dampen R&D efforts and it is important that resources be maximized. A culture of open innovation is crucial to share knowledge, technology and repositories, particularly in the current financial climate. Repositories may include demographic and biological databases (see Case study 4.6); bio-banks (e.g. cell lines, reference samples, microorganisms, bioreagents); biomarker banks (e.g. DNA, single nucleotide polymorphisms, proteins); standards libraries for common testing and validation; and compound libraries. Repositories should also include databases for traditional knowledge; social science data; archives protecting indigenous intellectual property; and platforms documenting health and social innovations (*72*).

Policy reform is necessary to create an open innovation platform. Most importantly, a global commitment is needed to develop sophisticated regulatory and intellectual policies to provide the framework for manufacturers to produce high quality products and sustain their competitiveness in the globalized marketplace.

Policy reform is necessary to create an open innovation platform. Most importantly, a global commitment is needed to develop sophisticated regulatory and intellectual policies to provide the framework for manufacturers to produce high quality products and sustain their competitiveness in the globalized marketplace. A recent initiative by

CASE STUDY 4.6

Knowledge sharing to control soil-transmitted helminths and schistosomes in sub-Saharan Africa

An open-access knowledge management platform has been established to document the prevalence of soil-transmitted helminths and schistosomes for the whole of sub-Saharan Africa (*73*). In recent years, geographical information systems technologies, global positioning systems in field surveys and the increased availability of online electronic gazetteers have expanded the project with geo-position survey data at actual location. These data provide essential information for control programmes and for the research community to know where and when to target control and treatment initiatives for helminth infections in sub-Saharan Africa.

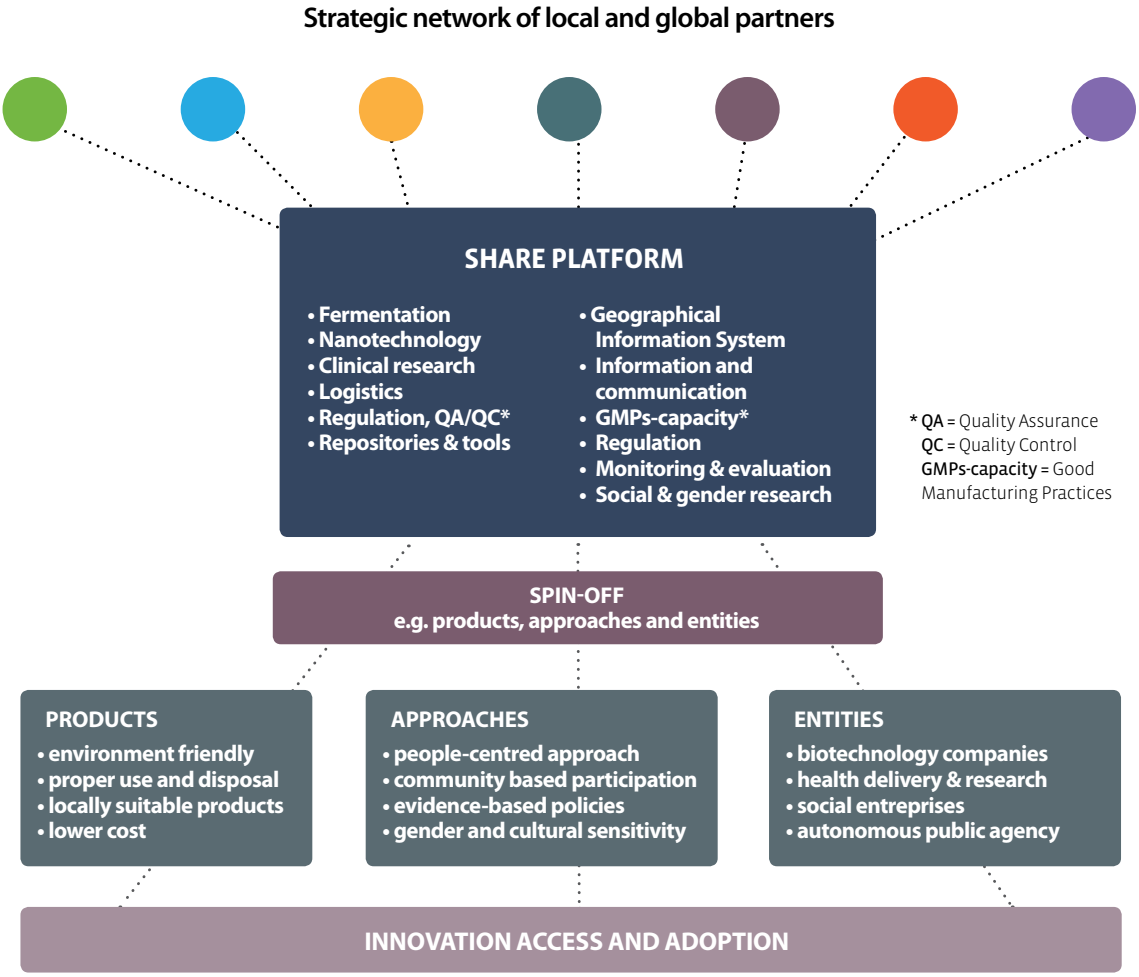

Fig. 4.2. From technology platform towards innovations. Open innovation platform as a mechanism for driving and supporting "home grown" innovations in low and middle-income countries.

the World Intellectual Property Organization, WHO and the World Trade Organization aims to improve access to patent information for public health and access to medicine, and freedom to operate with the help of a user-friendly database that contains public information on health-related patents (*74*).

> **A culture of innovation needs to be created in the workplace, among governments and researchers. Complementary platforms and an open-innovation environment are necessary for exchange of resources, information and human capital.**

BUILDING NETWORKS AND AN INNOVATION PLATFORM – TYING KNOTS THAT WILL HOLD

Because health encompasses both the physical and mental well-being of an individual – and is influenced by many social, economic, environmental and biological factors – an investment in health services alone is insufficient to maintain a nation's health and competitiveness in the globalized world. Investment in a responsive health innovation system needs to be an integral part of the national innovation system, and should translate across organization levels and government sectors to respond adequately to local, as well as cross-border, health issues.

Addressing the complexity of infectious diseases of poverty and reducing the gap in health inequalities will require breaking down the silos of traditional research and funding programmes. New innovations

focusing on cross-cutting platform technologies will need to be fostered so as to achieve synergy between programmes and sectors at the local and regional levels. An open innovation environment is necessary for this to occur (see Fig. 4.2), where information and resources can be shared and complementary platforms of technology can be applied to find the best solutions in local contexts where infectious diseases and poverty are co-endemic.

Basic and translational research activities conducted through shared research and technology platforms may result in spin-offs in product development and health services, in new approaches to disease control, or in new mechanisms for delivering health services. To achieve sustainable results, these technology platforms should be regionally based to support local R&D. A culture of innovation needs to be created in the workplace, among governments and researchers. Complementary platforms and an open-innovation environment are necessary for exchange of resources, information and human capital.

An open innovation platform should bring together independent but cooperating agencies and consortia (*75*). Networks of researchers, community members and health workers can help progress research; monitor health indices; undertake community audits and evaluation; better manage intellectual property; and distribute financing. With the increase in large-scale drug-based multi-disease control programmes, there is a need to monitor pharmacological side effects and community attitudes towards health technologies and to strengthen capability to translate technologies into local solutions.

New approaches to partnership can capitalize on local skills and create larger markets. Significant LMIC participation in these networks, beyond a simple transfer of tools from innovating countries to LMICs, is essential. Genuine efforts to build capacity will increase the suitability, uptake and sustainability of health innovations. It will ensure greater return on initial investments by donors or multinational companies and enable the development of necessary expertise and "home-grown" solutions for infectious disease control. Increasing the capacity of LMICs is important to changing the research paradigm: from how and where products are developed, to changing disease priorities and the organization of funding.

Existing regional networks have been established but are in their formative stages. Launched in 2010, the African Network for Drugs and Diagnostics Innovation seeks to strengthen national capacity by building regional networks to address local health needs. Other such networks include the Association of Southeast Asian Nations Regional Network for Innovation and the Network for Drugs and Diagnostics Innovation in China, India and Latin America.

Criteria to guide the efforts of LMICs in aligning local or regional needs for infectious diseases with the technology platform needed to deliver appropriate solutions should include:

- relevance of the diseases and technology in the context of LMICs
- potential for implementation in the LMICs
- sustainability of the proposed measures
- potential for value chain creation across health sectors
- potential to strengthen networks of LMICs
- commitment of LMICs, along with enabling policies and earmarked budget
- external support and commitment of international stakeholders to support and assist LMICs.

CASE STUDY 4.7

Suppressing dengue transmission in *Aedes* populations

Recently, researchers in the United States of America and Australia successfully managed to introduce the intracellular bacterium Wolbachia into wild mosquito populations of *Aedes aegypti*, the dengue vector. This interfered with the reproductive capacities of the mosquitoes, the transmission of the dengue virus and the lifespan of the mosquito. The Wolbachia-carrying mosquitoes were released in two suburbs in Cairns, Australia. Prior to release the researchers undertook strong community engagement to garner community support and also sought appropriate regulatory approval from the Australian Pesticides and Veterinary Medicines Authority. Results from this study show that, by protecting mosquitoes from transmitting dengue fever, it might be possible to prevent the 50 million human cases of the disease reported every year. Further trials are planned to be undertaken in Brazil, Indonesia, Thailand and Viet Nam.

Source: Reference (80).w

INNOVATING FOR "ONE WORLD, ONE HEALTH" – ONE PHRASE SAYS IT ALL

Health innovation is only possible with interdisciplinary learning and integrated delivery with other programmes. In an increasingly interconnected world many factors – social, economic, environment and biology – influence an individual's health. Investing in health innovations without incorporating the broader determinants of health will not be sufficient to maintain a nation's health and R&D competitiveness.

Instead, we need investment that fosters interdisciplinary collaboration; integration of health innovation within national innovation systems; and products and tools which are translatable across government sectors and organization levels. Focusing on cross-cutting technological platforms – such as fermentation technology, clinical trials capacity, information and communication technology, and wireless communication for operation and field research – increases the likelihood of developing innovations for the control and prevention of multiple diseases appropriate for the community in the local context.

The "One World, One Health" approach (see Chapter 2) presents an important lens through which policy-makers, funders and the academic community must view infectious diseases of poverty (*76*). There is an inextricable link between human–animal health and the environment. Exciting possibilities for innovation exist at this interface (see Case study 4.7). For example, genomic tools can be used to quickly identify and understand newly emerging viruses, their mutations, interactions with other receptors and replication in their hosts. Such analysis could enhance our understanding of how different host pathways affect the outcome of zoonotic transmission (*77*). Plant-derived pharmaceutical proteins can offer new products for the treatment of diseases. Examples

> **"If we are serious about innovating to address infectious diseases of poverty, we need an innovative system with a focus beyond product development."**

of proteins closest to commercialization include the hepatitis B virus surface antigen (hepatitis b), Lactoferrin (gastrointestinal infections), and rabies glycoprotein (for rabies) (*78*). Plant molecular farming has the potential to yield higher agricultural outputs as well as maximizing the yield of recombinant proteins in seeds; such studies have important implications for enhancing human health and developing new treatments for disease (*79*).

Conclusion – innovate or fail

If we are serious about innovating to address infectious diseases of poverty, we need an innovative system with a focus beyond product development. This system needs to be able to respond to changing global health needs, translate technological development, deliver useful innovation and, eventually, ensure greater sustainability and equity for the world's poorest populations.

LMICs must be actively involved in the health innovation system so that the tools and innovative approaches necessary to deal with infectious diseases are developed with significant participation of the countries affected by those diseases.

RESEARCH QUESTION:

We need to better understand the "eco-social" factors which facilitate resistance. What strategies – biological, chemical, genetic, cultural and social – exist to better control pathogens and vectors?

Disparate research capacities need to be brought together to consolidate and expand research and innovation in disease prevention, control and treatment. Enabling policies and mechanisms (i.e. harmonization of science, technology and innovation policies, intellectual property management, sustained financial commitment, incentives for intersectoral cooperations) are crucial to support R&D to enable significant innovations, attract partnerships with private sectors and help to reduce the investment risk for all stakeholders.

Innovation is not easy. It is complex, time-consuming work that requires global and local input, partnerships and collaborations, funding, enabling policies and long-term commitment. The rewards make it worthwhile to pursue: improvements in public health which took Europe 150 years to achieve in the 19th century were achieved by Latin America and east Asia in only four decades of the 20th century. This was due to significant human development and technological and medical interventions (*15*). In the 21st century, such achievements are possible globally.

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5 Research and development funding for infectious diseases of poverty: from landscape to architecture

IN CHAPTER 5:

- Current funding landscape and recent trends
- Funding of R&D for infectious diseases of poverty
- Diseases being funded
- Type of research being funded
- Future trends in the funding landscape
- Key challenges in funding R&D
- The future funding architecture

5

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Chapters 1 to 4 of this report have highlighted the importance of research – at all levels and in different disciplines – in tackling infectious diseases of poverty. There are currently many funders of such research and a wide range of stakeholders involved in the research process. However, resources are limited, so it is critical that funds are distributed and used so that they address the public health needs of disease endemic countries in the most effective way. To do this, we need to improve understanding of the research and development funding landscape, a landscape that has become increasingly complex in recent years. We address this issue in this chapter.

What are the issues at stake?

Deciding how to allocate financial resources for research and development (R&D)[1] relating to health opens up a complex web of competing and sometimes conflicting priorities, in which the needs of the recipients do not always match the interests or the motivations of the donors. With the shadow of the global financial crisis hanging over us, and as we face increasing constraints upon resources, it is not surprising that the funding of R&D for infectious diseases of poverty[2] raises many issues that give cause for concern.

Despite these gloomy times, there does appear to be some good news. Despite a slight decline in 2010, at US$ 3.06 billion, global expenditure on R&D for neglected diseases is nearly 19.5% higher than in 2007 (1, 2). This is a significant rise which, if invested wisely, could produce great dividends. However, we need a better understanding of how research is funded (i.e. of the funding landscape) in order to ensure that funds are directed to where they are needed most.

In this chapter we review the existing knowledge on funding flows and describe the mechanisms through which this funding is channelled and the type of research it supports. We briefly describe the different categories of funders that will be useful for newcomers to the field and for potential recipients of R&D funding; analyse available information on where and how these funders are applying their resources; and outline disease categories plus types of R&D activities targeted by funds aimed at tackling infectious diseases of poverty. We also provide a vignette of findings from an unpublished WHO/TDR commissioned study – the TDR Research and Development Funding for Infectious Diseases of Poverty Landscape Analysis – performed in a partnership involving the Global Forum for Health Research, Policy Cures and Biblioteca Regional de Medicina (BIREME) in Brazil. Building on other studies, this study focuses on infectious diseases of poverty and broadens the scope of R&D to include implementation research and capacity building – areas of research most pertinent for health in disease endemic countries where health systems and research capacity are often weak. The methodology for this WHO/TDR commissioned study is provided later in Box 5.1.

This chapter concludes with recommendations on the ways that the financial architecture governing these flows can be strengthened so that it reflects the key priorities of countries and populations at risk and increases the efficiency with which funds are applied.

The big picture: current funding landscape and some recent trends

A COMPLEX LANDSCAPE

There are three main sources of funds for R&D for infectious diseases of poverty: (i) the public sector (e.g. ministries of science and technology or aid agencies); (ii) the private sector (e.g. multinational pharmaceutical companies or biotechnology companies); and (iii) philanthropic foundations and individuals/private charitable organizations such as The Bill & Melinda Gates Foundation (Gates Foundation) and the Wellcome Trust. One might therefore expect funding flows to be relatively simple – but this is not the case. The funding landscape is confusing for both donors and recipients. Its complexity is characterized by multiple, diverse and overlapping sources of funding; multiple recipients for funding; multiple mechanisms of funding and a multiplicity of

1 The term "research and development" (R&D) traditionally refers to activities undertaken for the discovery or development of a new product such as a drug or diagnostic tool. In this chapter, and in the WHO/TDR commissioned unpublished study (TDR Research and Development Funding for Infectious Diseases of Poverty Landscape Analysis), we refer to R&D in a broader sense, including areas of research such as implementation research, capacity building and social and environmental drivers of infectious diseases. However, at times we refer to earlier studies (such as those presented in G-FINDER reports) which use a narrower definition of R&D.

2 The term "infectious diseases of poverty" (as defined in Box 1.1) is used throughout this chapter unless specifically referring to other studies. For instance, the term "neglected diseases" is used when referring to G-FINDER reports (these define "neglected diseases" by means of a three-step filtering algorithm).

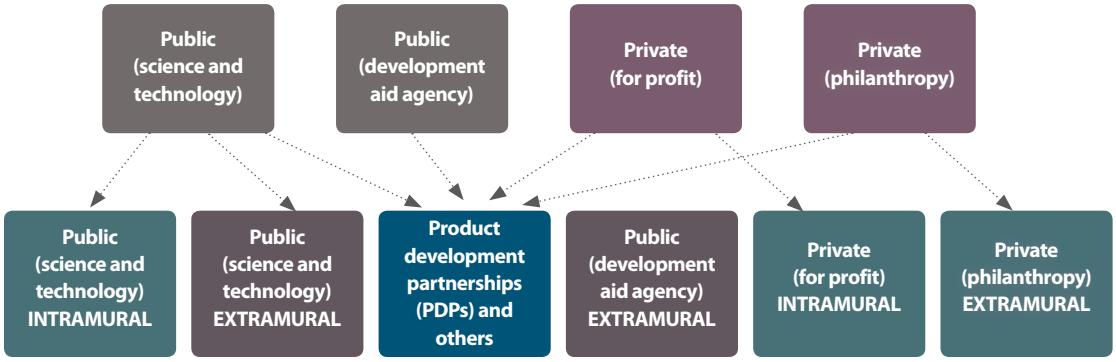

FIG. 5.1. Funding flows for R&D for neglected diseases. *Intramural refers to in-house funding by a donor, such as the National Institutes of Health's (NIH) funding of its own research activities. Extramural refers to funding provided to others, such as NIH or Medical Research Council (MRC) research funding to universities. Development agencies tend to undertake limited amounts of in-house research, so most of their funds go directly to outside researchers or to PDPs.*

Source: *Based on information from reference (2).*

roles; absence of overall coordination and prioritization; and a lack of comprehensive data and impact measurement. A full understanding of the financial flows into R&D for infectious diseases of poverty is further complicated by the fact that funders often participate in different mechanisms of support for R&D. Recipients also receive funds from diverse sources; disentangling these is not straightforward. Fig. 5.1 provides an overview of funding flows for R&D which illustrates the complexity. While a multiplicity of funding sources can have advantages, a lack of overall coherence and incomplete data are blunting potential benefits. There is no reliable figure for the proportion of donor funds "wasted" through duplication and un-coordinated initiatives, but it would be expected that better coordination would lead to a release of funds that could be directed to areas of research where they are most needed.

UNMET TARGETS

Council on Health Research for Development (COHRED) recommendations dating back to 1990 suggest that low and middle-income countries apply 2% of their total health budget (excluding the portion from external sources) to R&D. This commitment has been regularly reaffirmed at several international conferences such as those held in Mexico, Abuja and Bamako[3]. COHRED also recommended that donor countries spend 5% of their health-related aid on R&D and capacity building but no donor has ever committed to implement this target. Meanwhile, the international community continues to debate the figures and mechanisms to help implement these decisions effectively.

BALANCING FUNDS AND NEEDS

Funders can provide funds according to a wide spectrum of criteria. Some diseases need a concerted effort, with all stages of disease-related R&D requiring a large financial investment. For other diseases, a more modest contribution at a specific stage may suffice. In some cases there is a need for basic research, in others there is a need to focus on product development, clinical research or implementation research. The key question is: how can funders best target their support so that they provide the right type of investment, avoid wastage and build capacity? In order to address this question, funders need access to data and knowledge

3 The Ministerial Summit on Health Research, Mexico, 2004; The High Level Ministerial Meeting on Health Research in Africa, Abuja, 2006; and the Global Ministerial Forum on Research for Health, Bamako, 2008.

to inform their funding decisions, and tools to help them "access and compare disease burden, state of the science, and knowledge and product gaps, as the basis for deciding into which disease and product areas they can best invest in" (*3*).

> **"Some diseases need a concerted effort.... For other diseases, a more modest contribution at a specific stage may suffice. ...The key question is: how can funders best target their support so that they provide the right type of investment, avoid wastage and build capacity?"**

CONTRADICTORY TRENDS

In 2010, a WHO expert working group on research and development coordination and financing recommended that at least US$ 3 billion per year should be allocated for R&D directed at the health priorities of the world's poor (*4*). The total figure of US$ 3 billion directed towards R&D for neglected diseases (mentioned earlier) would therefore seem encouraging. Unfortunately, this note of optimism is tempered by trends that seem to go in the opposite direction. Firstly, contributions from philanthropic donors (such the Gates Foundation) and public sector organizations (including the United States of America's NIH) both fell in 2010, by 12.4% and 5.9%, respectively, compared to the previous year (*2*). Secondly, funding for basic research related to neglected diseases rose by nearly 15% between 2008 and 2010, much faster than overall allocations to R & D in neglected diseases which rose by 3.6% over the same period. This may have been at the expense of investment in implementation research (which could meet the more immediate need to have impact "on the ground"). For example, in 2010 more than half of the research funding for human African trypanosomiasis (sleeping sickness) went to basic research, despite the fact that control and management would benefit markedly from the development of new, safe, oral drugs that are active against the two stages of this disease (*2*).

IMPLEMENTATION RESEARCH FUNDING – THE POOR RELATIVE

Recent years have seen a shift in funding patterns, with governments and funders from low and middle-income countries playing a large part in R&D for infectious diseases of poverty. Traditionally, funding came from high-income countries. Now low and middle-income countries make greater funding available and there is increased inter-country collaboration between researchers in these countries ("south–south" collaborations). As the research capacity for novel work (basic research or product development) remains limited in low and middle-income countries, the likely priority for these countries is to ensure the delivery of drugs, vaccines and interventions developed elsewhere. Not surprisingly, as much as one third of low and middle-income countries' government funding for R&D related to infectious diseases of poverty goes to implementation and health systems research (*5*). However, funding for implementation research remains limited as funders from high-income countries (with the possible exception of philanthropic funders) give this lower priority.

This imbalance – whereby most global effort goes into the development of new drugs rather than the development of new ways to deliver products effectively to the poorest populations in an acceptable form and manner – needs to be addressed. The creation of incentives to complete the research

cycle from product development to product implementation is key to controlling infectious diseases of poverty. It is also crucial to advance health systems research, given its broader approach to answering implementation-related questions that affect a range of health problems at the same time.

> **The creation of incentives to complete the research cycle from product development to product implementation is key to controlling infectious diseases of poverty.**

THE ROLE OF PRODUCT DEVELOPMENT PARTNERSHIPS: CAN SUCCESS BE MAINTAINED?

PDPs are intended to bring together for-profit enterprises, academic researchers and others for the purpose of developing a drug, vaccine or intervention that does not have a ready market, a feature characteristic of infectious diseases of poverty. The idea is to facilitate collaboration and provide financial support to promising initiatives involving academics and commercial entities. Over the last decade, the emergence of PDPs that focus on areas such as malaria and diagnostics has helped to maximize the value of contributions from governments, philanthropic funders, academic research centres and private industry by leveraging their individual competencies towards specific goals. Prominent examples of PDPs include the European

BOX 5.1. METHODOLOGY AND DATA SOURCES FOR THE WHO/TDR COMMISSIONED STUDY – THE TDR RESEARCH AND DEVELOPMENT FUNDING FOR INFECTIOUS DISEASES OF POVERTY LANDSCAPE ANALYSIS

As well as other information sources (such as G-FINDER reports) this chapter draws on original research commissioned by WHO/TDR, undertaken in partnership with the Global Forum for Health Research (now part of COHRED), Policy Cures and BIREME, with financial support from the European Commission. This work focuses on infectious diseases of poverty (as defined in Chapter 1) and uses a broad description of R&D that includes implementation research. The research comprised both quantitative and qualitative analyses as outlined below.

Quantitative study

The WHO/TDR commissioned study provided an in-depth analysis of R&D spending for infectious diseases of poverty by four major sources – two public sector entities (the United States of America's NIH and the European Commission) and two private foundations (Gates Foundation in the United States of America; Wellcome Trust in the United Kingdom). These four organizations account for nearly three quarters of global spending on R&D for infectious diseases of poverty (*6*).

Qualitative study

Semi-structured telephone interviews with representatives from 34 public sector funding agencies from 32 countries in the 6 geographical regions defined by WHO were conducted as part of the study. This survey examined the extent to which public sector funders from high-income and disease endemic countries are involved in R&D for infectious diseases of poverty and the priorities that guide their R&D funding activity. Of these interviewees, 16 funders were from high-income countries (6 bilateral aid agencies, 10 national science and technology agencies) and 18 were from low and middle-income countries (7 national health research institutions, 11 national science and technology agencies). Investment data on R&D funding for infectious diseases of poverty between 2007 and 2009 were collected during the interviews and supplemented with data from the 2009 G-FINDER survey (*3*).

Research output

The study also carried out a bibliometric study of 173 578 articles on infectious diseases of poverty, published between 2000 and 2009, in order to investigate the research outputs produced by low and middle-income country researchers, their research collaboration with other countries and their ownership of research. In this chapter we also use information from literature published post-2009, including the 2010 and 2011 G-FINDER reports (*2, 5*) that focus primarily on basic and applied (product development) research funding provided by more than 200 institutions, including almost all major high-income country funders and a few of the major low and middle-income country funders such as Brazil, Colombia, India and South Africa.

Some limitations

A combination of the complexity of the financial flows associated with R&D funding for infectious diseases of poverty, the difficulty of obtaining data on funding in relation to certain types of implementation research and the fact that interest in funding of R&D for infectious diseases of poverty is of relatively recent origin means that the information available on the subject is necessarily limited. This is particularly true for implementation research, in-kind support and for funding flows originating in low and middle-income countries. Differences in methods across studies also make comparison of funding flows and their aggregation difficult (*6*).

Notwithstanding these data collection difficulties, the information on funding flows emanating from the qualitative study referred to in this chapter is a reasonable representation of the characteristics of research spending on infectious diseases of poverty, except for implementation research or on-the-job innovation. This is because the study captured information on organizations with the highest levels of investment in infectious diseases of poverty R&D, and also because all the major categories of agencies known to be involved in R&D funding for infectious diseases of poverty (aid agencies, science and technology agencies and private foundations) were included in the study.

and Developing Countries Clinical Trials Partnership (EDCTP), International AIDS Vaccine Initiative (IAVI), Program for Appropriate Technology in Health (PATH), Aeras Global TB Vaccine Foundation (Aeras), Medicines for Malaria Venture (MMV) and the Drugs for Neglected Diseases initiative (DNDi). Since their inception, PDPs have benefited greatly from non-financial contributions: for instance, the pharmaceutical industry has donated drugs and made molecule databases and technical expertise available at little or no cost[4]. Such collaborative efforts have allowed PDPs to deliver nine new drugs, diagnostics and vaccines for malaria, tuberculosis (TB), meningitis and visceral leishmaniasis.

PDPs have also developed the largest pipeline of products for neglected diseases ever assembled: over 140 projects are currently in development (3). Yet, despite this success, in 2010 PDPs received US$ 97 million less funding than in 2008 (2). It is too early to say whether this indicates that PDPs are losing their place as "flavour of the day" for large donors, but it is certainly a cause for concern at a time when several PDP products are reaching the Phase III human clinical trial stage.

4 In 2012, for example, a number of pharmaceutical companies and global health organizations formed a new partnership to combat neglected tropical diseases through drug donation, sharing of expertise and knowledge, and support for R&D. (**http://www.unitingtocombatntds.org**, accessed 29 February 2012).

A more detailed picture of funding of R&D for infectious diseases of poverty

WHAT IS THE TREND FOR R&D FUNDING?

Detailed long-running data on funding of R&D for infectious diseases of poverty are unavailable. With the exception of HIV-related R&D funding, little is known about funding of R&D for infectious diseases of poverty prior to 2007. What is known is that expenditure on total health R&D increased by more than four times in nominal terms during the period from 1986 to 2005 (*7, 8*) – an increase beyond inflation. It is likely that the last decade also experienced much faster growth in funding of R&D for infectious diseases of poverty compared to the 1980s and 1990s, in line with overall health R&D. This is particularly true due to increased support from the Gates Foundation; increased funds from private companies, philanthropists and governments for a number of PDPs; and new funding vehicles such as GAVI Alliance and the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund). Compared to preceding decades, public–private partnerships (PPPs) led to significantly expanded efforts towards new drug development in the period from 2000 to 2005 (*7, 9*). Countries such as Argentina, Brazil, China, India and South Africa also account for a small but rising share of funding for R&D in the first decade of the millennium (*2, 8*). For instance, Brazilian funding of R&D for health grew by nearly 29% in real terms between 2000 and 2005 (*10*).

G-FINDER reports are currently the only source providing aggregated data covering major public, private and philanthropic contributions to funding directed towards R&D for neglected diseases for the period from 2007 to 2010. These G-FINDER reports do not include estimates on R&D funds related to implementation research, capacity building or "knowledge translation". This means, for example, that data on funding via bilateral agencies that focus on health service financing or delivery issues are excluded; nor do they include information on funding for research on social and environmental drivers of health.

As mentioned earlier, funding of R&D for neglected diseases increased by nearly 20% between 2007 and 2010, with total funding of just over US$ 3 billion in 2010 (*2*). Although comparable estimates for earlier years are unavailable, estimates for R&D on all health were in the region of US$ 105 million at the beginning of the millennium (*7*). This gives some perspective on the tremendous growth in R&D for infectious diseases of poverty that has occurred over the last decade.

Figure 5.2 shows the total funding for R&D during 2007–2010, and indicates how funding levels have increased since 2007 (funding for 2010 was lower than for 2009, possibly reflecting the global financial crisis' delayed effect on public and philanthropy funds).

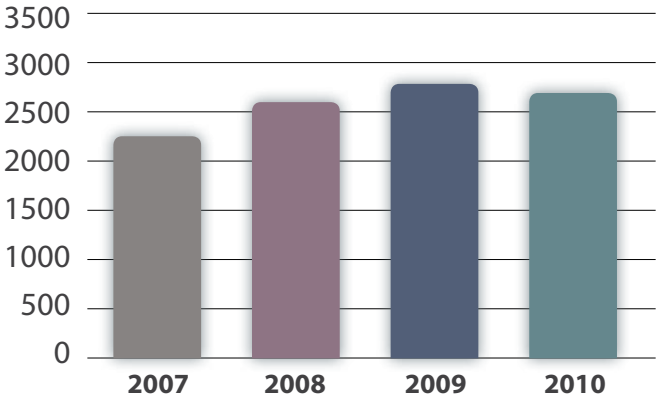

FIG. 5.2. Total R&D funding of neglected diseases (2007–2010, US$, millions).
Source: *Based on Table 2 in reference (2)*

WHO IS FUNDING R&D?

As mentioned at the start of this chapter, funding flows for R&D related to infectious diseases of poverty are complicated. They involve a mix of *sources* of funds such as the Gates Foundation, NIH and the United States Agency for International Development (USAID) and sometimes *(multiple) intermediaries*, such as the Global Fund, GAVI Alliance and various PDPs that bring together funds from multiple sources before transferring them directly to recipients (*5,11*). Bilateral agencies such as USAID or Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) can provide funds directly to the final recipient. Estimating the full magnitude of funding for R&D without double counting requires a separation between ultimate sources of funds and intermediaries, just as under the national health accounts framework commonly used for studying flows of funds for financing health care (*12*).

Data from the G-FINDER report for 2010 are summarized in Fig. 5.3 (*2*). This shows that high-income country governments are the major sources of R&D funds for neglected diseases, followed by philanthropies and private enterprises (two of the largest being the Gates Foundation and the Wellcome Trust, both based in high-income countries). Government funding from low and middle-income countries (such as India and South Africa) accounted for only about 2.1% of R&D funding. Although not displayed in Fig. 5.3, private pharmaceutical companies located in low and middle-income countries also fund R&D related to infectious diseases of poverty. Taken as a share of overall R&D allocations by private companies in both high-income and low and middle-income countries, however, their spending is rather small (*2, 13*). In summary, the picture that emerges is that the bulk of funding towards R&D for neglected diseases originates in high-income countries.

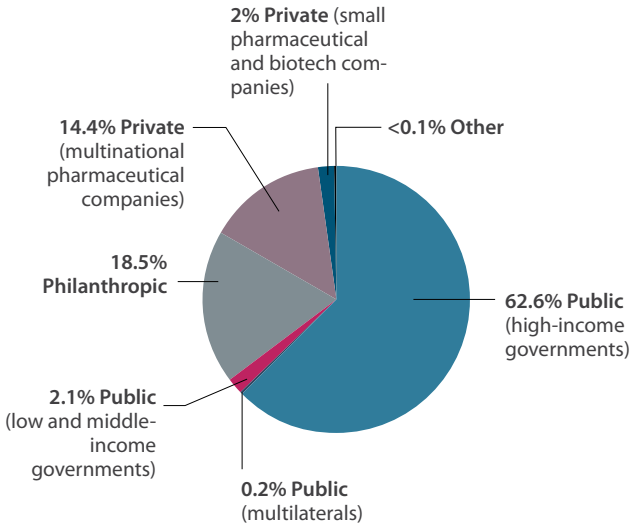

FIG. 5.3. Sources of funds for R&D on neglected diseases, 2009 (% shares of total funding).

Source: *Based on Fig. 24 in reference (2). Note that these estimates do not include in-kind support or support for implementation research or capacity building.*

Public sector funding: in high-income countries, governmental funding of R&D for neglected diseases is channelled mainly via science and technology agencies such as the NIH in the United States of America and the MRC in the United Kingdom. Counterpart agencies in low and middle-income countries include the Indian Council of Medical Research (ICMR) and the National Council for Scientific and Technical Research (Consejo Nacional de Investigaciones Cientificas y Técnicas, CONICET) in Chile. However, the picture is more complicated than it first appears, with funds ultimately coming from a number of different sources in various ministries. In Brazil, for instance, sources of funding include the Ministry of Health, the Ministry of Science and Technology, and the Ministry of Education (*10*). Public funds can also be directed via bilateral aid agencies such as USAID (United States of America), the Department for International Development (DFID) (United Kingdom) and the Swedish International Development Cooperation (SIDA) (Sweden) and sometimes in the form of government contributions to multilateral institutions/ international organizations such as The World Bank and WHO.

Among public sector funders, the United States of America was the single largest provider of contributions for neglected diseases R&D, giving approximately US$ 1.39 billion in 2010 [5] – nearly ten times as much as the United Kingdom, the next highest government funder (*2*). Most of these funds were provided via the NIH. The United Kingdom and the European Commission together provided a total of US$ 256 million. Other individual European countries such as France and Germany also made significant funding contributions, and Europe as a whole accounted for more than one fifth of all public funding of neglected diseases R&D.

Neither the Russian Federation nor China contributed data from a significant number of funders for either of the G-FINDER series of reports, so the contribution to R&D for neglected diseases from these countries is poorly represented. In other emerging world economies for which data are available, India and South Africa made major investments, with India featuring in the top 12 public funders of R&D for neglected diseases worldwide (*2*).

Private sector funding: the private sector provides a significant chunk of R&D funding for neglected diseases. Private sector funding was dominated by large multinational pharmaceutical companies that invested a total of US$ 442 million (87.9% of private contributions) in 2010. An additional US$ 61 million (12.1%) was contributed by smaller pharmaceutical and biotechnical companies (*2*).

Pharmaceutical companies also contribute (in cash or kind) to the development of vaccines and diagnostics – either directly or as participants in PDPs. For example, DNDi (see Box 5.2) obtained approximately US$ 2.8 million of its financing in 2010 (about 8% of its annual expenditures) from multiple sources that included GlaxoSmithKline, Sanofi-aventis and Epichem Pty Ltd, along with other non-profit and government entities (*2, 14*). There are a number of areas where private enterprises reported contributing in kind including, for example, the transfer of technology for developing and distributing products (e.g. sharing best practices and donating equipment); provision of technical expertise (e.g. as research collaborations, support for clinical trials, etc.); and training (through courses, conferences and in-house attachments). Companies have also shared databases and provided support for the

5 This is almost certainly a conservative estimate of contributions from the United States of America, since funding via USAID directed to health systems strengthening interventions was excluded (2).

BOX 5.2. THE DRUGS FOR NEGLECTED DISEASES INITIATIVE

The Drugs for Neglected Diseases initiative (DNDi) was launched in 2003 as a collaborative partnership between multiple institutions: the Oswaldo Cruz Foundation in Brazil, Indian Council of Medical Research, Kenya Medical Research Institute, the Ministry of Health in Malaysia, the Institut Pasteur in France, Médecins Sans Frontières (MSF) and WHO/TDR. It operates on a not-for-profit model which is directed and driven by the public sector.

DNDi's primary goal is to support the development of new drugs for key neglected diseases such as human African trypanosomiasis, visceral leishmaniasis and Chagas disease. For this purpose it seeks to address key gaps in the R&D pipeline through three types of work (i) long-term projects – relating to the identification of new compounds in basic research; (ii) medium-term projects – validating compounds that have not reached the stage of clinical development; and (iii) short-term projects – on new formulations of products that are already available.

To meet its goal DNDi has collaborative arrangements with both industry and academia. In 2010, most of DNDi's funding came from government sources (aid agencies) and private foundations. Some in-kind contributions came from private entities and universities. In 2010, DNDi spent a total of €24.9 million, 75% of which was devoted to R&D activities for neglected diseases.

Recent successes from this collaborative effort include the registration of two artemisinin-based combination therapies (ACTs) for the treatment of malaria as well as drugs for sleeping sickness and visceral leishmaniasis.

Source: *Reference (14).*

completion of regulatory requirements related to the registration and approval of drugs. No monetary estimates of these in-kind contributions were available.

Funding from private charitable organizations/philanthropic foundations and individuals: this category is dominated by the Gates Foundation and the Wellcome Trust. In 2010, the Gates Foundation contributed around US$ 456 million and the Wellcome Trust provided US$ 80 million to neglected diseases R&D. Together, the two organizations accounted for over 94% of all philanthropic spending (*2*).

HOW ARE FUNDS BEING CHANNELLED?

The main flow of resources from funder to recipient is shown earlier in this chapter (Fig. 5.1). These are intramural or self-funding (direct funding for internal researchers) or extramural funding (either direct funding for external researchers or allocated via PDPs and other intermediaries).

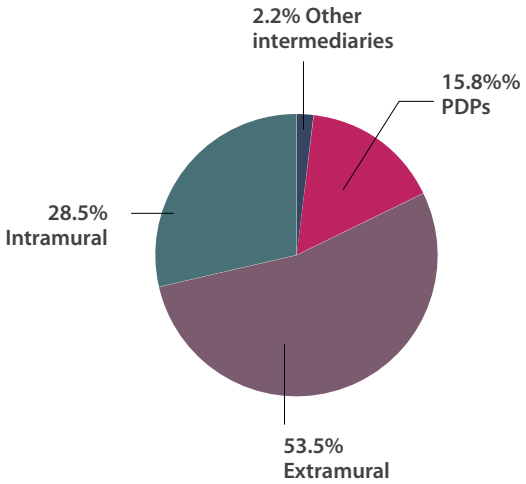

FIG. 5.4. Summarizes the G-FINDER 2011 survey *findings on the respective shares of the different channels of funding (2). Intramural funding accounts for around one quarter of all R&D whereas extramural funding goes mainly to researchers and on contributions to PDPs.*

Source: *Based on Figure 27 in reference (2).*

Intramural or self-funding (direct funding for internal researchers): funding of internal research is common among both science and technology agencies and private sector entities. Providing for institutional, salary and research support, this type of funding is usually restricted to large organizations such as pharmaceutical companies, the NIH, MRC, ICMR and the Institut Pasteur. In 2010, the total amount of self-funded R&D for neglected diseases reported by G-FINDER respondents was almost US$ 872 million. Intramural funding from major government science and technology agencies (including the NIH and MRC) equalled approximately one fifth of their expenditures in 2010, even though there was considerable variation across agencies (13% for NIH, more than 69% for MRC)(*2*). Data about NIH funding suggest a relatively stable share of intramural funding in recent years (see Fig. 5.5).

Almost all (99%) of R&D funding from private corporations was intramural. In sharp contrast, all of the R&D funds from major philanthropic organizations such as the Gates Foundation and the Wellcome Trust were extramural in nature (2). The same is true for government funding channelled via bilateral agencies such as DFID, SIDA and USAID. Respondents from science and technology agencies in 15 low and middle-income countries also reported that nearly one quarter of their R&D allocations were intramural (WHO/TDR commissioned study).

Funding from public and philanthropic sources also supports academic–industry partnerships and small business R&D ventures (often known as PDPs – such as MMV, see Box 5.3), or PPPs (15, 16).

The Gates Foundation, DFID, USAID and European bilateral aid agencies have been a major source of funding for PDPs (see Table 5.1). PDP contributions often account for the entire R&D contribution of many bilateral agencies (2). This is in contrast to funding by science and technology (government) agencies (such as the NIH) which are not listed among major funders of PDPs in the G-finder 2011 report (2) and accounted for only about 1.4% of PDP funding in 2009 (5).

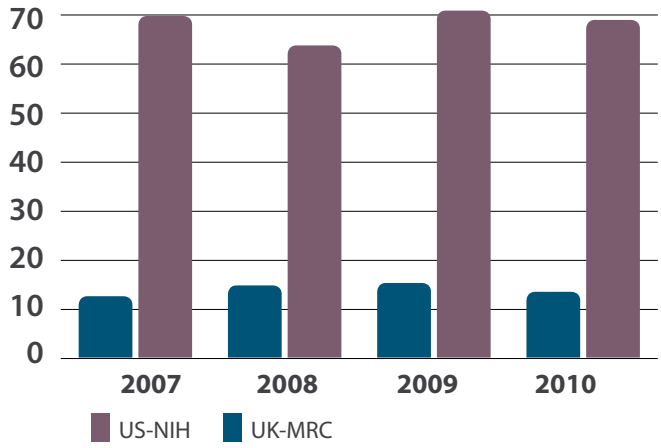

FIG. 5.5. **Recent trends in shares of intramural funding in National Institutes of Health and the Medical Research Council,** *2007 to 2010 (%).*

Source: *Tables 30 and 31 in reference (2).*

TABLE 5.1. MAJOR FUNDERS OF PRODUCT DEVELOPMENT PARTNERSHIPS (PDPS), 2007–2010

Funder	To PDPs 2007 (US$)	To PDPs 2008 (US$)^	To PDPs 2009 (US$)^	To PDPs 2010 (US$)^	% of org's funds given to PDPs 2010	Share of total PDP funding 2010 (%)
Gates Foundation	231,183,854	351,426,826	288,742,058	**253,755,901**	**55.7**	**52.5**
UK DFID	33,430,151	28,094,083	77,492,166	**97,229,720**	**100.0**	**20.1**
USAID	40,776,000	40,052,987	37,730,743	**40,243,034**	**46.8**	**8.3**
Dutch DGIS	32,170,024	19,807,172	19,454,348	**15,833,146**	**92.1**	**3.3**
Norwegian NORAD	13,271,949	12,389,471	11,667,625	**9,047,299**	**100.0**	**1.9**
European Commission	4,034,158	--	1,468,993	**7,914,688**	**8.6**	**1.6**
Spanish MAEC	3,426,196	13,116,474	14,323,053	**7,159,668**	**100.0**	**1.5**
Irish Aid	23,586,318	6,820,567	5,227,392	**6,508,789**	**99.7**	**1.3**
MSF	7,187,885	7,275,268	4,563,905	**4,725,479**	**100.0**	**1.0**
Swedish SIDA	10,505,567	11,188,482	7,952,989	**4,231,695**	**31.9**	**0.9**
Swiss SDC	1,861,163	1,870,609	2,009,185	**3,764,103**	**86.2**	**0.8**
World Bank	3,610,000	3,477,842	2,802,745	**2,757,154**	**100.0**	**0.6**
Subtotal top 12 PDP funders*	426,662,580	528,101,928	485,636,091	**453,170,675**	**56.9**	**93.8**
Total PDP funding	**469,392,952**	**580,084,383**	**530,049,041**	**483,166,820**		
% of total PDP funding (top 12)	**90.9%**	**91.0%**	**91.6%**	**93.8%**		

^ Figures are adjusted for inflation and reported in 2007 US dollars

* Subtotals for 2007, 2008 and 2009 top 12 reflect the top funders for those years, not the top 12 for 2010

\- No reported funding in category

Source: *G-FINDER report*

BOX 5.3. THE MEDICINES FOR MALARIA VENTURE

The Medicines for Malaria Venture (MMV) was launched in 1999 with initial seed money from the governments of Switzerland, the Netherlands and the United Kingdom (DFID), as well as the World Bank and the Rockefeller Foundation. This not-for-profit PDP has the stated aim of "discovering, developing and facilitating delivery of new, effective and affordable antimalarial drugs".

Funding and support for MMV is now received from government/public sources, the private sector, private foundations, philanthropies and multilateral and bilateral agencies. MMV is focused on delivering products which are safe and effective against resistant malaria strains for treatment and for prophylactic use by children and during pregnancy. Activities include supporting discovery research on antimalarials as well as clinical trials bringing together academia and industry. In 2010, 77% of MMV's budget was spent on R&D, and another 9% on activities to enhance the delivery of antimalarials to populations in low and middle-income countries. In 2008, MMV successfully registered Coartem® Dispersible, a paediatric antimalarial treatment. The majority (63.9%) of the US$ 55.3 million funds spent in 2010 came from the Gates Foundation. Other significant funders included DFID (15%), the Netherlands Ministry of Foreign Affairs, (3.4%), the Wellcome Trust (4.1%), USAID (2.5%), Irish Aid (2.3%) and the Spanish Agency for International Cooperation (2.1%).

MMV's dependence on resources from philanthropic organizations has belied the initial expectations of major funding from the public sector. Contributions originating from industry consisted primarily of expertise and resources. MMV insists on exclusivity with respect to licensing of programme-specific intellectual property. To enable the development and launch of drugs for the benefit of target populations, licenses are preferably royalty free and transferable.

Source: *Reference (17).*

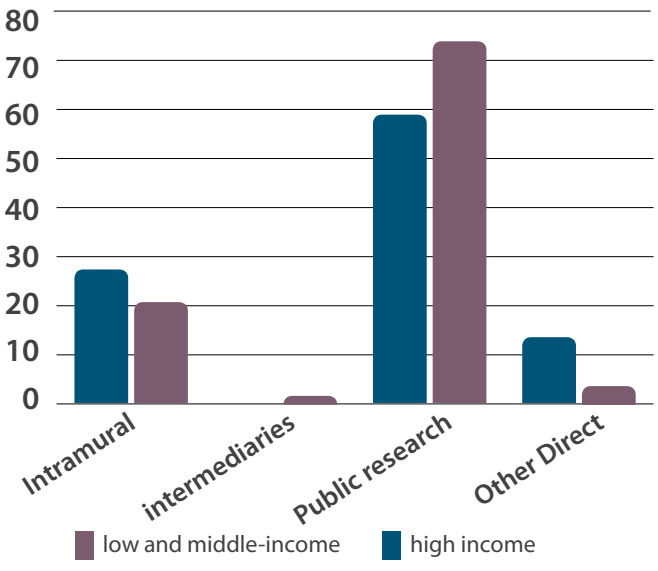

FIG. 5.6. Science & technology agency allocations (%) of R&D for infectious diseases of poverty: comparison between high-income and low and middle-income countries, *2009*.

Source: *WHO/TDR commissioned study*

Extramural funding (direct funding for external researchers or allocated via PDPs and other intermediaries): this is the main mechanism by which many funders support R&D, accounting for nearly 53% of all allocations in 2010 (*2*). Science and technology agencies rely overwhelmingly on this channel to transfer resources for R&D. Estimates based on a survey of 10 major science and technology agencies in high-income countries suggest that nearly 74% of their funding for infectious disease of poverty in 2009 was channelled as direct external research funding (WHO/TDR commissioned study). As one illustrative example, in 2009, NIH allocations to PDPs, other intermediaries and intramural research amounted to about 16% of its aggregate allocations, so that more than 80% of its funds directly supported external R&D (*5*). A similar proportion of R&D funds provided by 14 of the agencies contacted in low and middle-income countries supported external research. The breakdown by shares of R&D allocated in the two sets of countries is reported in Fig. 5.6.

In contrast to science and technology agencies, the funding pattern of aid agencies was characterized by a heavy emphasis on PDPs, other intermediaries and nongovernmental organizations (NGOs). The data indicate that 75% of development agencies' funding of R&D for neglected diseases was channelled via PDPs (*2, 5*).

How are R&D funds allocated?

There are three main ways to look at the data related to funding of R&D for infectious diseases of poverty.

1. Which diseases is funding focused on?

2. What type of research is funded?

3. Who is being funded?

WHICH DISEASES IS FUNDING FOCUSED ON?

The allocation of funds for neglected diseases in 2010 is shown by disease category in Fig. 5.7.

The data highlight the dominant place of the so-called "big three" diseases (HIV, TB and malaria) in the allocation of research funds. Funds for these three diseases together account for more than 70% of total R&D for neglected diseases allocations. Other significant, but much smaller, allocations went towards R&D for diarrhoeal diseases, dengue and diseases caused by kinetoplastids such as human African trypanosomiasis.

Fig. 5.8 attempts to capture variations in R&D allocations across different categories of funders by examining the distribution of funds across four types of funding agencies – (i) government sources in high-income countries; (ii) government sources in low and middle-income countries; (iii) philanthropic organizations; and (iv) the private sector. Fig. 5.8 clearly shows the dominance of the "big three" diseases in the funding of R&D for neglected diseases, irrespective of the ultimate source of funding. The combined share of funding for these three diseases accounts for approximately 52% of funding from low and middle-income country governments and more than 76% from high-income country governments. However, low and middle-income country government funders allocated relatively greater shares of their R&D spending towards other conditions – for example, over 10% of their spending was directed towards dengue R&D; another 26% went to diarrhoeal diseases, kinetoplastid infections and helminth infections. Even within low and middle-income countries there were significant variations in government R&D funding by disease (not shown). For example, South Africa heavily emphasized HIV/AIDS, TB and malaria over other conditions in its R&D funding for neglected diseases. This is not surprising given the significant challenges posed by these three conditions in that country. More than 90% of South Africa's public funding on R&D for neglected diseases is allocated to this disease cluster. The distribution of R&D funding by Colombia, with its heavy emphasis on kinetoplastid infection, dengue and malaria, similarly reflects local disease priorities (5).

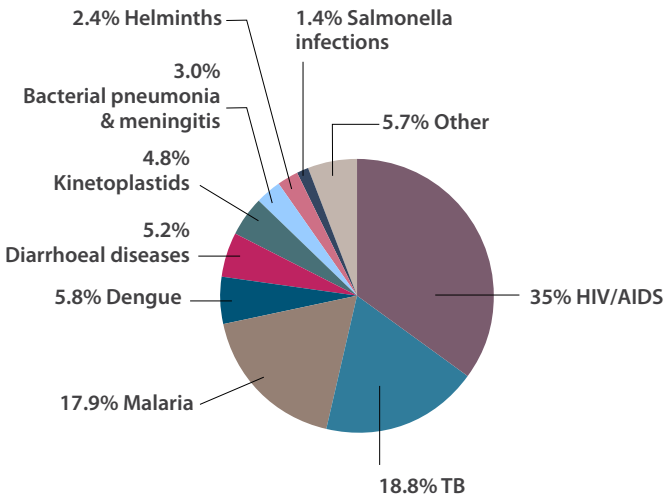

FIG. 5.7. Allocations of R&D for neglected diseases, *2010 (%).*

Source: *Based on Table 2 in reference (2).*

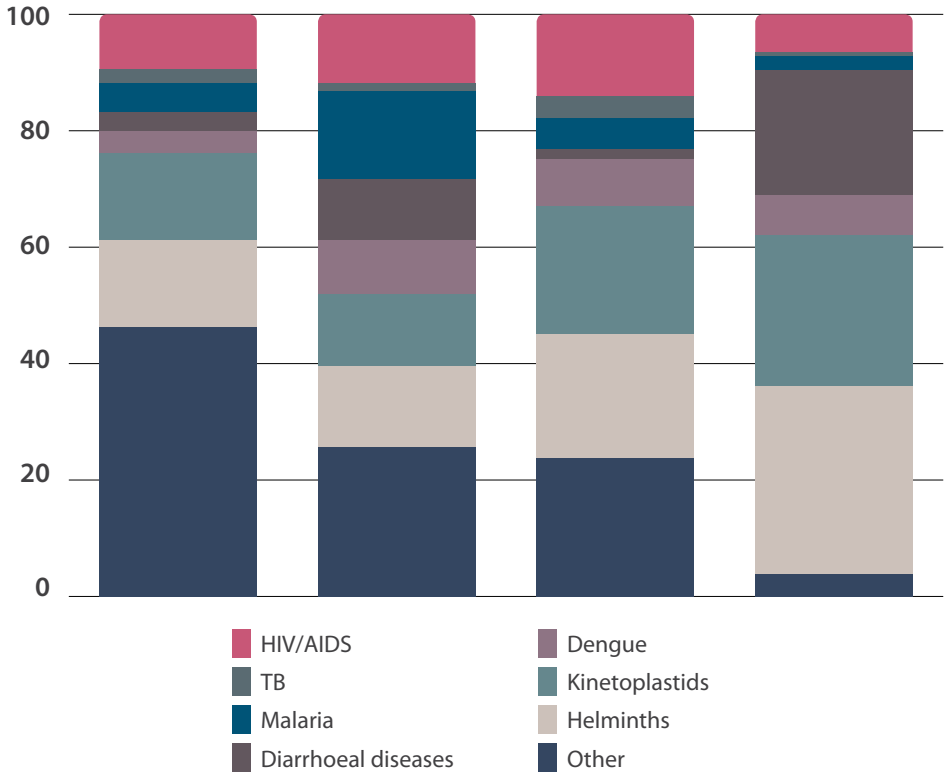

FIG. 5.8. R&D allocations by disease, *2010 (%).*
Source: *Based on Tables 22, 23, 25 and 26 in Reference (2)*

A second observation from Fig. 5.8 is the considerable variation in the relative share of funding towards R&D for HIV, TB and malaria across types of funders. The public sector in high-income countries allocated the largest proportion of its R&D spend towards HIV/AIDS but that was not the case for any of the other funders in 2010. Conversely, both low and middle-income country governments and philanthropic organizations placed emphasis on malaria. For private entities, TB and malaria appear to have greater priority.

The different patterns in R&D spending by high-income (compared with low and middle-income) country government (public) funders leaves open the question: is the variation in allocations to different health conditions a reflection of a real difference in priorities of the different sets of funding organizations that ought to concern policymakers, or does it reflect a degree of *tacit* collusion to avoid duplication in resource use? There is a need for clarity on the ways in which the different institutions prioritize their funding of R&D – an issue that is addressed later in this chapter.

Data on trends in allocations of R&D funding to different health conditions are not easily obtained from the G-FINDER dataset. This is due to the differences in respondent participation in the three years for which the data were collected, especially among private sector enterprises and low and middle-income country governments. For this reason Fig. 5.9 reports the changing shares of HIV, TB and malaria versus other diseases in the funding allocations of high-income country governments and philanthropic organizations only, given that data from these sources were collected on a reasonably consistent basis from 2007 to 2010 (*2*).

Fig. 5.9 shows that the share of high-income country spending on R&D for neglected diseases that went to HIV, TB and malaria has declined slightly in recent years – from 79.2% in 2007 to 76.1% in 2010. The declining share of public sector spending on HIV/AIDS R&D accounts for much of this reduction – in fact the reduction in the share of R&D spending that went towards HIV/AIDS exceeds the overall decline in the share of the "big three" diseases. The resulting "space"

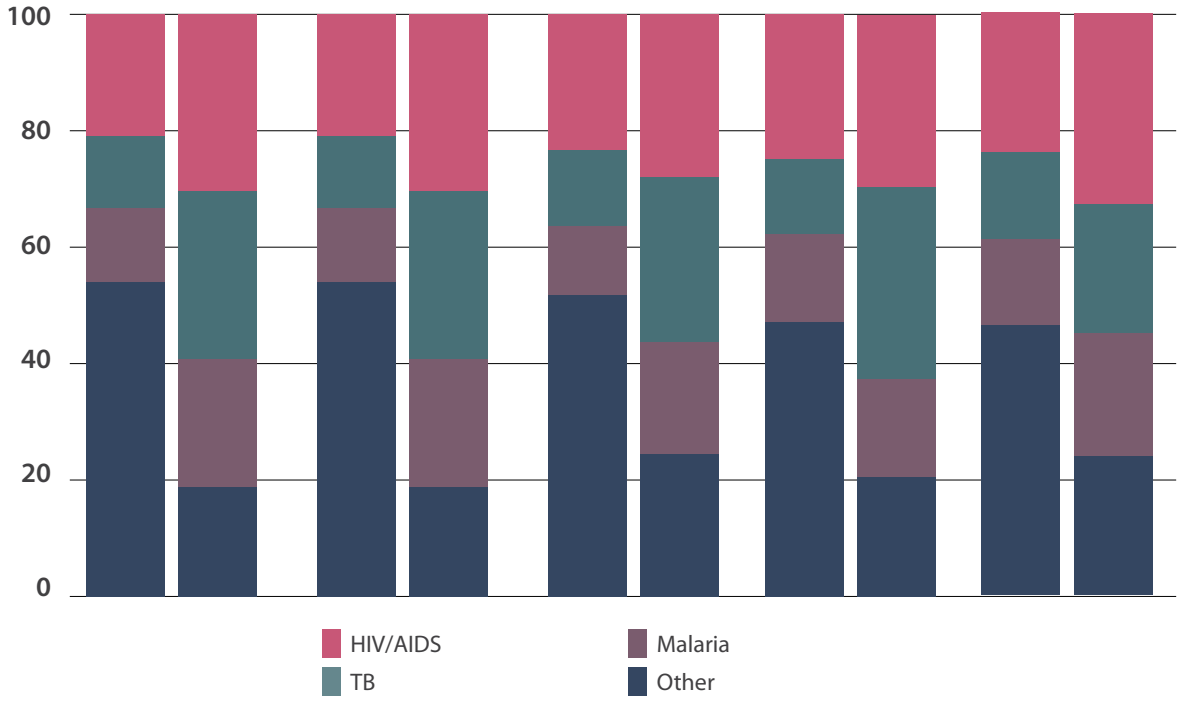

FIG. 5.9. Share of HIV/AIDS, tuberculosis and malaria in R&D spending on neglected diseases, *2007 to 2010 (%).*
Source: *Based on Tables 22 and 25 in reference (2).*

has been filled to some extent by a rising proportion of spending towards TB and malaria, as well as an increased proportion of spending towards diarrhoeal diseases and diseases caused by kinetoplastids. The share of spending on the "big three" diseases has declined among philanthropic organizations too, from around 70% in 2007 to 67% in 2010. The share of philanthropies' contributions towards TB R&D has remained stable over this period but there was a decline in the share for malaria in 2010. However, the share of "other conditions" seems to be increasing, mainly for dengue and helminths.

In contrast to the huge allocations made to HIV, TB and malaria – and, in recent years, the rising allocations to dengue, diarrhoeal diseases and diseases caused by helminths and by kinetoplastids – some other categories of infectious diseases of poverty receive relatively very small amounts of financing. Thus, in 2010, R&D funding for HIV/AIDS, TB and malaria was approximately US$ 1.12 billion, US$ 0.60 billion and US$ 0.55 billion, respectively (*2*). This contrasts markedly with funding dispersed towards R&D for Buruli ulcer (US$ 0.006 billion), trachoma (US$ 0.005 billion) and rheumatic fever (US$ 0.002 billion) (*2*). It is also noteworthy that R&D funding for bacterial infections causing rheumatic fever and trachoma has not been increasing, at least if the trends in the four years for which there are data (2007, 2008, 2009 and 2010) are any guide.

WHAT TYPE OF RESEARCH IS FUNDED?

Funding for infectious disease-related R&D can potentially support three major categories.

1. Basic research encompasses studies into the etiology of a disease or studies that increase scientific knowledge and understanding of a disease, disease processes or the pathogen or vector. They are not yet directed towards a specific intervention, product or health technology.

2. Product development constitutes a second category of research and is characterized by the discovery and development of new products and interventions (including drugs, vaccines, diagnostics and vector control

tools). This includes research activities and processes necessary to develop and improve new compounds or devices specifically designed to prevent, diagnose, treat or cure infectious diseases of poverty. This category includes clinical trials.

3. Implementation research includes the development of delivery mechanisms for existing and new products, including interventions aimed at the broader health system to decrease the burden of infectious diseases of poverty. This category also includes behaviour-linked research that has implications for the prevention of infectious diseases of poverty (e.g. community willingness to use a product).

Although not readily classifiable under the above categories, implications for the sustainability of research programmes dictate that resource flows to *build research capacity* should also be included as an area of R&D that receives support. For greater precision though, only those elements of capacity building directly associated with research on infectious diseases of poverty ought to be included as a funding priority.

Detailed data on R&D allocations for infectious diseases of poverty are not readily available for all of these categorizations. The G-FINDER survey essentially collected data on the first two categories of research for neglected diseases – basic research and product development. Fig. 5.10 shows this information for 2010, with the product development category further broken down into prevention, therapeutics and diagnostics.

Overall, 24% of R&D for neglected diseases (US$ 721 million at 2007 prices) was allocated to basic research, and about 69% to product development, of which funds for prevention (vaccines) were a major component (*2*). R&D funding for preventive vaccines for five health conditions – HIV, TB, malaria, dengue and diarrhoeal diseases – amounted to just over US$ 1 billion in 2010, more than one third of the R&D allocations reported in the survey for that year (*2*).

Underlying this aggregate picture are differences in practices across the different categories of ultimate funders. For example, about 36% of all R&D spending by science and technology agencies from high-income countries went towards basic research: 13% of bilateral aid agency/multilateral institution R&D spending went on basic research (WHO/TDR commissioned study).

No data were available on the amounts of funding allocated for capacity building and/or implementation research, but the research teams' interviews with aid agency representatives suggest that capacity building was a priority concern (WHO/TDR commissioned study). In contrast, only a few of the science and technology agency representatives (3 of the 10 high-income countries covered by the study) cited capacity building as an important priority. However, in practice, the distinctions between the science and technology agencies and aid agencies with regard to capacity building goals may not be as sharp. There are multiple examples of other ways in which science and technology agencies help build capacity for R&D in low and middle-income countries, such as via funding of research collaborations between groups from such

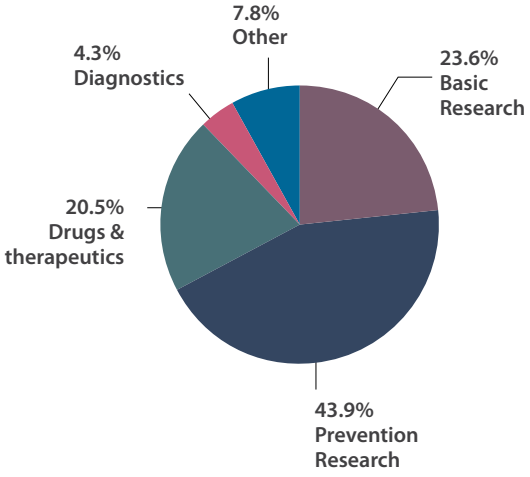

FIG. 5.10. Allocation of R&D funds for neglected diseases by type, *2010*.

Source: *Based on Table 20 in reference (2).*

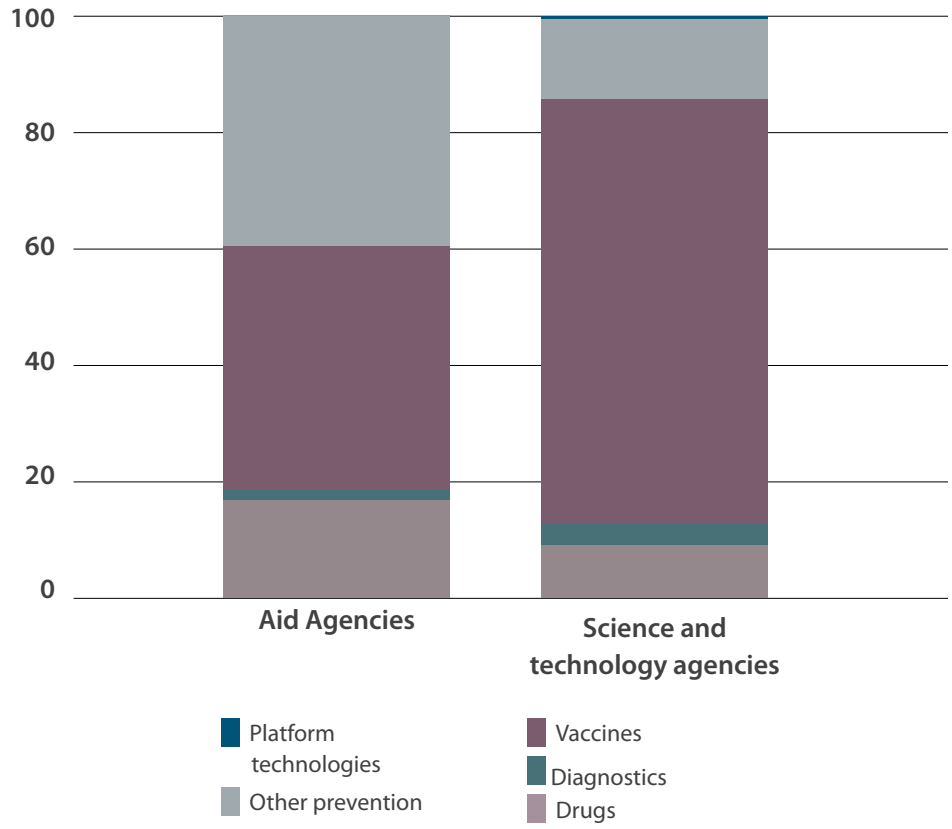

FIG. 5.11. Contributions to product development research: comparing science and technology and aid agencies in high-income countries, *2009 (%).*

Source: *WHO/TDR commissioned study.*

countries and higher-income countries such as Canada, Japan, the United Kingdom and the United States of America (WHO/TDR commissioned study, *(18)*). The WHO/TDR commissioned study also highlighted that the Canadian Global Health Research Initiative (which develops capacity for clinical trials research among researchers) works in the field of capacity building and that the MRC supports capacity building by co-funding activities in collaboration with DFID (WHO/TDR commissioned study).

Fig. 5.11 shows the allocation of funding from high-income country science and technology and aid agencies according to different types of research activity. Vaccine development accounts for the largest share of R&D spending on infectious diseases of poverty by both types of organization. The other noteworthy observation from Fig. 5.11 is the significant share of spending by aid agencies that support drug development R&D – primarily via PDPs.

There is limited published information available on the support that low and middle-income country agencies provide for R&D on infectious diseases of poverty. Interviews and quantitative data suggest that implementation research accounts for a substantial proportion of their allocations, perhaps as much 35% of all allocations for infectious diseases of poverty-related activities (WHO/TDR commissioned study). Estimates suggest that, of the funds allocated for R&D, one third was allocated to basic research, product development and implementation research, respectively. The lack of data on implementation research funding for infectious diseases of poverty by agencies in high-income countries means that a direct comparison is not possible. However, it should be noted that at least some of the implementation research in low and middle-income countries was funded from grants made available by organizations such as the Global Fund which, in turn, are funded by high-income country governments, philan-

thropies and multilateral institutions (WHO/TDR commissioned study).

Despite the difficulty in making comparisons across high-income and low and middle-income country funders, there are good reasons to believe that the share of research funds allocated to implementation research for infectious diseases of poverty by low and middle-income country institutions is larger than their high-income country counterparts. Local funders in low and middle-income countries reported that their limited research capacity for novel work in the areas of basic research and product development caused them to turn their attention to the delivery of drugs, vaccines and interventions developed elsewhere. For the same reason, their funding programmes tended to have a greater focus on capacity building; this was highlighted in interviews with funder representatives of Brazil, Colombia, India, South Africa and the United Republic of Tanzania (WHO/TDR commissioned study). Interviews conducted with multiple public sector funders from high-income countries confirmed this observation of differences between low and high-income countries: high-income country funders give lower priority to implementation research relative to low and middle-income country funders. The study also highlighted the fact that existing legislation in South Africa requires a minimum of 30% of R&D funding to be allocated to capacity building; Brazil, Colombia, India and The United Republic of Tanzania all reported implementing specific strategies aimed at developing capacity for research and industry development.

WHO IS BEING FUNDED?

About one quarter of all R&D funding (excluding implementation research) is intramural funding from large private enterprises and science and technology agencies of high-income country governments. The private enterprise component of R&D funding is almost all intramural and, as these firms are based primarily in high-income countries, the majority of funds are automatically directed towards high-income country researchers. The share of intramural allocations in total R&D funds of high-income country science and technology agencies are relatively smaller, but the basic claim – that most intramural funds go to high-income country researchers – remains valid.

Extramural funds from agencies and philanthropies account for about 54% of all R&D spending. Funding may be provided as project grants, career development awards or fellowships. Sometimes the grant requires a co-contribution by research partners or other sponsors. The funds are usually awarded competitively after a scientific peer review of proposed research and, as in the case of intramural allocations, go mostly to domestic (high-income country) researchers. Direct external grants among science and technology agencies in high-income countries were geared predominantly towards domestic (high-income country) researchers. Six of the ten science and technology agencies interviewed stated that all, or almost all, of their direct external spending on infectious diseases of poverty went to local/domestic researchers (WHO/TDR commissioned study). When the agencies supported overseas research, this was mostly in the context of collaborative projects between high-income and low and middle-income countries. Some high-income country agencies also collaborated with each other in formulating joint invitations for grant proposals, again mostly for proposals directed at local (high-income) researchers. One exception is the Canadian Global Health Research Initiative that funds overseas researchers even in the absence of Canadian collaborators (WHO/TDR commissioned study).

As noted earlier, funding by high-income country aid agencies tends to be directed towards PDPs which focus on product development. Most recipients of R&D funds via the PDP vehicle (which usually serves as an intermediary) tend to be researchers and firms in high-income countries. In 2007, more than 70% of disbursements through PDPs went to private companies, academic and public research institutions in wealthy donor countries, while less than 13% of the available funds was directed to research organizations and companies in low and

middle-income countries. Although some organizations such as DFID and USAID have allocated grants towards R&D for infectious diseases of poverty through a competitive process (usually in the context of health systems strengthening), in most cases aid agencies allocated funds on the basis of their past experience with specific recipients and their own strategic priorities. Development agencies also sometimes team with philanthropic organizations and/or science and technology agencies for specific grant-making activities related to capacity building. Examples include DFID's collaboration with the MRC and the Wellcome Trust to support clinical trials and research capacity building in Africa (WHO/TDR commissioned study). Much the same pattern of funding is observed in low and middle-income countries.

Funding of R&D for infectious diseases of poverty: implications of a bibliometric analysis

Research outputs of low and middle-income country researchers can help improve our understanding of R&D funding flows for infectious diseases of poverty directed towards them. For example, assessing patterns in research output from low and middle-income country research institutions can shed light on funding directed towards capacity building and implementation. Moreover, in cases where the research has been funded locally, research outputs can also help us better understand the priorities of low and middle-income country funders. If greater research productivity translates into increased likelihood of receiving research income in the future, trends in research output can perhaps also serve as indicators for the direction of future funding flows.

A bibliometric study of research into infectious diseases of poverty (part of the WHO/TDR commissioned study), provides some information in this regard. The study reviewed about 173 500 articles and reviews published on infectious diseases of poverty between 2000 and 2009 and was able to identify the country of affiliation of the first author in almost 150 000 cases. Of this total, 69.4% had first authors affiliated to high-income countries, 27.7% to middle-income countries and the remainder (2.9%) to low-income countries. Table 5.2 lists the top three countries with institutions to which the largest percentages of first authors were affiliated, categorized according to low, middle and high-income country. Not surprisingly, the United States of America and the United Kingdom emerge at the top in terms of publications. Among first authors

TABLE 5.2. PROPORTION OF PUBLICATIONS ON INFECTIOUS DISEASES OF POVERTY WITH A FIRST AUTHOR BY COUNTRY, CATEGORIZED ACCORDING TO WORLD BANK INCOME CATEGORIES, 2000–2009.

High-income		Middle-income		Low-income	
Country	Number of articles (share)	Country	Number of articles (share)	Country	Number of articles (share)
USA	37 693 (25.9%)	**Brazil**	8 447 (5.8%)	**Kenya**	441 (0.3%)
UK	10 911 (7.5%)	**China**	8 191 (5.6%)	**United Republic of Tanzania**	414 (0.3%)
France	7 241 (5.0%)	**India**	3 576 (2.5%)	**Ethiopia**	400 (0.3%)
All countries	100 852 (69.4%)	**All countries**	40 296 (27.7%)	**All countries**	4233 (2.9%)

Source: *WHO/TDR commissioned study.*

from middle-income countries, the largest group, comprising almost 5.8% of publications, was from Brazil, followed by India and China. Researchers from Kenya dominated the list of first authors from low-income countries, followed by researchers in Ethiopia and the United Republic of Tanzania.

PROMISING TRENDS

Although only about 30% of all the research papers on infectious diseases of poverty published during the period from 2000 to 2009 identified by the study had a first author affiliated to a low or middle-income country institution, the actual level of engagement in research (as indicated by the publication of articles with first authors affiliated to low and middle-income countries) overall has been increasing steadily over the past decade. When articles are analysed by year, the proportion of published articles on infectious diseases of poverty with first authors from low and middle-income countries increases from 5% in 2000 to 13% in 2009.

There are also positive features in the composition of the research being undertaken in low and middle-income countries. One recent study found that malaria featured in nearly 48% of the papers that had an investigator affiliated to a sub-Saharan African institute as the first-author, compared to global figures showing that 17% of the papers were on malaria[6]. The proportion of articles on HIV/TB co-infection, human trypanosomiasis and Buruli ulcer co-authored by researchers from sub-Saharan Africa was three times the global proportion of research articles published on these diseases. The proportion of articles on helminths and on TB matched global patterns but research articles addressing bacterial and protozoan infections, as well as dengue, had few sub-Saharan researchers as first authors. Overall, these trends suggest a growing research capacity and the emergence of a distinct research agenda in the region.

6 Feletto M [draft report]. Analysis of R&D spending for infectious diseases of poverty. Geneva, Global Forum for Health Research, 2011.

DRIVERS OF RESEARCH FUNDING FLOWS FOR INFECTIOUS DISEASES OF POVERTY: WHAT DO THE FUNDERS SAY?

Financial flows for R&D for infectious diseases of poverty are a function of the resource constraints faced by funders as well as their strategic priorities. In an attempt to understand what these priorities might be the WHO/TDR commissioned study conducted semi-structured interviews with representatives of 34 funders in 32 countries from different parts of the world in order to assess the criteria upon which public sector donors selected their funding priorities (WHO/TDR commissioned study). Table 5.3 summarizes their responses.

Most public sector R&D funding agencies follow some guidelines that drive their funding strategy. Science and technology agencies and/or health research institutions tend to focus on national research agendas, although these may range from general science and technology frameworks (independent of health priorities) – as in the case of Japan's Ministry of Education, Culture, Sports, Science and Technology (MEXT) – to Australia's National Health and Medical Research Council (NHMRC) that has well-defined health research priorities. In addition, the guidelines are loose enough to allow local researchers to have key influence. For most funders, especially in high-income countries, the scientific quality of proposals is usually of primary importance when funds are awarded. As indicated by interview responses, low and middle-income country agencies seem to have less flexibility (relative to their high-income counterparts) in the selection of their R&D funding strategy. This may be because low and middle-income country agencies are more likely to face greater constraints on funds and so have greater reliance on donor groups that may have a separate set of priorities (although no quantitative assessment is available to substantiate this). However, in a recent report (10), the Global Forum for Health Research analysed the funding patterns of science and technology agencies in a number of Latin American countries – Argentina, Brazil, Chile, Cuba,

Paraguay and Uruguay. This found that there is little evidence of compromised priorities in allocations among science and technology agencies from better off (middle-income) nations. Moreover, the relatively high allocations to communicable diseases among their poorer counterparts (such as Bolivia and Paraguay) also suggests that local funding is not too misaligned with the disease burden.

Development aid agencies differ from science and technology agencies in that broader development issues, rather than scientific and technical considerations, may be driving their funding strategies and influencing their

TABLE 5.3. PRIORITY SETTING IN R&D FOR INFECTIOUS DISEASES OF POVERTY: RESULTS FROM INTERVIEWS WITH 32 FUNDING AGENCIES, 2009.

Questions	Number of agencies surveyed		
	10	6	18
	High-income country science and technology agencies	**High-income country** aid agencies	**Low-income country**
Is there a national research agenda that serves as a guide?	Yes, general national research framework and/or health-specific	Follow government department agendas. Some agencies have specific global health research frameworks	Yes, majority have national health research agendas These may not always be followed, especially in low-income countries
Influenced by funding patterns of other agencies	No	Yes	Yes: low-income countries No: middle-income countries
Use of external priority-setting framework	No	No	Yes, but only as an aid to priority setting, therefore often adapted to local context
Relevance of priority setting factors			
Scientific and technical factors	High	Low	High
Investigator driven agendas	Yes	No	Seldom
International agendas	Occasionally	Frequently	Frequently
Disease burden	Yes (mostly national)	Yes (global)	Yes (only national)
Political agenda	Low to medium	High	Low
Results driven agenda	No	Yes	No
Economic	Occasionally	High	Frequently
Donor priorities	Seldom	Frequently	Frequently

Source: *WHO/TDR commissioned study.*

funding allocations. In addition, their focus tends to be global and so includes global disease priorities. This means, for instance, that the Millennium Development Goals (MDGs) are incorporated in their R&D funding strategy. In turn, this also implies that the funding strategies of agencies of a similar nature are likely to influence each other's priorities, as reflected in the survey responses from their representatives (see Table 5.3).

Future trends in the funding landscape

These can be considered from the standpoint of short-run concerns and longer-run demand and supply pressures. In the *short run*, the ongoing global financial crisis is likely to impose serious constraints on the growth of funding for R&D for infectious diseases of poverty. In fact, there already appears to be a slowdown and even a decline in allocations (*2*). Even the NIH, which increased fund allocations between 2008 and 2009, was able to achieve this increase only on the basis of the stimulus spending introduced by the American government in 2009. Once the stimulus funding ended, the NIH experienced a decline in its funding in 2010 (*2*). The Gates Foundation contributed a smaller amount of funds to infectious diseases of poverty in 2009 than in 2008. In contrast to high-income countries, however, many middle-income economies (such as Brazil, China, Colombia, India and South Africa) are experiencing rapid economic growth and can be expected to fund increasing levels of R&D for infectious diseases of poverty. For instance, both Colombia and South Africa have already set ambitious agendas for research R&D on infectious diseases of poverty (*2*). Clearly, as a consequence of the global finance crisis, the poorest and donor-dependent countries will face resource constraints given that they are likely to be much more dependent on R&D funds from high-income countries rather than from middle-income nations experiencing rapid growth.

Longer-run trends may also be relevant in influencing R&D fund availability for infectious diseases of poverty. Interviews with representatives from high-income country science and technology agencies showed that a significant majority expected their funding of R&D for infectious diseases of poverty to either remain the same or decline in future years (WHO/TDR commissioned study), due to a combination of overall resource restrictions as well as diversion of funds to address the rising incidence of noncommunicable diseases in low and middle-income countries (*19*). A similar sentiment was expressed by all aid agency representatives that took part in the study. As well as budgetary constraints, these agencies also expressed dissatisfaction with current funding mechanisms that they felt were inefficient and failed to contribute sufficiently to research capacity building in low and middle-income countries. In contrast, funding agencies in middle-income countries covered by the study were optimistic about rising allocations to R&D for infectious diseases of poverty in the future. Some of these agencies expressed a need for a greater indigenization of research capacity and agendas and were moving in that direction by promoting local research capacity on a priority basis.

In addition to the trends outlined above, other issues will likely put pressure on R&D funding for infectious diseases of poverty. As outlined in Chapter 2, climate change may increase the risks of infectious disease in the tropical regions where many of the poor live. This will probably lead to further pressures on available resources for R&D, even within the infectious diseases of poverty group (*20*). With increasing demands from multiple directions for R&D funds (e.g. for noncommunicable diseases and for new forms of infectious conditions), it is not surprising that pressures on existing resources will increase and that donors are increasingly concerned about "value for money", looking for increased effectiveness in the funding of R&D for infectious diseases of poverty (WHO/TDR commissioned study).

Key challenges in funding R&D

A major challenge for funding of R&D is to ensure that available resources are well-spent. This effectiveness criterion can be used to assess the existing pattern of financial flows and the associated institutions that form the "financing architecture".

At least *four* elements influence effectiveness:

1. **making the right type of R&D investments (allocative efficiency)**

2. **avoiding wastage (technical efficiency)**

3. **capacity building leading to a sustainable agenda**

4. **strengthening the data reservoir to help decision-making on funding flows.**

The first two elements should ensure that existing funds are spent so as to achieve the desired outcomes (i.e. gains in health via R&D) at the lowest cost possible. However, given that the health policy concerns to be addressed by R&D are not a one-shot problem, there is also the challenge of ensuring that priority setting responds to changing circumstances and that information is available for this purpose.

MAKING THE "RIGHT TYPE" OF R&D INVESTMENTS

When funding is limited, at least three criteria are likely to be important to determine the "right" activities to support: (i) the health condition of the population should warrant investment; (ii) the investment is aligned with the priorities of the target population; (iii) the investment has a high probability of success.

It is generally accepted that a high burden of infectious diseases of poverty is closely linked to low socioeconomic status. The likelihood of success for R&D investment will depend on whether tools and technologies (such as drugs, vaccines and diagnostics) that can be readily developed into products already exist. Often, such tools do exist and therefore the mechanism of implementation becomes the central priority (*21*). However, translational research and social innovation (for the production, delivery and uptake of products directed towards low and middle-income countries) tend to receive much less funding relative to other areas and needs – particularly for diseases other than HIV/AIDS, TB and malaria. Indeed, as we have already discussed, implementation and health systems research are primarily of local interest and much less attractive to external funders. There also needs to be a general shift away from drug development investments towards more investment in implementation research (for all infectious diseases of poverty, not just the "big three").

A focus on implementation in relation to existing tools and technologies is apparent when analysing the R&D funding patterns of low and middle-income country science and technology agencies (WHO/TDR commissioned study). However, priorities differ even within low and middle-income countries. For instance, in South Africa, the Department of Science and Technology places a high priority on research funding for addressing HIV/AIDS, TB and malaria; in India, the ICMR emphasizes diarrhoeal diseases; and, in Brazil, the Department of Science and Technology provides considerable funding towards research on dengue and kinetoplasmids in addition to the "big three". As most existing funding for R&D for infectious diseases of poverty comes from high-income countries, it is important that funding is not skewed by their priorities but is congruent with low and middle-income country priorities, at least until R&D funds from low and middle-income countries begin to catch up. Local priorities may also change over time, so there is a need for much greater input from low and middle-income countries in setting research priorities. Currently, this does not appear to be very common. At the very least there is a need for strong low and middle-income country research partners in collaborative arrangements with researchers within high-income countries, so that the former can influence research questions. Un-

fortunately this is not observed in practice – for example, African biomedical collaborations follow the classical partnership pattern i.e. partnerships are built with institutions in Europe and the United States of America but levels of local funding of R&D are low. The net outcome is a lack of local ownership of the research undertaken (*22*).

The problem of control and moral hazard: The flip side of low and middle-income countries having a greater say in the direction of funds from high-income countries is the creation of incentive problems. Funders would likely be unhappy to lose control over their funding and want to see results from their contributions. Conversely, easier access to large amounts of funds to meet local priorities might generate moral hazard problems as low and middle-income country counterparts come up with proposed activities for funding that will not be cost effective, and that will yield outcomes that are not easy to measure. Local contributions to create an incentive for such funding arrangements between high-income and low and middle-income countries are a useful option but will not really solve the problem, given the disproportionate size of their relative contributions. For this reason, collaborative arrangements involving strong links between various low and middle-income countries, and characterized by strong leadership from such countries, are likely to be much more effective in addressing low and middle-income country priorities. Another example of a south-led initiative for R&D funding related to infectious diseases of poverty is the African Network for Drugs and Diagnostics Innovation (ANDI) which focuses on the discovery, development and delivery of tools to address Africa's health needs (*22*). ANDI aims to establish "the African innovation fund", a US$ 600 million endowment to support a portfolio of collaborative projects and partnerships that (a) generate health product innovation at all stages of the value chain; and (b) build capacity and support for the infrastructural development of African institutions.

To strengthen their ownership of their research agenda, low and middle-income countries can credibly commit to a particular set of priorities related to R&D funding requirements for infectious diseases of poverty through various policies. Ideally, such policies should be backed by legislation and used to develop plans to guide appropriate donor investments and efforts to strengthen health systems. A prerequisite for establishing such research agendas is the existence of appropriate legal frameworks that support national policies for health research and that may also enable low and middle-income countries to achieve greater control over research performed within their borders and on their behalf. Such a system could oblige funders to align their policies and practices with nationally defined R&D agendas.

AVOIDING WASTAGE

Efficiency in funding of R&D for infectious diseases of poverty can be enhanced in the following three ways.

1. ***Reduce duplication and improve coordination of R&D funding for priority conditions.*** Duplication is most obvious in the case of PDPs. For example, development of antimalarials is on the agenda of both MMV and DNDi. Several PDPs also focus on the enhanced delivery of services to get their products to poor populations in need. The GAVI Alliance states one of its missions to be: "saving people's lives and protecting people's health by increasing access to immunisation in poor countries". In this endeavour GAVI Alliance funds not only the provision of vaccines to needy populations, but also activities that help enhance health care delivery mechanisms. MMV includes similar activities in its portfolio, including supporting health care services and improving the supply chain. Enhancing access to health services is also a key goal of DNDi. Instead of separate funded programmes focussed on improving health care services – a tradition with vertical programmes – an integration of health care delivery interventions at the country level is likely to be more efficient.

2. ***Reduce competition for funds as this is a source of wastage.*** For example, different PDPs compete for funds from the same group of donors (usually bilateral donors and private foundations). Advocacy activity by one PDP entity potentially impacts the ability of others to benefit from the same "pot". Consequently, these other groups then need to invest more in advocacy relating to their activities. Overall advocacy-related expenditures are increased as a result. This inefficiency is likely to be greater as resource constraints related to R&D for infectious diseases of poverty increase. This argument can also be carried beyond competition for funds between PDPs; competition for funding is likely to increase as NCDs place an increasingly greater burden on low and middle-income countries. An appropriate course of action would be to better integrate funding decisions for R&D across diseases and rely more on competitive awards.

3. ***Improve the coordination of priorities for action.*** This should lead to a harmonized approach to funding of R&D. This could be similar to that proposed by the WHO Expert Working Group on Research and Development Financing (*4*). The proposal envisages (a) the establishment of working groups and a supervisory group to draw up research agendas and set priorities on the basis of information from a range of sources, including a new global health research observatory; (b) working and supervisory group recommendations on the distribution of the elements of the required R&D among researchers working in different settings, including basic research laboratories, development or scale up plants, clinics, health services and communities, in both public and private environments in different countries; (c) creation of a mechanism for the funding and coordination of global health research and innovation to facilitate and support, involving targeted R&D into new drugs, vaccines, diagnostics and intervention strategies for health conditions of the poor for which adequate interventions are not presently available; and (d) support for research disciplines (primarily conducted in low and middle-income countries) that includes health policy and systems research, social science and behavioural research, implementation/operational research and research on the determinants of health.

CAPACITY BUILDING

Research capacity building is needed for the purposes outlined above, especially as the local capacity for research is limited. It would also help create local expertise in low and middle-income countries to help define health priorities that can be used to influence the funding priorities of high-income country agencies. Local capacity for health research would help focus on topics related to operational and implementation research in low and middle-income country settings that have not yet attracted much funding from high-income country agencies. Finally, improvement of local research capacity will help strengthen existing research and training institutions in these countries and therefore contribute to the future generation of scholars.

STRENGTHENING THE DATA RESERVOIR TO HELP DECISION-MAKING ON FUNDING FLOWS

There is much that we still do not know about funding flows related to R&D for infectious diseases of poverty. Data are lacking in a number of key areas, including implementation research; support for capacity building; and a broader class of research activities that explore aspects of behaviour, economics, politics, trade and the environment as they apply to infectious diseases of poverty. There is also a need for information on a larger set of countries, mainly low and middle-income countries, and to develop a classification system to organize data on R&D for health. Apart from deciding what to include or exclude under the definition of "R&D for infectious diseases of poverty", there is also a need to address the issue of separating ultimate funders from recipients of funds and from intermediaries (such as PDPs). A good model for this is the work on National Health

Accounts for which an updated classification system was recently developed (through a collaborative arrangement by the Organisation for Economic Co-operation and Development [OECD], the WHO and the European Commission). The project involved a number of researchers from around the world with expertise in health financing (*12*). Information systems to help capture data on funding flows for R&D on health would certainly be needed to support this work.

What would the future funding architecture look like?

The funding landscape for infectious diseases of poverty is full of promise and it would be irresponsible to leave the reader of this chapter with the impression that infectious diseases of poverty have not benefited greatly from investments already made into R&D for these diseases. Yet, much remains to be done to ensure that R&D funding for infectious diseases of poverty is able to address health policy priorities effectively. We therefore conclude with three key challenges that constitute the cornerstones for the future funding architecture, as we would like to see it.

Firstly, *funding must be relevant to the needs on the ground*. This has to face the reality of imbalances between high and low and middle-income countries, associated political pressures and differences in priorities in what is a very competitive environment. We have seen that basic research is well catered for but implementation research – which can make a practical difference for affected populations – remains the "poor relative". Mechanisms to ensure that there is a better balance between funds for various kinds of R&D therefore need to be established.

Secondly, there needs to be *a drastic reduction in the many forms of wastage that presently plague the funding landscape*. Competing and overlapping research agendas between PDPs; duplication of efforts to secure funds; and too much funding in small amounts going towards research efforts that are unlikely to make a real impact are all part of the wastage that needs to be tackled.

Thirdly, in the long term the research effort for mitigating the negative impact of infectious diseases of poverty cannot be sustained by funds from high-income countries alone. Regions and countries most directly concerned by infectious diseases of poverty have a wealth of research potential, and there is likely to be considerable new funding capacity for supporting R&D in emerging economies such as Brazil, China and India. Moreover, the research agenda is still too often influenced by factors and considerations that do not integrate capacity building right from the start. This must change, so that *capacity building is considered integral to funding activities*.

The funding architecture for R&D into infectious diseases of poverty will begin to take shape once we have found ways of starting to address these challenges – a task that must be shared by all parties concerned.

> **The three cornerstones of the future funding architecture:**
>
> 1. **The funding must be relevant to the needs on the ground.**
> 2. **Wastage must be drastically reduced.**
> 3. **Capacity building must be integral to all funding activities.**

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6 Agenda for action

IN CHAPTER 6:

- A new development indicator based on the prevalence of infectious diseases of poverty
- A "One Health, One World" strategy in relation to research for infectious diseases of poverty
- Research ownership with enabling policies by disease endemic countries
- An innovation platform to foster a culture of innovation to benefit public health
- An online global platform to inform on strategies, policies and funding commitments

6

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Those living in poverty have little political voice. As a result, the infectious diseases they endure lie low on a long list of public health priorities – despite causing immense suffering and limiting prosperity. As clear from Chapters 1–4, we lack full understanding of the diseases and the populations they affect. There are only a few treatments and limited prevention and control strategies, while most of those affected by these diseases are difficult to reach in order to provide remedies. Policy-makers, funders and researchers all need to take urgent action to change this state of affairs. To help them in their task we present in this chapter five high-level options for action which, if implemented appropriately, we believe will help break the vicious cycle of infectious disease and poverty and so save lives, reduce misery and be of economic benefit to disease endemic countries.

Setting the scene for action

A common theme underpins all the chapters of this report: that infectious disease and poverty are linked in a vicious cycle, and that breaking this cycle will lead to socioeconomic returns that will be felt in villages as well as by national, regional and global communities. This cycle clearly needs to be broken, and in this report we focus on how this might be done by addressing the problem of infectious disease[1].

> **Improvements in health ... depend on a vibrant research enterprise, through which new knowledge is translated into technologies and services that really work.**

Tackling infectious disease needs continued and increased investment in health. Such investment should be valued as an investment in human capital in much the same way that investment in education is valued. Fortunately, this now seems to be happening and health is back on the global agenda. The last two decades have seen increased political will to meet global health challenges, and investment in disease control programmes (particularly for infectious diseases of poverty such as malaria) has received a tremendous boost through initiatives such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) and the activities of the Bill & Melinda Gates Foundation.

Improvements in health depend on a vibrant research enterprise through which new knowledge is translated into technologies and services that really work. This means that investment in health needs to be accompanied by investment (in terms of funds, manpower and infrastructure) in health research. Research at all stages (from the laboratory to delivery in the community) and in various disciplines (ranging from agriculture to sociology) also provides the body of evidence that helps policy-makers to develop rational, cost-effective and sustainable health policies. In effect, research is the engine that drives both technical advances and health policies forward. We believe that concerted research efforts from the global community (particularly from policy-makers, funders and researchers) could quadruple the dividend of investment in both research and control and lead to a greater impact on global health, especially among poor populations.

A strategic approach to the funding and support of research and to the generation and use of research outputs is urgently needed if research is to fulfil its promise to reduce the suffering caused by infectious disease. The first step in such an approach is to identify high-level actions on which policy-makers, funders and researchers should focus when developing their health research related strategies. These actions must convey credible promises that millions of lives will be saved.

With this need for high-level actions in mind, we have reviewed and evaluated a myriad[2] of valid actions for infectious diseases of poverty research. Recognizing that limited resources and urgent needs make it imperative that actions are pragmatic and assure much more than a "reasonable" return on investment, we have used our collective experience, published literature (including consideration of geopolitical and socioeconomic factors discussed in earlier chapters),

1 A discussion on how the vicious cycle of infectious disease and poverty might be broken by addressing poverty is beyond the scope of this report, which focuses specifically on research for infectious diseases of poverty. See also: World Development Report (WDR) 2000/2001: attacking poverty (http://web.worldbank.org/WBSITE/EXTERNAL/TOPICS/ EXTPOVERTY/0,,contentMDK:20194762~pagePK:148956~piPK:216618~theSitePK:336992,00.html, accessed 22 February 2012).

2 Possible actions were reviewed and evaluated through The Global Think Tank on Research Priorities for Infectious Diseases of Poverty, a multidisciplinary group of experts from across the globe, created and convened by TDR in 2009. The Think Tank was divided into 10 reference groups, each of which produced a report that served as the technical basis for this *Global Report*. Research priorities outlined in the reference group reports served as the basis for discussion between Think Tank members and authors of this report and stakeholders.

BOX 6.1. OPTIONS FOR ACTION ON RESEARCH FOR INFECTIOUS DISEASES OF POVERTY

1.	Create and use a new **index of infectious diseases of poverty** to serve as a surrogate marker of national socioeconomic development.
2.	Implement a **"One Health, One World"** strategy in relation to research for infectious diseases of poverty.
3.	Actively promote **research ownership** with enabling policies by disease endemic countries.
4.	Create an **innovation platform** to foster a culture of innovation to benefit public health.
5.	Create an **online global platform of research resources** to inform on strategies, policies and funding commitments.

These five options for action are described in further detail in this chapter, along with an outline of the context and reasoning for each.

as well as findings from the TDR Think Tank and regional and national stakeholder consultations, to propose five high level options for action for research on infectious diseases of poverty. These options for actions are listed in Box 6.1.

These actions should be viewed as high-level priorities, all of which are necessary to change the landscape of infectious diseases of poverty – although the order of implementation may depend on individual stakeholder resources and timeframes. Some of the concepts behind the proposed actions are not totally new and, in these instances, our options for action build on ideas that have already been raised among the global community. Here they are shaped to be specific to infectious diseases of poverty and to be more ambitious with regard to outcome and anticipated impact on these diseases.

Collectively, these five options for actions address the ten reasons for research outlined in Chapter 1 of this report. If implemented by the combined efforts of policy-makers, funders and researchers (together with other stakeholders), these high-level actions should sustain the achievements of the Millennium Development Goals (MDGs) beyond 2015 and ensure that research results are better positioned to make a real difference to human health. Most importantly, they should help break the vicious cycle between infectious disease and poverty. We therefore believe that implementing these five actions will change the research agenda and ensure that, in years to come, lives are saved, suffering is reduced and the socioeconomic burden of infectious diseases of poverty on disease endemic countries and communities is substantially decreased.

The call to action

OPTION 1: CREATE AND USE A NEW INDEX OF INFECTIOUS DISEASES OF POVERTY TO SERVE AS A SURROGATE MARKER OF NATIONAL SOCIOECONOMIC DEVELOPMENT

The prevalence and incidence of infectious diseases of poverty should form the basis for the development of indicators to use as "barometers" of health and development; these will help guide investment in research and disease control and help countries to monitor their own state of development.

An index of infectious diseases of poverty, based on the prevalence and incidence of infectious diseases, can act as a barometer of health and development. Such an index, updated at regular intervals, can be used by countries to assess and monitor their progress in the control of infectious diseases of poverty. Its outputs can also generate major interest from the media, other stakeholders and the general public that in turn persuades policy-makers, funders and researchers to invest in improving health in order to attain socioeconomic prosperity.

The context for action

Throughout this report, information has been gathered from a wide range of sources to highlight the complex interrelationships between infectious disease and poverty. However, this has been a laborious task. At present, there is no simple, easily understood composite index or rating system on the status of the control and elimination of infectious diseases of poverty – even though such diseases are one of the most important factors limiting a country's economic development and keep communities in poverty (*1*). An index can focus national and global attention, and can define and clarify key health issues. It can be used to identify areas where investments need to be increased, which control activities need to be put in place, or where research efforts need to be enhanced. It can also be used to measure the success of policies or investments for the reduction of poverty.

Recently, there has been renewed interest in multidimensional approaches to assessing poverty, and statistical data and indicators have already proven to be essential in gaining political commitment and moulding some global health initiatives. For instance, the Multidimensional Poverty Index (MPI)[3,4] is used effectively by the United Nations Development Programme (UNDP) as a means to provide annual assessments of country progress and ranking on agreed international human development indicators. Interestingly, MPI includes two health indicators: child mortality and nutrition. These two indicators bear a close relationship with the infectious diseases of poverty described in this report, since most childhood deaths in poor settings are caused by infectious diseases (*2*) and parasitic diseases are a widespread cause of malnutrition.

Use of such an index highlights the potential value of an index on infectious diseases of poverty. As well as being of practical benefit, an infectious diseases of poverty index can also raise the profile of these diseases and – by generating major interest among development organizations, other stakeholders and the media – it can serve as ammunition with which to encourage decision-makers at national level to focus on these diseases.

3 The UNDP adopted the MPI in 2010 as a replacement for the Human Poverty Index that had been used since 1997. The MPI measures "the percentage of the population that is multidimensionally poor, adjusted by the intensity of the deprivations" (http://hdr.undp.org/en/statistics/mpi, accessed 22 February 2012).

4 Multidimensional Poverty Index 2011 (http://www.ophi.org.uk/wp-content/uploads/OPHI-MPI-Brief-2011.pdf?cda6c1, accessed 22 February 2012).

This is particularly important as infectious diseases of poverty lost much of their visibility during the first ten years' implementation of the MDGs[5]. An infectious diseases of poverty index could also influence the MDGs in their next iteration (e.g. through identification of target diseases among target populations), and so influence future global action.

Action to be taken

The index of infectious diseases of poverty would need to be openly available in an interactive, user-friendly format, drawing together datasets that already exist as part of national, regional and global statistics and coupling these with new information on the success of interventions obtained with support from health systems research, discussed in Chapter 3.

Indicators used for the index would need to be researched and developed through intersectoral collaboration with multidisciplinary teams who have experience in this area (see later). The lack of health information systems in many low and middle-income countries may pose a challenge to implementation of this action, therefore it would be important to develop indicators that do not need new monitoring/data collecting systems so as to avoid putting additional strain on countries with already stretched resources[6].

Indicators would need to be agreed on and their monitoring sustained if they are to be used to report on progress, strengths, limitations and weaknesses in terms of the control of infectious diseases of poverty within and across countries. Depending on which indicators are developed, the index could be modelled so that progress on research and its contributions to disease control could also be easily assessed and visualized. Different statistical data would need to be selected for each indicator. These would be used and shared, to highlight both positive achievements and negative outcomes of activities and initiatives in all countries in relation to infectious diseases of poverty.

The index could become a dedicated part of an openly available repository and be provided in conjunction with appropriate protocols and templates to allow direct uploading of country data. Importantly, the data should be routinely collected within specific, regular time frames to allow evaluation of the long-term effectiveness of health and development initiatives, interventions, strategies and policies. Data could be presented using interactive graphics (infographics) to provide a visual output – for example, relating disease to economic development, or highlighting efforts on control in relation to disease incidence or prevalence. Users such as policy-makers could also download the data contained within the index and create bespoke maps, graphs and charts for national, regional and global policy development.

Achievement of this action would require concerted effort from all health and development stakeholders. The methodology used to develop such an index and the individual indicators would need to be transparent, sustainable and validated – with a focus on collating and elaborating information that is currently available, identifying gaps and defining how to ensure adherence to agreed strategies and policies. We envisage that there would be three phases of development, as illustrated in Fig. 6.1.

5 Other than the "big three" (HIV/AIDS, TB and malaria), infectious diseases were hidden in the "other diseases" category of MDG6. The mid-term review of the MDGs led to the addition of new indicators for MDG6; however none of the original or revised indicators is specific for infectious diseases of poverty.

6 In her opening remarks at the Forum on Delivering Results for Women and Children held in Canada in November 2011, Dr Margaret Chan, Director-General of the World Health Organization stated that "At present, some 85 countries, representing 65% of the world's population, do not have reliable cause-of-death statistics. This means that causes of death are neither known nor recorded, and health programmes are left to base their strategies on crude and imprecise estimates." (http://www.who.int/dg/speeches/2011/women_children_21_11/en/index.html, accessed 22 February 2012).

Fig. 6.1. Phases of index development

Phase one: *Establishment of a framework of indicators for the index, based on a series of commissioned reviews and other research.*

Partners (such as the George Institute for International Health[7], Google.org[8] and the UNDP) who have experience in developing indicators and interactive reporting tools – as well as expertise in measurement, data availability, statistics and infectious diseases of poverty – need to be actively engaged in the development of this barometer of health and development if it is to be a success. Partners would need to identify relevant indicators through commissioned in-depth literature reviews and consultation with relevant parties. Possible indicators that could be considered for use in the composite index are outlined in Box 6.2.

Phase two: *Identification of institutions and other stakeholders, and provision of funding to support development, piloting and small scale validation, in partnership with relevant stakeholders.*

Regional institutions with experience in health statistics and data collection programmes (such as WHO's health systems observatories[9]) should be fully engaged at this stage. Efforts should also be made to obtain low and middle-income countries' active participation in collecting and collating data for the index in order to promote ownership, foster utilization of data and ensure that the index is developed in a way that will be of most use to these countries. Data collation is a costly exercise. Funding agencies would need to adopt this project and provide a framework for the funding of any activities needed to develop the index on a small scale, generate the data and monitor and evaluate their potential usefulness and validity.

Phase three: *Development of a stakeholders' platform to review, agree and recommend a strategy and framework for scale-up and implementation of the index.*

International agencies including WHO, UNDP, the World Bank and the European Union could provide the forum via which stakeholders would provide input into the index and decide on how the index might be funded, scaled-up, implemented and utilized. Updating of the index at agreed, periodic time points might also need to be coordinated and overseen by an international agency that has the ability to instill stakeholder confidence in the indicators and the index itself (such as a United Nations' agency). Such an agency would, in effect, serve as an advocate for the index.

7 The George Institute for International Health conducts the G-FINDER project (with funding from the Bill & Melinda Gates Foundation) which focuses on the global funding of innovation for neglected diseases. Data from surveys is presented in yearly G-FINDER reports (https://studies.thegeorgeinstitute.org/g-finder/, accessed 22 February 2012).

8 Google.org is the philanthropic arm of Google. It "develops technologies to help address global challenges and supports innovative partners through grants, investments and in-kind resources." (http://www.google.org/, accessed 22 February 2012).

9 The Global Health Observatory (2012) (http://www.who.int/gho/en/, accessed 22 February 2012).

BOX 6.2. POSSIBLE INDICATORS* FOR FORMING THE BASIS OF THE INFECTIOUS DISEASES OF POVERTY INDEX, LISTED TOGETHER WITH SOME EXAMPLES OF RELATED STATISTICAL DATA THAT WOULD NEED TO BE COLLECTED

Burden of disease. Measures impact of disease at local, national and global levels.
Data might include:

1. yearly prevalence, incidence, disability-adjusted life-year (DALY) and mortality rates for infectious diseases of poverty;
2. geographical distribution and demographics associated with the infectious diseases of poverty;
3. impact of disease on afflicted individuals and families – including financial costs (e.g. for treatment, or in terms of lost productivity).

Health system strength and public health infrastructure. Measures ability of the health system to predict, prevent and deal with disease outbreaks and to deliver effective interventions.
Data might include:

4. per capita expenditure on health;
5. percentage of the population that is actively vaccinated (e.g. with vaccines under the Expanded Programme on Immunization [EPI]);
6. access to a health care provider or health care facility;
7. number of public health laboratories per 10 000 head of population;
8. number of trained health workers per 10 000 head of population (in both rural and urban settings);
9. number of public health veterinary laboratories per 100 000 domestic animals (this is important given the need to address zoonoses and several emergent infections).

Government commitment. Measures the willingness of governments to tackle infectious diseases of poverty. Data might include:

10. existence of a national research policy that specifically mentions infectious diseases and poverty;
11. investment in research for infectious diseases of poverty, including in research and development (R&D) and implementation research;
12. presence of a pandemic preparedness plan.

Socioeconomic factors. Measures social determinants of health.
Data might include:

13. access to water and sanitation (rural, urban and total);
14. deaths due to nutritional deficiencies (lack of nutrition leads to an immunocompromised population that is more susceptible to infectious disease);
15. social impacts of infectious diseases of poverty such as:
    - stigma associated with disease affecting employment, marriage and education opportunities;
    - community acceptance and uptake of new disease control strategies;
    - mental health issues associated with disease.

* These are only illustrative suggestions. The final set of indicators and associated statistical measures will need to be selected by experts and agreed upon through the three phases of index development described on page 152.

What would success look like?

The index could be used to quickly monitor and evaluate trends in relation to infectious diseases of poverty and the impacts of interventions. A regularly updated index that could be disaggregated according to local, national or regional criteria would allow policy-makers in disease endemic countries to monitor and evaluate their own efforts in tackling infectious diseases. Funders could use the index to prioritize areas of research so that funding is geared according to need. This could lead to more effective use of funds and possibly the creation of novel funding mechanisms (such as the funding set aside for operational research by the Global Fund)[10]. Finally, use of such an index could ensure that funds are allocated according to both needs and achievements. Progress against infectious diseases of poverty at national level could then be rewarded with increasing investments.

Successful adoption of this particular option for action would be measured by evaluating national and international acceptance of the index, and monitoring its influence in guiding policies, investment and research. The responses of policy-makers, funders, researchers and other partners (especially those in disease endemic countries) could also be monitored in terms of provision of support for areas shown to lack progress to date.

10 The Global Fund encourages the inclusion of operational research in the HIV/AIDS, TB and malaria control programmes it supports with a view also to tackling obstacles to scale-up. Programmes are recommended to spend between 5% and 10% of their grant budget on monitoring and evaluation, which could include spending on relevant operational research (http://www.theglobalfund.org/en/me/documents/operationalresearch/, accessed 22 February 2012).

OPTION 2: IMPLEMENT A "ONE HEALTH, ONE WORLD" STRATEGY IN RELATION TO RESEARCH FOR INFECTIOUS DISEASES OF POVERTY

Policy-makers, funders and the academic community need to embrace a "One Health, One World" strategy, to foster essential multidisciplinary and multi-sectoral approaches for a full continuum of research.

We propose that the global health community implements and expands on the strategy of "One World-One Health" (discussed in Chapter 2) to "One Health, One World" so that human health can benefit from efforts in other disciplines (e.g. agriculture and animal health) and with other goals (e.g. poverty reduction). These efforts can contribute to the full continuum of research for infectious diseases of poverty, beyond "bench to bedside" all the way through to policy change and delivery to the community. Engaging all health and development stakeholders in this strategy should lead to more rapid development of tools and strategies for the control and management of infectious diseases of poverty, and their more effective and sustainable deployment and use. Overall, it will improve the nature of research and will result in a more holistic approach to addressing health and development issues.

Context for action

Environmental and social changes can have wide-ranging effects on patterns and types of infectious disease, particularly on zoonotic disease (see Chapter 2). Urbanization and migration patterns have changed water use, caused deforestation and made agricultural practices more intensive. Ongoing environmental degradation may lead to loss of biodiversity, enabling pathogen emergence and loss of potential natural products that could be developed into treat-

ments for disease. Increasing resistance to drugs among microorganisms (such as Tuberculosis bacilli and malaria parasites) and increasing resistance to insecticides among vectors (such as malaria-transmitting mosquitoes) have increased the urgency to find new and improved drugs and vector control tools. Meanwhile, explosive human population growth, coupled with environmental change, has put greater numbers of people in close contact with wild and domestic animals, altering the ecological balance between pathogens and their human and animal hosts. While some diseases have almost been eliminated, others are emerging or re-emerging (*4*). Since 1970, 32 diseases never previously reported in humans have emerged. Disease outbreaks can be catastrophic for poorer economies, particularly when much of the population is totally dependent on livestock for their livelihoods – consider, for instance, the devastation resulting from the Nipah virus outbreak in Malaysian pig farms and the avian flu pandemic of 2009 (see Chapter 2).

Environment and climate change are not the only fields with relevance to disease control efforts and research for health. Despite being medically diverse, infectious diseases of poverty share common features such as prevalence in rural settings, in urban slums or in conflict zones that allow them to cluster and frequently overlap. This means that efforts on poverty reduction and new technologies in environment management would also be useful for the control of infectious diseases of poverty.

Under the proposed "One Health, One World" strategy, researchers from diverse fields such as agriculture, climate, environment and poverty reduction would work together with researchers for health, so that better tools and strategies can be developed to address their combined needs.

In the meantime, there have been significant advances in agriculture and animal health. These fields have benefitted from some novel interventions. The "One Health, One World" strategy would also encourage researchers to share ideas, information and research practices through collaborative efforts; human health could thus benefit from advances in these other fields. For instance, savings in time spent on the discovery and development of potential drug candidates could be achieved if compound databases developed and used for animal health or for agriculture were shared collaboratively among researchers. Such collaboration has already proven to be useful: currently the antiparasitic drug ivermectin, originally developed for veterinary use, is used widely to treat onchocerciasis (river blindness) and lymphatic filariasis.

A compendium of research that can benefit communities should therefore not be limited to studies on infectious agents and human health. It should encompass results from both an environmental and a socioeconomic outlook that includes the links between climate, agriculture, natural resources, the environment and health, as well as new developments that change the milieu for emerging diseases (discussed in Chapter 2).

Action to be taken

For this option to be effective, governments of disease endemic countries must develop intersectoral frameworks that encourage cooperation and foster active collaboration across various ministries. These should improve regional capacity to share information and resources without additional bureaucracy. For example, disease endemic countries could set up a "national health commission" coordinating a number of government departments such as agriculture, health, science and technology, environment protection and finance. Funders, international organizations, nongovernmental organizations, philanthropists and the private sector need to broaden their perspectives to support multidisciplinary research programmes and to actively encourage intersectoral collaboration. It is important that educators and researchers also respond by developing cross-disciplinary research teams and incorporating research and training models into their work to encourage interdisciplinary thinking and sharing of intellectual property. At the same time, civil society needs to cam-

paign and advocate for "One Health, One World" and, where appropriate, champion community-based strategies. New knowledge and technologies from newly configured multidisciplinary teams of researchers must be widely disseminated and shared as suggested in Option 4 (on innovation). The new paradigm mandates a massive culture change and the coordinated use of resources (human and financial) from different sectors.

What will success look like?

As mentioned earlier, the adaptation and successful distribution of ivermectin for elimination of blindness caused by onchocerciasis is a good example of the output and potential benefits of an expanded scope and multidisciplinary approach to research for health. Uptake of the "One Health, One World" strategy should lead to an increase in collaborative research as well as increased interaction between government departments and other stakeholders. It should also lead to improved collaboration and partnership and more sustainable ways to tackle the problem of infectious diseases of poverty. Effective implementation of this option should ultimately lead to development of better interventions at a faster pace.

Success of this option and uptake of the "One Health, One World" strategy will be measured by the development of common strategies and effective use of resources, a more collaborative and effective workforce, increased anticipatory decision-making and enhanced understanding of salutogenic factors.

OPTION 3: ACTIVELY PROMOTE RESEARCH OWNERSHIP WITH ENABLING POLICIES BY DISEASE ENDEMIC COUNTRIES

Ownership, active engagement and investment in the research enterprise for control of infectious diseases of poverty must be strengthened with effective policies if countries where infectious diseases are endemic are to reap the full benefits of advances in research for health.

All of the infectious diseases of poverty discussed in this report place a significant burden on countries with limited resources. These countries therefore need to play a central role in the development of research priorities – to strengthen their own role in leading research, to learn from one another and to improve the way in which policies related to health research are developed and taken up. Crucially, countries also need to increase their own investment in research.

Context for action

The first observation on disease outbreaks and its impact is often made at country level. It is these countries that have to find resources to obtain and deliver new drugs and vaccines and incorporate new intervention strategies into their health care systems, and it is these countries that have to monitor disease presence and oversee its control within their borders. However, limited resources limit their ability to do so, and often solutions to their problems only come when recognized at global level.

It is therefore essential that disease endemic countries establish clear research priorities so that research efforts and resources are directed towards their specific needs. To date, the research agenda and implementation strategies for infectious diseases of poverty have

largely been driven by international agencies (*5*). This must change. Disease endemic countries must guide and have ownership of research efforts into infectious diseases of poverty, so that their needs are met and implementation strategies are more applicable and sustainable.

As well as setting a research agenda that is directed towards their needs, countries themselves need to spearhead research if they are to benefit fully from research for health. However, most disease endemic countries are unable to mount a research enterprise or even to access full research information produced by others. Often new tools and strategies derived through research have not been deployed or scaled-up within countries, despite their availability and proven effectiveness. This may happen if there has been inadequate research on delivery, use and community acceptance of research outcomes. New tools and strategies need to be socially accepted, cost effective and easily implemented in the local context. Early engagement and ownership of the research agenda could foster this.

Researchers cannot work without a supportive, enabling policy framework. Moreover, national researchers have few incentives to address the most critical health research priorities without policies that support access to national and international resources. Over the last few years there have been encouraging signs that disease endemic countries can play a more central role in both setting and implementing the research agenda. Several disease endemic countries (such as BRICS[11] countries: Brazil, China, India and South Africa) have taken the lead in research and have demonstrated that strategic policies which allow them to build their own research enterprise lead not only to the development of interventions that suit the country's own requirements, but also to increased economic development (*6*). Despite such successful examples of research ownership, many low-income countries are still not benefiting as they should from the impacts of such advances in research.

Finally, disease endemic countries need to increase their financial support for research if they are to truly have research ownership so that research can help them to address their own health needs. In 2008, many countries demonstrated their commitment to research by pledging to allocate 2% of their health budgets to national health research programmes (*7*). However, very few countries have achieved this as yet.

Action to be taken

It is clear that countries need to play a leading role in developing national research and health priorities in the context of their needs and the global resources available to them. Developing their own research agenda and participating in global agenda setting (e.g. through participation in national and global think tanks and consultations – such as the think tank and consultation process involved in the production of this report and related reference group reports) is a crucial part of such activity. Governments, funders, international organizations, nongovernmental organizations and other stakeholders need to actively encourage and support such input.

Researchers in disease endemic countries need to increase research and their research leadership in the development and implementation of tools and strategies relevant for their needs and applicable in their disease settings. This means that research capacity and infrastructure needs to improve and that countries need better access to international funds and training and development schemes. Researchers also need to participate actively across the whole spectrum of research, from bench to field. As outlined in Option 2 (on "One Health, One World"), work in cross-sectoral teams would enable them to learn from, and work together with, other disciplines. Mechanisms through which researchers in different countries can learn from one another (e.g. the BRICS countries) also need to be established – possibly through regional partnerships, new networks, online forums, exchange programmes and collaborations.

11 There are five BRICS countries – Brazil, the Russian Federation, India, China and South Africa.

Countries need to demonstrate their commitment to health research by creating an "enabling environment" with policies that allow them to fund research and, in turn, use research outputs to underpin other policies. This would require early engagement of policy-makers with research entrepreneurship. Disease endemic countries also need to learn from BRICS' country examples when developing their own research policies, and need to increase the investment that they make into research at all stages of the research continuum.

To facilitate ownership of health research entrepreneurship by disease endemic countries as outlined above, all stakeholders need to engage in long-term partnerships with universities; public health and research institutes; and health care systems in low and middle-income countries. Funders also play a part in promoting research ownership by disease endemic countries. They need to provide a framework that will allow leading research institutions and policy-makers in disease endemic countries to acquire expertise and capacity for priority setting, policy formulation and monitoring and evaluation of the effectiveness of actions.

Targeted action by new international initiatives might help smaller, low-income economies with limited past success in applying for international research funding to gain access to resources. As an example, the creation of ESSENCE[12] is a welcome addition in the field. Similar groups with a greater geographical coverage could expand their activities to provide services focusing on smaller countries.

They could also work with investigators in these countries to help design protocols, organize peer reviews and identify relevant partners and funding sources (especially around priorities identified by the countries and regions). Such expanded engagement with stakeholders will enhance ownership of research by smaller disease endemic countries while strengthening partnerships with funders. Some funds might be placed in a special pool to develop the capacity of low-income countries to conduct research in partnership with others. Global funder communities could develop a framework to match levels of any increased investment by disease endemic countries in research that supports policy formulation. Funder communities could also provide assistance to researchers in order to access innovative funding mechanisms (such as the funds specifically earmarked by the Global Fund).

Thus, under this option for action, disease endemic countries should:

- develop research priorities congruent with the burden of infectious diseases of poverty in their own populations;
- increase their own research activity and improve research leadership;
- develop regional partnerships to build research infrastructure, human resources and research capacity;
- create policies and develop plans to guide national and international investments towards the identified research priorities;
- aim to increase their national support for research and translation of research to strategies for health.

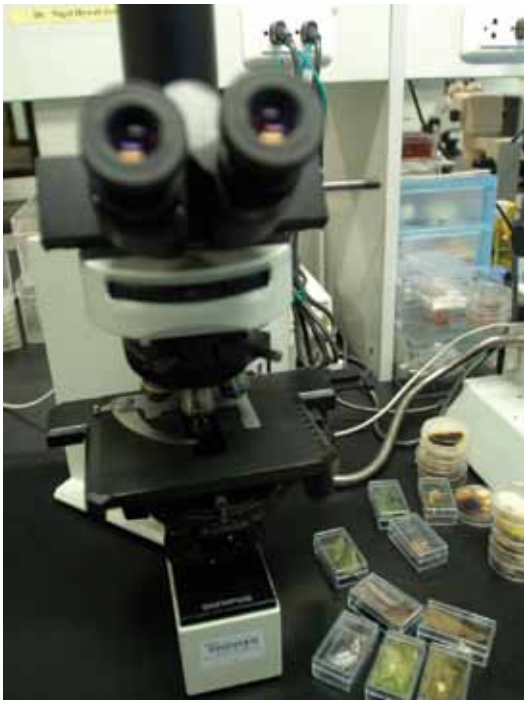
Disease endemic countries also need to design policies to make health systems research more prominent, so that both attention and funds flow into this important research area. Health systems research provides an insight into the relationship between health systems, population health outcomes and the social and economic determinants of health. Such research is essential to guide global, regional and country approaches on how to overcome the tension between the disease control programmes (which are often viewed as working in silos) and health. Research outcomes could provide a synergistic approach, enhancing the control programmes while also increasing access to health care.

12 ESSENCE is a group of global funders of research that aims to harmonize and improve the effectiveness of their activities, focusing on research and capacity strengthening in Africa (http://apps.who.int/tdr/svc/partnerships/initiatives/essence, accessed 22 February 2012).

What will success look like?

Establishment and implementation of research policies tailored to suit their own needs would make up somewhat for the voice that disease endemic countries have not yet had. These countries would have a stronger role in setting their own research agendas as well as a stronger say in global agenda-setting. There would be a disease endemic country-owned research agenda responsive to relevant locally identified public health priorities, and there would be a sustained commitment by all stakeholders to build local research capacity – including human, management and governance capacity as well as infrastructure. As this broader perspective on research ownership is adopted, funding for research would no longer be narrowly targeted; there would be investment all along the continuum of research.

Success of this option would be measured by an increased number of countries with research policies that have legal/financial support; increased delivery and uptake of relevant research results; increased access to effective tools and strategies; closer links between research and the provision of health services; and greatly strengthened, synergistic health and research systems leading to improved health.



OPTION 4: CREATE AN INNOVATION PLATFORM TO FOSTER A CULTURE OF INNOVATION TO BENEFIT PUBLIC HEALTH

A culture of innovation must be developed within countries burdened by infectious diseases of poverty; this culture should support and promote the social, legal, political and regulatory environment that promotes innovation in public health systems.

Innovation is not only about problem identification followed by solution, discovery and delivery. There must be a paradigm shift in the social, legal, political and regulatory environment to view innovation more broadly and create a *new culture of innovation in public health*. Strategies and incentives that promote indigenous participation in both technological innovation and in change due to social innovation must take an approach that is systems based and which fosters a spirit of entrepreneurship. Access to information is a prerequisite to advancing this objective. A new, *open innovation platform* – where information and resources can be shared and the full potential of new technologies can be realized beyond initial intended use – would provide the backbone for this. Such a multidisciplinary, cross-cutting platform would support synergy between programmes and sectors at local and regional levels and would help sustain the "One Health, One World" strategy outlined earlier as Option 2 and ownership as outlined in Option 3.

Context for action

A culture of innovation in disease endemic countries is of paramount importance if health inequalities are to be addressed and poor populations are to benefit from scientific advances. Yet innovation tends to be viewed solely as the development of a new drug, diagnostic, pesticide or vaccine. To have a real impact on health, innovation needs to be viewed more broadly – for instance, it should include social innovation and encompass new delivery mechanisms, such as the community-directed treatment and interventions mentioned in Chapter 4. Disparate research capacities also need to be brought together to consolidate research and expand innovation (also see Option 2 on "One Health, One World"), while silos of traditional research and funding programmes need be demolished. This shift in culture needs to be supported by an appropriate social, legal, political and regulatory environment that facilitates unbridled access to information.

Disease endemic countries need to embrace and participate in this innovation culture. They specifically need to play a more central role and be recognized for their contributions, and they need to change how they collaborate and share technologies to promote long-term health outcomes. Yet, to date, most disease endemic countries have not devoted efforts towards developing innovative approaches and new technologies, and most product development partnerships (PDPs) have been concentrated in high-income countries, with only a handful of centres of research excellence actually based in disease endemic countries. This means there is low engagement between innovators/researchers and disease endemic country policy-makers, resulting in a mismatch between efforts and needs. Option 3 already highlights the need for country ownership of research, yet disease endemic countries lose much of their best research talent because of the brain drain whereby researchers are tempted to work in other countries with a more vibrant research culture. The problem needs to be addressed.

> **If new multidisciplinary science is to save lives in poor populations, there needs to be considerable transformation in the innovation arena, leading to a new model for how knowledge is accessed, shared and used.**

If new multidisciplinary science is to save lives in poor populations, there needs to be considerable transformation in the innovation arena, leading to a new model for how knowledge is accessed, shared and used.

Action to be taken

Sustainable innovation must allow local participation in the innovation process and support the sharing of its end products.

The following three steps should be seen as priorities.

1. **A new paradigm of an "open innovation culture", with a broader definition of innovation, should be encouraged**, particularly in disease endemic countries. This environment should be created mainly through the collaboration of research and development agencies, industry and academia – both "north" and "south" – with disease endemic countries. The definition of innovation should be broadened and supported by the social, legal, political and regulatory environment. Enabling policies and mechanisms (i.e. harmonization of science, technology and innovation policies, intellectual property management, sustained financial commitment, incentives for intersectoral cooperations) are crucial to support research and development through to significant innovations, and to attract partnerships with the private sector and help to reduce the investment risk for all stakeholders.

2. **The research, development and implementation capacity of disease endemic countries should be strengthened**, with appropriate roadmaps for innovative development and use of tools. Home grown capacity for scientific research and technological know-how should be built up with the support of a strong health research and development policy, in parallel with an improved research infrastructure and enhanced budget. International donors and other funders would need to assist this process through active collaboration. To address the brain drain, countries should also examine how they can encourage scientists in the diaspora to return home to enhance the country's research enterprise. Countries would need to develop schemes to allow this – for instance, grants could be given to returning scientists and their universities to establish centres of excellence over a given number of years. Such centres could form the nucleus for networks such as those outlined in Chapter 4. A number of the BRIC countries (Brazil, Russia, India and China, see Chapter 4) provide models of how to foster technological innovation; they could act as partners for smaller countries.

3. **An "open access innovation platform" should be created and adopted**, comprising a repository of tools and enabling mechanisms that both respond to the needs of disease endemic countries and expedite the global community's efforts to meet the challenges of diseases of poverty (see Fig. 6.2). Open access to research information and to raw data (with new concepts and information on intellectual property), must be promoted as part of this platform. Countries would need to develop mechanisms for joint ownership[13] and sharing of intellectual property rights through fair and legal frameworks in order to develop this platform. Creation of such a new innovation platform would expand access to resources, enhance use of valuable assets beyond intended targets, and stimulate the search for novel

13 www.wipo.int/uipc/en/guidelines/pdf/ip_policy.pdf (accessed 22 February 2012).

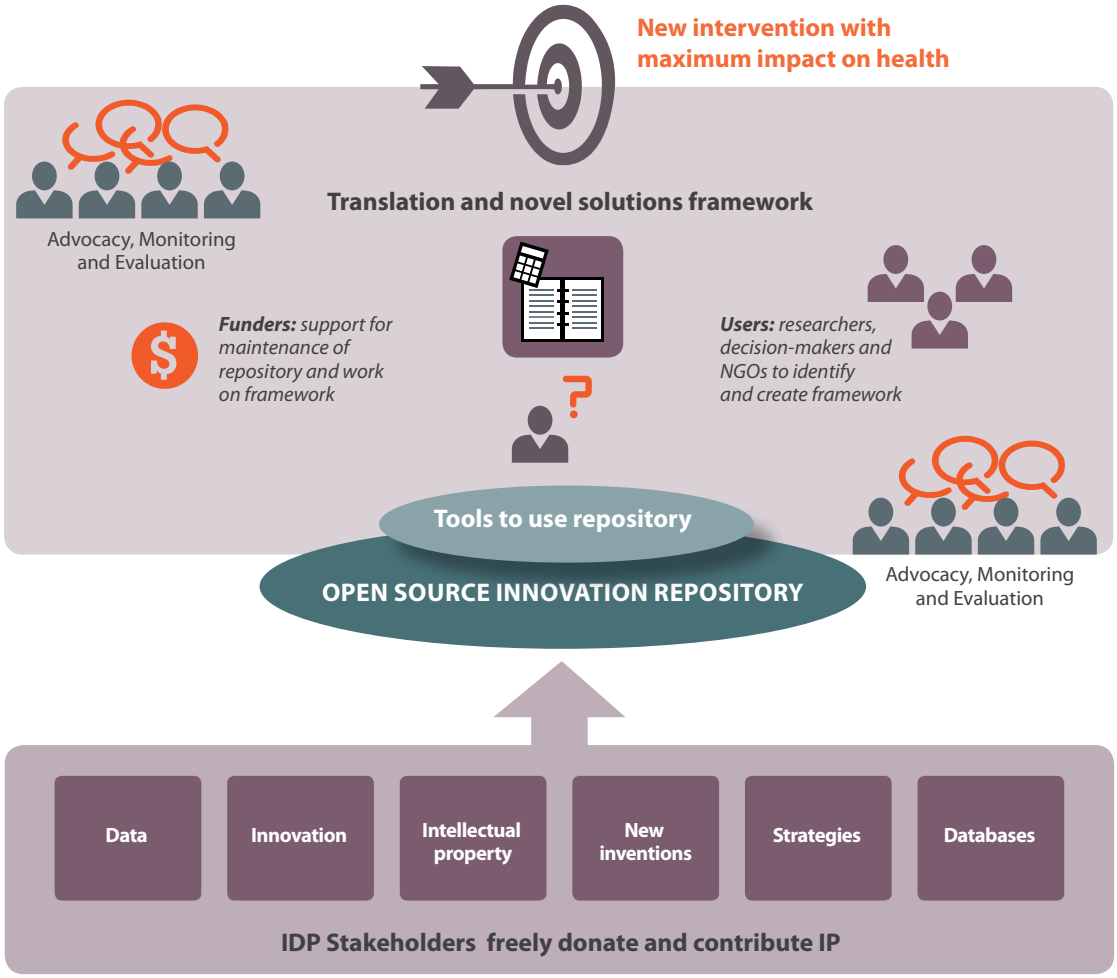


Fig. 6.2. An open access innovation platform based on discussions and input from stakeholders

Source: *TDR/Oduola & Certain.*

discoveries and the development of new health interventions. The platform should facilitate in-depth understanding of the specific social contexts in which interventions will be delivered, and allow strong engagement with communities in these settings to ensure maximum and sustainable implementation and uptake.

Creation of a new culture of innovation and associated innovation platform is an ambitious, long-term goal. In the short term, efforts should focus on establishing a few centres of excellence and changing the legal and regulatory structures of countries to facilitate innovation, and on providing funding and incentives for innovators/risk takers.

What will success look like?

Implementation of this action will lead to a broader definition of innovation and more innovation-focused research, with disease endemic countries playing a more central role. Creation of an open innovation platform should improve access to and sharing of data and so speed up scientific discovery and production of interventions. A cross-cutting innovation platform will mean that technical advances will go hand in hand with social innovation so that new tools and strategies are rapidly scaled-up and delivered to those in need.

Progress towards a new culture of innovation can be measured by monitoring the development of innovative models of sharing information and delivering new technologies, and monitoring the sharing of intellectual property to help tackle infectious diseases of poverty.

OPTION 5: CREATE AN ONLINE GLOBAL PLATFORM OF RESEARCH RESOURCES TO INFORM ON STRATEGIES, POLICIES AND FUNDING COMMITMENTS

Periodic systematic analysis of the research resource landscape for infectious diseases of poverty should be performed to identify resource gaps and provide information to guide strategic planning.

An easily accessible, online global platform on resources for health research will enable policy-makers, funders and researchers to develop their own new priorities and strategies to support research for infectious diseases of poverty. Although it would not be confined to focusing on financial resources (see later), the electronic platform would have information on "who funds what?" together with where, when and how much funding is available. Used together with the research needs identified through use of the index of infectious diseases of poverty (outlined in Option 1) and the innovation platform (outlined in Option 4), the resources platform will help improve ownership by low and middle-income countries (described in Option 3) and allow better, more cohesive and effective support for research for infectious diseases of poverty. It will thus be of enormous benefit in the battle against these diseases.

Context for action

Currently there is no single, transparent and user-friendly tool widely available to policy-makers, funders and researchers to help them to devise new strategies, policies and mechanisms to support health research (particularly research for infectious diseases of poverty). There is a dearth of information on resources (financial and non-financial) for health research, meaning that gaps in funding and other resources, including manpower and infrastructure, have been hard to identify. As a result, certain areas of research have not been able to attract much needed resources e.g. funding for research on how to get new products (such as vaccines and drugs) to poor communities. Such underfunded areas of research can only be identified, and resource needs met, through a thorough mapping of resource and funding flows.

Policy-makers will continue to struggle to make the right decisions and investments until such information becomes easily available to them. They need access to information on who funds what; levels of financing; who is engaged in research and innovation; and on research outputs (as well as associated benefits to public health) so that they can make their decisions on how most effectively to address resource issues in relation to research needs.

Funders also need to know whether the full continuum of research is being funded, or if there are funding gaps that could be filled with new funding initiatives. They also need to recognize duplication of effort so that they can better direct their financial investment and reduce inefficient use of funds. While some efforts – such as the G-FINDER surveys and associated reports on funding for neglected diseases (*8*) – have been made to address this lack of information, the scope of such work has been limited. For instance, G-FINDER focuses on financial investment rather than other resources such as manpower, and does not cover areas such as implementation research and operational research (which are particularly important for low and middle-income countries). In Chapter 5 of this report, although we have broadened the scope of our analysis to include implementation research, we do not look at issues of manpower or infrastructure. Nevertheless, activities such as the work done for Chapter 5 and that carried out for the G-FINDER surveys will help guide the development of the global resource platform.

It is therefore clear that a central platform where all such information is available would be of great help to policy-makers and funders while they devise their strategies and policies. It would also be useful to researchers, who need to know who is funding what research and how to direct their research proposals so as to secure appropriate funds.

Action to be taken

An easily accessible, online global platform providing a database and detailed analysis of resources and financial investment in health research will be able to provide policy-makers, funders and researchers with information they need to guide their activities. Populated with information gathered from various sources – on manpower, funding, infrastructure, and strategies and policies for health research – alongside stakeholder profiles (see Figs. 6.3 and 6.4), the database and associated analysis would allow strategic engagement of decision-makers in low and middle-income countries. It would help to modify existing policies and to highlight both positive and negative examples of disease endemic country engagement with research. The platform could be used to advocate for support for research (e.g. by civil society) and to encourage the use of research results for policies for the control of infectious diseases of poverty. It would also allow the identification of funding gaps, duplications and challenges, and would help identify research and disease priority areas that are either overlooked or oversubscribed by stakeholders.

Funds would be needed to create a database (based on review and analysis of data available) and identify resources to create, support and maintain the platform. If the platform is to be truly useful, updates at regular intervals also need to be supported. A systematic and recurring process would therefore need to be put into place to collect, collate, analyse and monitor resources and funding flows (e.g every three years). These reviews would need to provide a transparent picture of research resources and guide the intelligent creation of strategies, policies and partnerships. This information will help the relationship between research and health outcomes to be understood and will provide the evidence base for future investment in research programmes relevant to disease endemic country priorities.

What will success look like?

The online platform would provide valuable information to policy-makers, funders and researchers on resources for research. Taken together with information emerging from the infectious diseases of poverty index (Option 1) and the innovation platform (Option 4) this action could lead to better support of research for infectious diseases of poverty in terms of strategies, policies and funding commitments.

As an example, the infectious diseases of poverty index may indicate the need to tackle a particular infectious disease in isolated communities in parts of Africa. The resource platform might show that little research is taking place on this disease regionally but

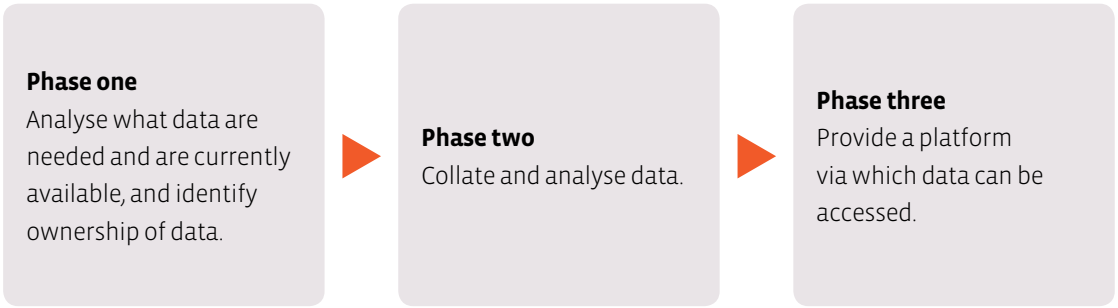


Fig. 6.3. Phases in the development of a global online platform on resources to support research for infectious diseases of poverty

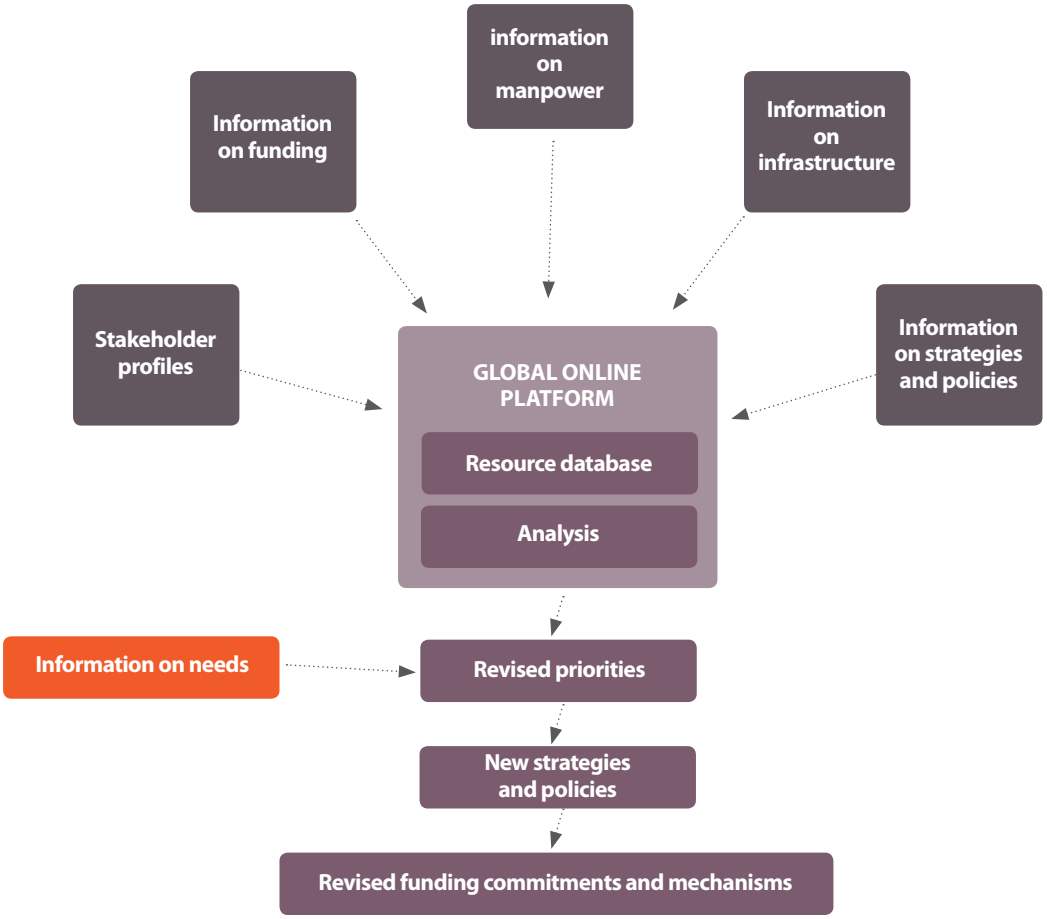


Fig. 6.4. An online global platform on resources and expected impact on research for infectious diseases of poverty. *The global platform would be populated by information from various sources to provide a database of resources for research for infectious diseases of poverty. This would be available online, in association with a detailed analysis of these resources. With information on research needs emerging from use of the index on infectious diseases of poverty outlined in Option 1, the platform (which would be updated at regular intervals) could be used to identify priority resource needs. This would then enable policy-makers, funders and researchers to develop new strategies and policies to address infectious diseases of poverty and, in turn, would lead to development of new funding commitments and mechanisms of funding.*

Source: *TDR*

that similar work is being carried out in parts of India. The funding analysis might show that no global funding is currently committed to this. Further analysis through the platform for innovation might indicate that, although drugs are available, the best regime for rural use has not been worked out. Working together under the "One Health, One World" strategy outlined (Option 2), policy-makers in agriculture, health, and science and technology might decide this issue needs to be addressed as the disease is a potential threat to agricultural workers, and parts of Africa affected by the disease grow profitable crops. Funders, including aid agencies, might provide financial commitment to a collaborative effort to tackle the disease; researchers (e.g. from Africa and India) might work together to devise best ways to get treatments to those that need it, so that the disease is managed appropriately and transmission controlled.

The process should result in a more balanced portfolio of funding across the "One Health, One World" sectors, and enable funding of research on infectious diseases of poverty to be congruent with national priorities, burden of disease and types of research required for impact. All in all this action builds on, and is useful for, the other four actions that we have outlined in this chapter and could make a real difference to how research is supported.

Conclusions

This report has laid out the need for a systems-based approach to address infectious diseases of poverty, and has made a case for significant changes to be made to decrease the global disease burden.

The emergence of new institutions, partnerships, networks and funding streams focusing on infectious diseases of poverty is a proof of political will and offers great hope for the eradication of these maladies. However, greater transparency and coherence is essential for monitoring and evaluating the impact of ongoing research, resources and for sharing data and research findings. The scientific community, especially in countries heavily burdened by infectious diseases of poverty, needs a more enabling environment to access resources, share knowledge and contribute to disease control efforts. Partnerships need to be forged and sustained to capitalize on resources and to build capacity. Progress – both success and failure – needs to be monitored and gaps in knowledge about disease and affected communities identified if the true potential of the five actions proposed in this report is to be fulfilled.

Through this report, and the five options for action that we outline above, we are boldly making our call for action. Making the call is not enough – action still has to be taken. Much is being asked of policy-makers, funders, researchers, civil society organizations and of the communities that support and are supported by them. But if nothing is done, nothing will change. We believe our call to action will dramatically transform the global research landscape and result in a better life for those who suffer the most from infectious diseases of poverty, and benefit the communities and countries in which they live.

Before we conclude this report, let us return to the story of Christophe (the fictional mineworker introduced in the opening pages of this report) to glimpse the future that our action agenda might offer him (see Box 6.3).

If the key messages from this report are used to inform research strategies, then the possibility for a better future is one step closer to a reality. We call for policy-makers, funders and researchers to focus on the five options for action that we have outlined in this chapter. Technology has advanced, knowledge about diseases has improved and there is political resolve. This momentum must not be lost. The time for action is now. Let us use current political willpower to shift from a world of inaction further towards a world in action.

> **“But if nothing is done, nothing will change. We believe our call to action will dramatically transform the global research landscape and result in a better life for those who suffer the most from infectious diseases of poverty.”**

BOX 6.3. WHAT OF CHRISTOPHE?
THE IMPROVEMENTS IN PEOPLES' LIVES THAT COULD OCCUR WITH THE CHANGES RECOMMENDED IN THIS REPORT
(see page 16 for this fictionalized representation)

Disease endemic countries (such as the country where Christophe lives and works) will have developed a research agenda that better matches their own needs. Money will have been invested in research for better drugs and diagnostics for diseases that have a high national disease burden – diseases such as sleeping sickness.

A new culture of public health innovation will have led to concerted efforts to develop new diagnostics and treatments. Through this, a new rapid diagnostic blood test will have been developed to detect the infection that causes sleeping sickness, and an effective, non-toxic, oral drug will be available to treat the late stage disease. As a result of implementation research the best way of delivering these to relevant communities will have been developed. Local availability of these new tools will mean that diagnosis and treatment will be safer, more easily administered, less costly for the patient and more effective.

Adoption of One Health, One World will mean that various research disciplines and ministries (health, agriculture, science and technology) will be working together, in partnership with both human and animal health control programmes, sharing data and information and spearheading a more holistic approach to health. New geographical information system (GIS) and cellular telephone networks will be helping to assess disease risks and report health problems. They will also be used to deliver health messages to Christophe's mining colleagues, who now receive treatment for trypanosomiasis under an integrated programme targeting sleeping sickness while deploying tsetse traps. Cost-effectiveness research will have led to the development of an integrated strategy of preventative chemotherapy for helminthic infections within a river blindness programme. New monitoring and surveillance techniques will also be proving beneficial to such programmes.

Because there will be a new infectious disease development index (and associated media interest and public pressure), stakeholders in international development (such as aid agencies) will be investing in such programmes. The index will have compelled policy-makers to develop new regulations that ensure that the formal health system monitors community health. This will lead to improved data, which in turn will lead to resources being sent to where they are needed – such as to Christophe's small mining community.

Finally, monitoring of resources and funding flows will have indicated a number of funding gaps – such as investment in research on the association between infectious diseases of poverty and mental health problems. Funds will have been directed to this area and research and policy-makers will be stimulated to recognize these as important issues. Christophe's wife, a small trader at this point, will be able to use a newly adopted health insurance scheme resulting from research into health financing to cover costs of treatment. Christophe's mother, now partially blind as a result of poorly managed trachoma, will be able to access new drugs and therapies that make her life easier as her health deteriorates. Despite these demands, the health insurance scheme will decrease out-of -pocket expenditure on health by Christophe and his family, so they can afford to send their daughter onto higher education. Eventually Christophe's daughter will become a nurse, working at the local hospital that serves the miners.

References – Chapter six

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The *Global Report* is essential reading for health policy-makers, funders and research leaders. It includes important ideas for low and middle income countries trying to build a more prosperous and healthy future – both what they can do and what the global community can do to support this.

The full report and more details, resources, and visual aids, are available online at: www.who.int/tdr/stewardship/global_report

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