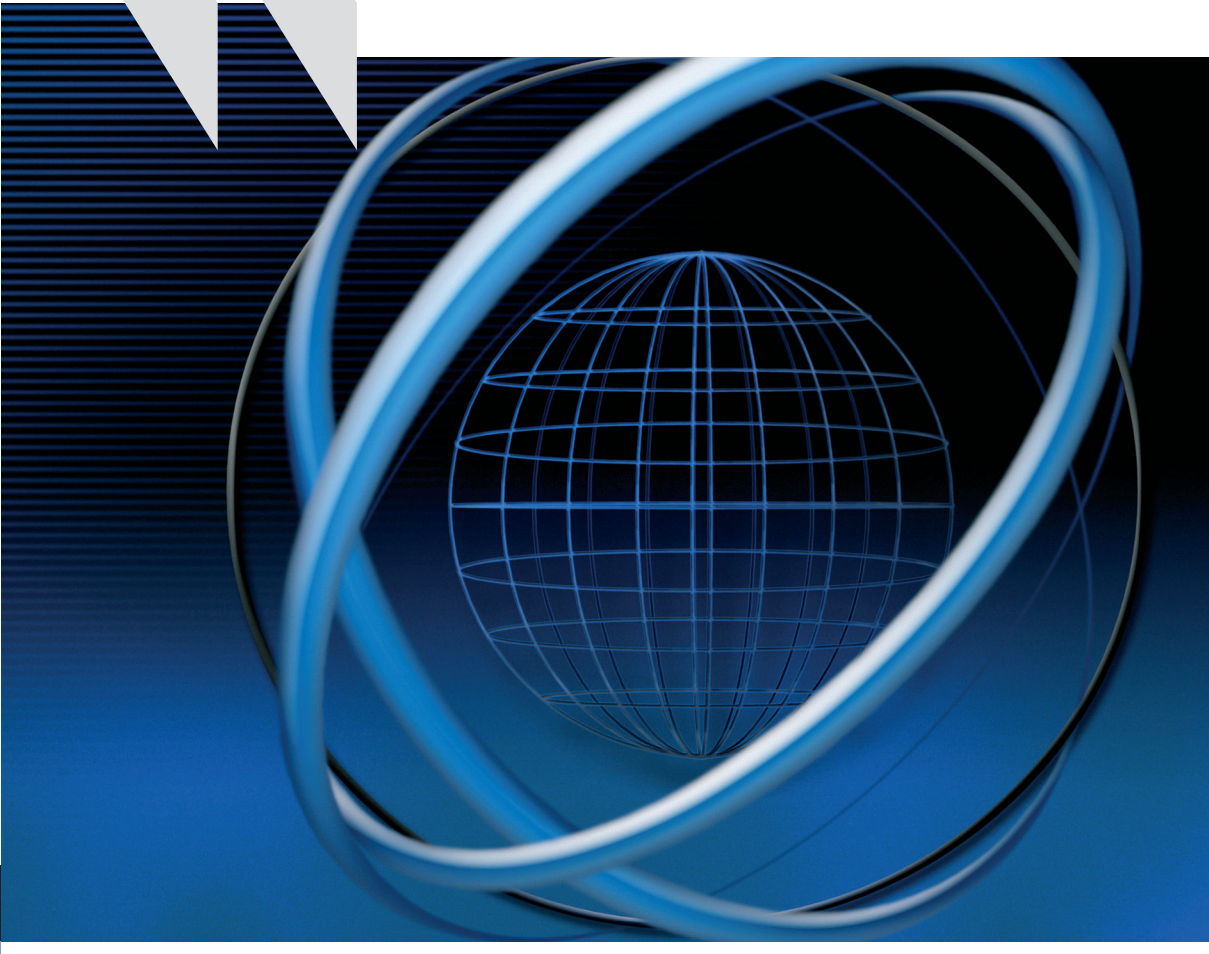
The Development Dimension

Coherence for Health

INNOVATION FOR NEW MEDICINES FOR INFECTIOUS DISEASES



OECD

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ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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Foreword

The prospects for developing countries are shaped by a wide range of issues. Domestic questions of governance and politics are important, but there are also a number of externally driven issues. Aid is one, but there are many more. As a result of globalisation, it is the "beyond aid" issues such as trade, investment, innovation and technology that play an increasingly important role in shaping the prospects of developing countries.

There is a strong relationship between the development prospects of a country and its health systems. The key question we ask in the OECD policy coherence for development (PCD) context is: Are the policies of OECD countries impacting the efforts of developing countries to improve their health systems positively or negatively? And are OECD countries' science, technology and health policies coherent with their development commitments, including the key Millennium Development Goals (MDGs) that deal directly with health: reduce child mortality (MDG 4); improve maternal health (MDG 5); combat HIV/AIDS, malaria and other diseases (MDG 6). The OECD's agenda on policy coherence for development promotes whole-of-government approaches, and the design of policy instruments available to the OECD countries that take account of potential impacts on health development objectives. In an interdependent world, achieving policy coherence is increasingly in the interest of both developed and developing countries.

Infectious diseases are one of the primary causes of mortality in the world and in developing countries they are a major barrier to economic development, social progress and human health. Nearly 1 billion humans suffer from a neglected infectious disease, according to the World Health Organization. Yet, less than 1% of the new drugs placed on the market since 1975 up to today were developed for these diseases. The health innovation system is failing to deliver the new medicines, vaccines and diagnostics that are required for neglected infectious diseases.

High costs and failure rates make the drug development business a very lengthy, technically complex and risky process. Given these costs, companies embark on research and development (R&D) for products where

they can be sure that the market will provide a reasonable return on investment. Because of low return on investment combined with high developmental risks, businesses are discouraged from engaging in research in the area of neglected infectious diseases that mainly affect the developing world. Mechanisms for addressing the lack of viable markets, expanding the global capacity for drug discovery, and increasing R&D productivity must be found.

Innovation is a multi-sectoral endeavour and demands strong policy coherence. The issue of policy coherence is important in improving the availability of medicines as a number of policy areas need to be brought together in a coherent manner – including health, trade, science and technology, development co-operation and finance – in such a way as to create an environment that will spur both investments in, and efficiency of, research and product development. In turn, these products need to be appropriate, affordable and available to the populations in need. If this is achieved, new health technologies could increase the effectiveness of development efforts for health.

This publication is an important contribution to enhancing PCD in the health sector. It aims to deepen the understanding of the different dimensions of our policy actions in order to improve their coherence and thereby achieve better outcomes both for developing and developed countries. It brings together the report, outcomes and background papers for the High-Level Forum on Policy Coherence: Availability of Medicines for Neglected and Emerging Infectious Diseases (HLF), held in June 2007 in Noordwijk-aan-Zee, Netherlands.

The High-Level Forum was organised by the OECD together with the Government of the Netherlands, with the purpose of building support for a coherent agenda to radically improve the availability of medicines for infectious diseases. The HLF issued a statement, called the Noordwijk Medicines Agenda (NMA), which identified specific actions which need to be taken to accelerate innovation in neglected and emerging infectious diseases. Participation at the forum was widespread in terms of geographical coverage and diversity of stakeholders. Over 200 high-level officials from OECD and developing countries, industry, researchers, funders, academics, philanthropic foundations, international and non-governmental organisations representing the innovation, development and health communities attended the forum.

We would like to acknowledge the generous support of the Dutch government as well as a grant from the German government. We would like to thank all forum participants for their important contribution to the outcome. The guidance provided by the OECD Steering Group for the High-

Level Forum on Medicines for Neglected and Emerging Infectious Diseases was instrumental and the support and advice of the World Health Organization colleagues was indispensable. Without the hard work of OECD staff in the Science and Technology Directorate and the Development Co-operation Directorate, the forum would not have been possible.

Roy Widdus (president of the Global Health Futures Network) was the rapporteur for the High-Level Forum, and was instrumental in articulating many of the action points for future work (Chapter 4). Barbara Slater wrote much of the main report, as well as co-ordinated and edited the various inputs to it. The background papers were prepared by Jeffrey Sachs and Sonia Ehrlich Sachs of Columbia University and the Earth Institute (Annex B); Michael Kremer and Heidi Williams of Harvard University (Annex C) and a third separate paper by Jeffrey Sachs (Annex D).

This publication is part of the OECD Policy Coherence for Development Programme, co-ordinated by Raili Lahnalampi. The report benefitted from inputs by Bénédicte Callan and comments from Alexandra Trzeciak-Duval and Jenny Hedmann were helpful in improving the analysis reported herein. The entire publication was edited by Julie Harris.

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Acronyms and Abbreviations

ACIP	Advisory Committee on Immunization Practices (United States)
ACT	artemisinin-based combination therapy
ADIPs	advanced development and introduction plans
ALRI	acute lower respiratory infection
AMC	advance market commitment
ARVs	anti-retroviral medicines
CGD	Center for Global Development (United States)
CTDL	currency transaction development levy
CMH	Commission on Macroeconomics and Health
DAC	Development Assistance Committee (OECD)
DALYs	disability adjusted life years
DCD	Development Co-operation Directorate (OECD)
DCP	*Disease Control Priorities in Developing Countries*
DECs	disease endemic countries
DOTS	Directly Observed Therapy Short Course
EPI	Expanded Programme on Immunization (WHO)
FDA	Food and Drug Administration (United States)
GAVI	Global Alliance for Vaccines and Immunization
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GDP	gross domestic product
GNP	gross national product
HFF	healthcare funding framework
Hib	haemophilus influenzae b
HIV/AIDS	human immunodeficiency virus / acquired immunodeficiency syndrome
HLF	High-Level Forum on Policy Coherence: Availability of Medicines for Neglected and Emerging Infectious Diseases
IAVI	International AIDS Vaccine Initiative
IFF	International Finance Facility (United Kingdom)
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IGWG	Intergovernmental Working Group on Intellectual Property Rights, Innovation and Public Health
IOWH	Institute for OneWorld Health

IP	intellectual property
IPRs	intellectual property regimes
MDGs	Millennium Development Goals
MDR-TB	multi-drug resistant tuberculosis
MTEF	medium-term expenditure framework
MVI	Malaria Vaccine Initiative
MVP	Meningitis Vaccine Project
MVP	Millennium Villages Project
NGO	non-governmental organisation
NIH	National Institutes of Health (United States)
NMA	Noordwijk Medicines Agenda
NTDs	neglected tropical diseases
ODA	official development assistance
OECD	Organisation for Economic Co-operation and Development
ORS	oral re-hydration solution
PATH	Program for Appropriate Technology in Health
PCD	policy coherence for development
PDPs	public-private partnerships for product development
PPP-PDs	public-private partnerships for product development
SARS	severe acute respiratory syndrome
STI	Directorate for Science, Technology and Industry (OECD)
TB	Tuberculosis
TDR	United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases
TRIPS	Agreement on Trade Related Aspects of Intellectual Property Rights
R&D	research and development
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Emergency Fund
WHO	World Health Organization

Chapter 1

Neglected and Emerging Infectious Diseases: Why It Is An Issue Now

This chapter introduces, and provides the context for, why neglected and emerging infectious diseases is an issue and why it is gaining attention today. It briefly sets out the the High-Level Forum on Policy Coherence: Availability of Medicines for Neglected and Emerging Infectious Diseases (HLF), held in June 2008 in the Netherlands as well as the the Noordwijk Medicines Agenda, the HLF's main deliverable.

Over the last century healthcare innovation has transformed the way medicine is practiced and has brought substantial benefits in the prevention, diagnosis and treatment of diseases. But to date, health innovation has not been able to adequately address the issue of infectious diseases that primarily affect the developing world.

Infectious diseases are one of the primary causes of mortality in the world, and in developing countries, they are a major barrier to economic development, social progress and human health.

The health innovation system is failing to deliver the new medicines, vaccines and diagnostics required to treat and combat neglected infectious diseases. The Global Forum for Health Research estimates that only 10% of global health research is devoted to conditions that account for 90% of the global disease burden (Global Forum for Health Research, 2004). These diseases include tuberculosis and malaria, but also neglected tropical diseases (NTDs) such as Human African trypanosomiasis, leishmaniasis, schistosomiasis, Chagas disease, lymphatic filariasis and onchocerciasis.

To date, most medicines used to deal with such diseases in developing countries were first developed for other markets or purposes. With these drugs, problems arise related to cost, safety, stability, formulation and resistance. What are needed are **new** medicines, vaccines and diagnostics that are safe, effective and appropriate for developing country diseases and delivery systems.

High costs and failure rates make the drug development business a very lengthy, technically complex and risky process. Given the costs, companies embark on research and development (R&D) for products where they can be sure that the market will provide a reasonable return on investment. Because of low return on investment, combined with high developmental risks, businesses are discouraged from engaging in research in the area of neglected infectious diseases that mainly affect the developing world. Mechanisms for addressing the lack of viable markets, expanding the global capacity for drug discovery, and increasing the R&D productivity must be found.

The innovation cycle needs to be examined and new ways of conducting R&D need to be found in order to render the system more efficient so that drugs can be produced faster and at lower costs. In order to address this issue, innovation is needed throughout the product cycle, from basic research through to delivery to the patient.

Why is it an issue and why are we paying attention to it now?

In poor countries neglected infectious diseases impose heavy socio-economic costs:

- Health – Globally one in six people currently suffer from a neglected tropical disease. About half of communicable disease deaths take place in sub-Saharan Africa.
- Economy – The annual costs of malaria in Africa have been estimated at a minimum of USD 12 billion; this resurgent disease alone may retard future African economic growth by 1.3 percentage points per year.
- Society – Disease impacts include lower physical endurance, loss of schooling, increased dropout rates, reduced investment incentives and postponement of the demographic transition.
- Security – As epidemics increase, large-scale migration exacerbates the situation in fragile states, as well as increases the possibilities of violent conflicts.

In the last decade, the issue of neglected and emerging diseases that disproportionately affect poorer populations has received increasing international attention, including in the following variety of ways:

- the emergence of public-private partnerships for product development (PPP-PDs/PDPs);
- strengthened collaboration for the production of vaccines and drugs, such as the Global Alliance for Vaccines and Immunization (GAVI);
- launch of an Advance Market Commitment (AMC) Pilot by G7 countries;
- new funding mechanisms, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM);
- increased philanthropic activity from foundations who have made infectious diseases their focus, such as Bill and Melinda Gates Foundation, Rockefeller Foundation, and Wellcome Trust;
- inclusion of new commitments for action and funding in the Millennium Development Goals (MDGs) and G8 meetings.

This trend has been accompanied by growing awareness that in addition to humanitarian reasons for fighting infectious diseases in developing

countries, industrialised/Organisation for Economic Co-operation and Development (OECD) countries have to pay attention to their own health needs.

There has also been growing recognition (as evidenced by the creation of PDPs) that reliance on the historical, market-incentivised approach to securing pharmaceutical development and delivery has not been sufficient for disease threats where markets are commercially unattractive and/or uncertain. Broader concerns have also arisen with regard to the declining productivity of traditional pharmaceutical innovation systems and whether a new approach to innovation needs to be considered. As such, there are also economic reasons driving OECD country involvement.

The policies and practices that are being put in place to enhance the availability of drugs, vaccines and diagnostics for neglected infectious diseases and to address innovation failures for neglected and emerging infectious diseases are also relevant to disease markets in advanced industrialised countries. These policies and practices could yield lessons relevant to health innovation generally. Creating efficiencies in the innovation cycle is the key to quickly delivering new medicines to market at reduced costs.

The High-Level Forum on Policy Coherence: Availability of Medicines for Neglected and Emerging Infectious Diseases

Preparation for the High-Level Forum

It was within this context, that the OECD launched a high-level forum to examine ways in which new ideas could be harnessed to improve efforts to combat neglected and emerging diseases, and possibly also garner lessons for pharmaceutical innovation relevant to the broader needs of OECD countries.

The High-Level Forum on Policy Coherence: Availability of Medicines for Neglected and Emerging Infectious Diseases (the "HLF") was organised by the OECD together with the Government of the Netherlands, to build support for a coherent agenda to radically improve the availability of medicines for infectious diseases that primarily affect the developing world, and to create a system that will produce a sustainable pipeline of new drugs.

With a grant from the German government, background papers on policy mechanisms to enhance investments in, and the productivity of, research and development for medicines for infectious diseases that mostly affect developing countries were commissioned and brought together in a

compendium (see Annexes B-D). The three background papers are respectively by Jeff Sachs and Sonia Ehrlich Sachs of Columbia University and the Earth Institute, Michael Kremer and Heidi Williams of Harvard University and a third separate paper by Jeff Sachs. The issues these papers discussed – measuring the economic burden of infectious diseases and evaluating the policy instruments for incentivising R&D into new medicines – form the background to the High-Level Forum agenda.

WHO co-ordination

The OECD closely collaborated with the World Health Organization (WHO) on the content of the meeting, its participants and timing in order to ensure alignment with other initiatives, avoid duplication of other efforts and to receive advice and guidance.

In 2006, the WHO received a report from the Commission on Intellectual Property Rights, Innovation and Public Health which had been asked to reflect on how countries could address the availability, accessibility and affordability of medicines. Subsequently, the WHO established an Intergovernmental Working Group on Intellectual Property Rights, Innovation and Public Health (IGWG) in order to deliver to the 2008 World Health Assembly a "global strategy and plan of action" to implement the Commission's recommendations. The Commission made over 50 recommendations; those that were relevant to the availability of new medicines included suggestions for: promoting research and discovery; identifying research priorities; improving innovative capacity; and encouraging technology transfer.

The High-Level Forum was seen by the WHO as being a useful complement to the discussions taking place in IGWG. There was regular communication between the OECD and the WHO on the HLF. Deliberations in the OECD as to what advanced industrialised countries can do to help improve availability of new medicines for diseases that affect the developing world is seen as a welcome parallel activity that could feed into discussions at the WHO. In addition, the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases (TDR) was intimately involved in the planning of the Workshop on Accelerating Neglected Diseases Drug Discovery.

OECD worked very closely with WHO TDR and IGWG in planning the speakers and content of the HLF and the two preparatory workshops. The OECD was invited to be an expert participant at the IGWG meetings. This collaboration is expected to continue, particularly in discussions with TDR

regarding how to approach the potential scale up of research networks, building on TDR's and other networks as the OECD moves forward with the action points that came out of the HLF.

Preparatory workshops

Leading up to the HLF, two preparatory experts' workshops were held back to back at OECD headquarters on 2-3 May and 3-4 May 2008. One workshop was on "Accelerating Neglected Diseases Drug Discovery" and was organised by the OECD Biotechnology Division and the WHO/TDR. The second workshop, "Policy Options and Policy Coherence to Enhance the Availability of Medicines for Neglected and Emerging Infectious Diseases" was organised by the OECD Development Assistance Division with help from the OECD Development Centre.

The Accelerating Neglected Diseases Drug Discovery workshop focussed on new approaches to radically accelerate drug development for neglected infectious diseases, and the potential scale up of such approaches. In particular, it explored the possibility of building on existing initiatives to create a global, virtual drug development network for infectious diseases. Discussions centred on what the scientific opportunities were, what organisational mechanisms were required to exploit these opportunities and some of the challenges to scaling up.

The second workshop, Policy Options and Policy Coherence to Enhance the Availability of Medicines for Neglected and Emerging Infectious Diseases, explored the policy options and policy coherence to enhance the availability of medicines for neglected and emerging infectious diseases. Discussions centred on the challenges and policy instruments for scaling up research on neglected diseases as well as the policy coherence required to deliver benefits from existing and newly developed medicines.

Both workshops provided comments on the Noordwijk Medicines Agenda (NMA) and the outcomes of the workshops were the basis for discussions at the HLF (Annex A: Summaries of the Preparatory Workshops).

The High-Level Forum

The OECD High-Level Forum on Policy Coherence: Availability of Medicines for Neglected and Emerging Infectious Diseases was held on 20-21 June 2008 in Noordwijk-aan-Zee, Netherlands. The forum was made possible by a voluntary contribution from the Dutch government (Ministries of Health, Sports and Welfare and Foreign Affairs) and was organised by

the OECD (Biotechnology Division of the Directorate for Science, Technology and Industry [STI] and the Policy Co-ordination Division of the Development Co-operation Directorate [DCD] in co-operation with the Development Centre and the African Partnership Forum).

To improve availability of medicines for neglected and emerging infectious diseases that disproportionately affect developing countries, it was recognised that a number of policy areas needed to be brought together in a coherent manner – including health, trade, science and technology, development co-operation and finance – in such a way as to create an environment that will spur both investments in, and efficiency of, research and product development. In turn, it was also recognised that the availability of appropriate new health technologies could increase the effectiveness of development efforts for health.

For these reasons, the High-Level Forum explicitly brought together the innovation, development and health communities to develop a common agenda to increase the overall scale of R&D financing and the effectiveness of R&D activities for the diseases of the poor. Over 200 high-level officials from OECD and developing countries, industry, researchers, funders, academics, philanthropic foundations, international and non-governmental organisations representing all the communities mentioned above attended the forum.

Queen Beatrix of the Netherlands attended the meeting, in addition to OECD Secretary-General Gurría, WHO Deputy General Anarfi Asamoa-Baah, ministers from the Netherlands, Cameroon, Liberia, Sudan, Tanzania, and the African Union, high-level government representatives from Belgium, Canada, France, Germany, Italy, Mexico, United Kingdom, Kenya, and Thailand as well as experts from all over the globe.

The forum focused on four critical issues:

1. the economic rationale for combating infectious diseases, including why OECD countries have an economic interest in addressing this issue;
2. the effectiveness and sustainability of major policy mechanisms available to increase incentives for private firms to bring to market new products for infectious diseases that primarily affect developing countries;
3. new models for improving the efficiency in the discovery, development and delivery of new medicines, vaccines and diagnostics for neglected infectious diseases in developed and developing countries;

4. building support for coherent and comprehensive strategies to improve the availability of medicines for neglected and emerging infectious diseases (this issue was discussed during a high-level government session).

The HLF was successful as it achieved consensus on the Noordwijk Medicines Agenda, which identified specific actions for accelerating innovation in neglected and emerging infectious diseases.

The Noordwijk Medicines Agenda

Process for developing the Noordwijk Medicines Agenda

The NMA is a summary of the main themes of the HLF and represents the general agreement of participants about the problems, goals, and work that needs to be done in order to improve the availability of medicines for neglected and emerging infectious diseases.

Though the NMA was not formally endorsed by all OECD countries and is not a legally binding document, the process that developed the draft Noordwijk Medicines Agenda discussed by participants at the HLF was inclusive and horizontal. The draft NMA benefited from the guidance of a Steering Group with representation from Canada, France, Germany, Japan, Netherlands, Portugal, Sweden, United Kingdom and the United States. There were multiple consultations at different points in the process with countries through different OECD bodies, including the:

- Working Party on Biotechnology (twice).
- Development Assistance Committee (twice).
- Health Committee;
- Executive Committee of OECD.

The preparatory workshops included participants from industry, non-governmental organisations and the research community. Each workshop had a session devoted to the discussion of the draft NMA, providing participants an opportunity to make suggestions for improving the text. Comments were also received in writing following the workshops. As such, the draft NMA that went to the HLF reflected multiple perspectives and came as close to a consensus among OECD country positions as possible.

At the HLF, panel members of each session were asked to specifically comment on the NMA. Both speakers and participants at the HLF provided written and verbal input during the day. The last session, made up of high-

level government officials as well as ministers, was devoted entirely to the NMA. Over the course of the High-Level Forum, the NMA was edited several times to reflect the issues and concerns raised by countries, speakers and participants.

The final NMA represents a consensus among participants at the HLF, and more broadly on what concrete actions are necessary to move forward on accelerating innovation for medicines, vaccines and diagnostics for neglected and emerging infectious diseases.

Key points of the NMA

The NMA is divided into three sections:

- The first section **recognises** some of the challenges to combating neglected infectious diseases that affect poor countries, as well as recognising the work undertaken to date by various actors to address those challenges.
- The second section **acknowledges** some of the shortcomings of existing initiatives which should be remedied and identifies some of the more promising initiatives which should be bolstered or scaled up.
- The third section focuses on the **specific actions** that can be taken to accelerate the availability of medicines, vaccines and diagnostics for neglected and emerging infectious diseases as well as enhance policy coherence in this area.

In order to improve the availability of new medicines, participants agreed that there is a need to improve the efficiency of the innovation system, which at present fails to deliver a robust pipeline of new medicines, vaccines and diagnostics for the neglected diseases of the developing world. Many of the suggested actions in the NMA focus on how to make the health innovation system for infectious diseases more open; how to encourage more collaborative research; and how to broaden the involvement of researchers, academic institutions, laboratories and companies globally in order to increase the efficiency, and lower the costs, of developing new, safe and effective medicines, vaccines and diagnostics.

The NMA calls for governments of OECD and developing countries to show political leadership and to join with a wide variety of stakeholders in multiple sectors to further intensify collaborative efforts and promote coherent policies to improve the availability of, and access to medicines, vaccines and diagnostics for neglected and emerging infectious diseases.

In particular, the NMA calls for:

- pursuing the viability of a global virtual collaborative drug development network that draws on and scales up existing initiatives (*e.g.* WHO Special Programme for Research and Training in Tropical Diseases, public-private product development partnerships and regional [*e.g.* south-south and north-south] technology networks) and is more open;
- prioritising R&D needs and aligning research to a common purpose;
- facilitating partnerships and networking among a variety of actors by building and sharing infrastructures and by encouraging more open innovation approaches;
- identifying infrastructure needs to underpin a global virtual collaborative network;
- forecasting accurate and effective demand of medical technologies;
- exploring collaborative mechanisms for intellectual property (IP) management;
- facilitating the development and operation of a sustainable architecture for sharing knowledge, data and research tools;
- creating incentives for R&D through new mechanisms to reward innovation;
- supporting developing country-led efforts in strengthening their own health, local production and research systems, including prevention, to ensure availability and accessibility of medicines, vaccines, diagnostics and other preventative technologies for neglected and emerging infectious diseases.

The Noordwijk Medicines Agenda will be used as a framework for future action for OECD as it moves forward to explore mechanisms and models to make the innovation system more efficient, so that medicines for neglected infectious diseases can be produced quicker and cheaper. The next chapter sets out the impacts of infectious diseases both on developing and OECD countries.

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Chapter 2

What Are the Problems? Why Is It in the Economic Interest of OECD Countries to Address these Problems?

This chapter outlines the impact of neglected infectious diseases in developing countries by citing current morbidity and mortality rates, elucidating the economic burden infectious diseases pose, highlighting the problems of lacking pharmaceutical products, explaining the drug research and development/innovation process, and discussing the economics of drug development. The chapter closes with a section on why OECD is interested in neglected and emerging infectious diseases that mainly affect developing countries.

Impact of infectious diseases in developing countries

According to the World Health Organization (WHO), nearly 1 billion people (one-sixth of the world's population) are affected by neglected infectious diseases (WHO, n.d.), yet less than 1% of new drugs placed on the market since 1975, have been developed for these diseases (Committee on Development, 2005). Of the few drugs available to treat these diseases, most are not widely used due to problems with safety, effectiveness, administration, cost and, increasingly, drug resistance. What is required is the development of new and effective medicines, vaccines and diagnostics (Hopkins, Witty and Nwaka, 2007).

Infectious diseases have a disproportionate impact on the poorest populations living in developing countries where the costs of the failure to control neglected infectious diseases are great in terms of mortality, morbidity, and productivity.

The excess disease burden borne by the poor results from a small number of conditions, creating enormous social and economic costs that are several times greater than the costs of addressing it. While some of the interventions to address the major sources of excess disease burden lie beyond the health sector and will not be solved by new technologies alone, medicines, vaccines and diagnostics are major tools for preventative and curative interventions and are important for reducing poverty and their consequences.

Morbidity and mortality

Illness and death from infectious diseases are largely preventable and treatable and, as such, are particularly tragic. In 2002, 75% of all deaths due to infectious diseases worldwide occurred in Southeast Asia and sub-Saharan Africa. Southern Africa, which is home to 10% of the world's population, accounted for more than 40% of deaths due to infectious diseases. More than 60% of all deaths in this region were due to infectious diseases (Global Health Council, n.d.).

Consider the following statistics:

- In developing countries, six in ten persons die from infectious diseases. Yet in developed countries, infectious diseases account for only one out of every ten deaths (Institute for OneWorld Health, n.d.).

- Malaria kills more than 1 million people a year and threatens 40% of the world population. The cost of this disease alone in Africa is estimated at nearly USD 12 billion a year in lost income and is one of the greatest barriers to Africa's economic development and poverty reduction today. Economists believe that malaria is responsible for a "growth penalty" of up to 1.3% per year in some African countries. When compounded over the years, this penalty leads to substantial differences in the gross domestic product (GDP) between countries with and without malaria, and severely restrains the economic growth of the entire region (IRIN, 2005).

- Infectious diseases also have a direct impact on Africa's human resources. Not only do infectious diseases such as malaria result in lost life and lost productivity due to illness and premature death, but they also hamper children's schooling and social development through both absenteeism and permanent neurological and other damage associated with severe episodes of the disease.

- Morbidity rates associated with neglected infectious diseases are high. A typical feature of many of these infectious diseases is that they impair or permanently disable a large number of people and have a silent, chronic progression (Burri, 2004).

- Across Africa, infectious diseases impose a heavy burden on health systems that do not always have the infrastructures needed to cope with treating them, even if treatments were available. Malaria, for example, swallows 40 % of public health expenditures and is responsible for the majority of all health centre visits and inpatient deaths (WHO/UNICEF, 2003).

Economic burden of neglected infectious diseases

From an economic perspective, health is a sound investment as it fuels economic growth, builds human capital and has a long-term impact on economies. Investing in health is a cost-efficient exercise. Every recent study that has examined the conditions of ill health in low-income countries has found that the cost-benefit ratio of disease control is enormously favourable.

The economic costs of disease include direct costs due to loss of life and work time; reduced productivity due to disability, absenteeism, and lack of physical strength required to work; loss of schooling and early dropouts; reduced inflows of investments into disease-endemic communities; and direct extra costs of healthcare (Sachs, 2007).

Yet controlling neglected infectious disease is cost effective. Estimated annual rates of return on investment in control of these disabling diseases are in the order of 14-30%. For example, for each dollar invested in control of Chagas disease in Brazil and in lymphatic filariasis in China, returns of USD 7.16 and USD 15, respectively, were realised. Guinea worm education is calculated to produce an economic return of 29% (Molyneux, 2004).

The mortality and morbidity rate of infectious diseases on children is especially high, which has indirect economic costs to the economic development of a country:

- The high mortality rate of children delays or prevents demographic transition, which is crucial to long-term economic development. As a response to high child mortality, families tend to choose to have a large number of children. The result of large families means that there tends to be low human capital investments per child, with regard to nutrition, education, and access to basic healthcare. This presents a fundamental obstacle to the inter-generational accumulation of human capital accumulation (Sachs, 2007).
- High morbidity among children affects school attendance, cognitive development, growth and overall productivity. The majority of infectious diseases often lead to severe disability impairing people's ability to earn a livelihood and be productive members of society (WHO, 2003).

Clearly there are real economic benefits to dealing with the issue of neglected infectious diseases. For instance, according to the World Bank, eliminating communicable diseases would almost completely level the mortality gap between the world's richest 20% and its poorest 80% (Burri, 2004).

Not only is the burden of infectious diseases greater in developing countries, infectious diseases benefit from relatively little innovation due to the lack of incentives for research and development.

Pharmaceutical products for neglected infectious diseases

While effective health systems, access, control and prevention of infectious diseases need to be considered and cannot be achieved solely by considering issues related to pharmaceutical products, the development of, and access to, pharmaceuticals (drugs, vaccines) and other health products (*e.g.* diagnostics) play an important, often essential, role in the control of infectious diseases.

The available armamentarium for combating neglected infectious diseases is limited, especially for malaria, tuberculosis, and various other neglected tropical diseases (NTDs) which cause a high morbidity burden among the poorest populations. Existing products for NTDs are frequently difficult to administer and may have severe side effects. Many of the products in wide use for neglected diseases have major shortcomings; for example, they may be only partially effective (current tuberculosis [TB] vaccines) or may entail lengthy treatment (*e.g.* typical TB treatment requires six months).

For some diseases that predominantly affect populations in developing countries, no product exists in a desired category. For example, no vaccines exist for malaria or HIV/AIDS. Yet, even where a reasonably satisfactory product exists, there is always the potential for improvement in efficacy: to reduce side effects or to make it easier to use in developing country settings where health system infrastructures are not well developed and, as such, access to medication is an issue.

The development of resistance must also be anticipated, not as something unusual, but sooner or later as a predictable consequence of the wide deployment of any drug. Innovation would be required to replenish the armamentarium with effective replacement treatments. Given the timeframe for bringing a new candidate product into use, typically over ten years, it is necessary to conduct R&D on replacement products well before there is recognition of emerging resistance to existing products.

The drug research and development/innovation process

Most activities relating to products for control of neglected infectious diseases fall into the stages described below.

Basic research provides understanding of the pathogens and disease processes and is the foundation for research and discovery. It is here that steps or events in the life cycle of a disease or pathogen are identified and validated.

Translational research transforms ideas from basic research into target identification and characterisation and then into "leads", *i.e.* potential candidate products. Activities at this stage include creating screens for identifying and selecting small molecules with potential activity against pathogens, based on targets identified through basic research including genomics, or the design of vaccines and diagnostics based upon knowledge of immunological responses. Many leads from this stage are needed to feed forward to subsequent steps as most leads will not necessarily result in approved products.

Product development identifies the most promising potential candidate products (usually from a portfolio of early leads) and moves these through the processes of clinical development, regulatory approval and testing for wide utility in developing country settings. Experience has demonstrated that failure rates of candidate products in pre-clinical and clinical development are high and unpredictable.

Regulatory activities include both initial marketing approval and ongoing attention to consistent quality of products and safety monitoring.

Ensuring access, *i.e.* delivery of useful products to those who can benefit. This is a complex process in itself. It entails: rational selection of products to be made available; affordable pricing; adequate financing ; reliable manufacturing and supply, based on accurate demand forecasting efficient distribution; appropriate prescribing; and ensuring patient adherence to correct utilisation. The WHO estimates that although there has been steady progress, approximately one-third of the global population still does not have access to essential basic medicines, and that in sub-Saharan Africa this may rise to 50%.

The successful translation of basic science discoveries into new treatments is a long, complex and expensive process which is especially problematic with treatments for infectious diseases that disproportionately affect the developing world, where low returns on investments discourage innovation into these diseases. Failures and inefficiencies in the innovation system can impede the development of health technologies that are required to tackle neglected infectious diseases in the developing world. These failures can occur all along the innovation cycle. The principal research output needed is new and improved diagnostic tools, and treatments combined with disease specific implementation. This requires innovation and incentives all along the research and development/innovation cycle.

For the process to function smoothly, the steps must be linked, *i.e.* there must be efficient and timely hand-offs of ideas and candidate products between different phases. The over-riding goal of this system is to get safe, quality-verified, effective products, appropriate to the health systems in which they are to be used, to those that need them.

The economics of drug development

Developing new drugs is a complex, costly, risky and long-term enterprise. Some studies have pointed out that it costs anywhere between USD 800 million to USD 1 billion to develop a new drug up to the regulatory approval process (Kettler and White, 2003). On average, drug companies can spend over 13 years studying the benefits and risks of new

compounds and then out of about every 10 000 chemical compounds initially tested for their potential as new medicines only 1 will have what it takes to receive regulatory approval.

While developed countries offer viable market incentives for research and development through individual purchasing power and purchasing through government-run health insurance programmes, in developing countries these mechanisms do not provide sufficient purchasing power to make markets viable (*e.g.* in Europe these mechanisms cover two-thirds of drug costs for 80%-100% of the population as opposed to 35% in Latin America and less than 8% in Africa) (Trouiller *et al.*, 2002).

With public spending on drugs at around USD 239 per person per annum in OECD countries, the pharmaceutical industry has a strong incentive to develop drugs for this market. By contrast, most developing countries spend less that USD 20 per person per year on *all* health programmes and in sub-Saharan Africa it is less than USD 6 per person per year, including drug expenditures (Trouiller *et al.*, 2002). This is the result of a market too small to attract private-sector investment in research and development for diseases that mainly affect developing countries.

This may explain why in the past 25 years (as of 2004), 1 393 new chemical entities came on the market world wide. Of these, only 13 drugs (1%) were for tropical infectious diseases and 3 were for tuberculosis. Of the 13 drugs, 10 were developed for veterinary or military purposes, leaving only 3 that were the result of genuine efforts to create new drugs for neglected diseases (Burri, 2004).

So, while 85% of the world's population live in developing countries, 90% of the USD 70 billion per year devoted to health research and development was spent on the diseases of developed countries and only 10% was spent on the diseases uniquely afflicting poor or developing countries (Jamison *et al.*, 2006).

The reality is that market forces alone will not lead to the development of new technologies for the diseases of the poor. If we are to tackle the issue of neglected infectious diseases that mainly affect developing countries, present structures and ways of doing and financing innovation must be examined.

Why is the OECD interested in neglected and emerging infectious diseases that mainly affect developing countries?

There are many reasons why the OECD has an interest in looking for solutions to combat neglected and emerging infectious diseases that mainly affect developing countries. The reasons for OECD involvement include ethical, humanitarian, health and economic concerns.

Clearly, OECD countries have to pay attention to their own health needs. A new infectious disease emerges on average every eight months and for many existing infectious diseases, drug resistance has become a serious problem. There have been 35 newly discovered infectious diseases during the past 25 years and more than 190 documented human infections with potentially pandemic influenza viruses. This is the first time in history that so many new infectious diseases have emerged in such a short period of time and it is commonly believed that novel infectious diseases will emerge with increased frequency during the 21st century (European Commission and European Federation of Pharmaceutical Industries and Associations, 2006).

In our interdependent and global economies, emerging infectious diseases can have large health and economic consequences. Pathogens know no borders and with the growing global population, overcrowded cities, rapid expansion in trade, foreign investment and international travel, infectious diseases spread faster than ever, and can impact health, economic growth and the security of OECD countries. Geographical distances no longer present barriers and disease born in any part of the world can become a global threat in a matter of hours (*e.g.* severe acute respiratory syndrome [SARS], which was first detected in southern China, spread within five months to 28 countries with estimated costs of USD 10-30 billion).

Given the globalisation of food production and distribution and the fact that over 75% of emerging infectious agents are from zoonotic sources (Molyneux, 2004), food security and agro terrorism are issues that OECD countries need to pay attention to. OECD countries are also concerned about security issues raised by biological terrorism, either with genetically engineered pathogens or with pathogens natural to the environment that took years to eradicate (*e.g.* smallpox) (Jamison *et al.*, 2006).

OECD countries and multilateral institutions give USD 55 billion in overseas development aid. As aid donors and with increased commitments to assist low-income countries with their development agenda, the OECD through the Development Assistance Committee (DAC) is very much interested in improving the effectiveness of development assistance and aligning aid to the needs of recipient countries, including in the field of

health. Efforts to promote "policy coherence" so that various national policies (*e.g.* development aid, trade, finance, innovation, health and technology) are mutually reinforcing rather than inconsistent have also been launched. The aims of policy coherence are best accomplished where different players agree on ultimate goals and understand where their activities fit into the bigger picture of development.

Policy coherence for control of neglected infectious diseases (and for many other problems) is very complex. Policies, and the strategies and activities through which they are implemented, need to be mutually compatible at many levels:

- among agencies and sectors in individual OECD countries;
- among agencies and sectors in individual low- and middle-income countries;
- across contributors to development aid;
- across developing countries;
- among "international" non-governmental organisations (NGOs), and between them and aid donors;
- between providers and recipients of development aid;
- among private for-profit entities (as far as possible) and between them and governments;
- globally across public and private sectors (as far as possible).

There are also economic reasons driving OECD country involvement. Widespread infectious diseases not only reduce output and incomes of developing countries but also reduce their contribution to growth in world trade and foreign investment. In many developing countries, non-communicable diseases play a key role in the disease burden with rates comparable to those in OECD countries. Trends over time reflect increases in infectious diseases in Africa and increases in non-communicable diseases in other developing countries. It is estimated that by 2030, HIV/AIDS is expected to be the leading global cause of disability adjusted life years (DALYs) followed by depression, ischaemic health disease and perinatal conditions (Global Forum for Health Research, 2006). Treatments for diseases that are mainly prevalent in OECD countries will also need to be tackled in developing countries and, as such, we need to find ways of making the innovation system more efficient so that ways can be found to make all drugs, vaccines and diagnostics quicker and cheaper.

Over the last ten years, the drug discovery and development process has become increasingly lengthy and expensive; a problem compounded by the fact that there has been a decline in the number of new drugs discovered and introduced in medical practice globally. Despite tremendous advances in basic research and enormous expenditures on biomedical research, pharmaceutical innovation is no more efficient now than it was two decades ago.

The diminishing productivity of the pharmaceutical sector has led to a re-evaluation of the drug discovery process. Many stakeholders are actively searching for solutions to increase the efficiency of the innovation process to ensure the continued emergence of effective new medical products. It has become evident that there is a need for new tools and approaches in order to make more informed choices throughout the drug discovery and development process, particularly in the translation of early stage projects into medicines that meet public health needs. Developing treatments and preventions for neglected infectious diseases will yield innovation lessons relevant to diseases in both developing and developed countries.

To quickly deliver new medicines to market at reduced costs, we need to create efficiencies in the innovation cycle. While important for developing medicines for developing countries, this is increasingly important in advanced countries where the environment is changing for innovation, due to:

- greater competition, shorter product lifecycles and shorter time to market, with growing costs and risks of innovation;
- markets for medicines shrinking and fragmenting as targeted and genomic technologies and interventions grow.

So, it would seem that many of the policies and practices being put in place to enhance the availability of drugs, vaccines and diagnostics for neglected infectious diseases will also be relevant for disease markets in advanced industrialised countries.

It is clear that it is in everyone's interest to examine the innovation system for efficiencies and effectiveness and to look to alternative models and mechanisms for achieving this. In recent years a number of policy mechanisms have been introduced to spur innovation. The following chapter reviews some of the policy solutions that have been undertaken.

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Chapter 3

Present Policy Solutions Being Used to Address the Problems of Neglected Infectious Diseases

This chapter provides an overview of "push" and "pull" mechanisms being experimented with to bring new health technologies on to the market. Push mechanisms include both product development public-private partnerships and targeted R&D tax credits. Pull mechanisms include: advance market commitments; fast-track regulatory approval; patent extensions; pharmaceutical industry involvement; and financing mechanisms, such as the International Finance Facility, the currency transaction development levy, an airline tax, and the healthcare funding framework.

Push and pull mechanisms are complementary models. Most commentators conclude that a combination of push, pull and PDP mechanisms is desirable and that the optimal mix may vary among different desired products and their stages of development.

In the past decade, various policy solutions have been undertaken to deal with the issue of infectious diseases that disproportionately affect developing countries. These mechanisms have been generally grouped into categories based on their principal intent. For diseases in developed countries, combinations of the mechanisms ("push" – reduces R&D costs and generates basic research; and "pull" – market demand for products that result from the research) provide the incentives for pharmaceutical and biotechnology companies to invest in research. Usually the push funding for basic research comes from government or the private sector, while the profits from markets provide the pull or incentive to translate basic research into useable products. The theory is that these same mechanisms should work when applied to medicines, vaccines and diagnostics for infectious diseases that mainly affect developing countries – where push funding is provided by various public private partnerships and pull funding is provided by governments and philanthropic institutions (Annex C).

Push and pull mechanisms

Push mechanisms provide incentives at the front end of the innovation cycle. They focus on encouraging research generally, rather than on delivery of specific end products. Push mechanisms are designed to reduce the costs or risks of product development (that are usually faced by commercial companies) and are most effective when they can push a particular line of research or when there is a clear technological path for research and development (R&D). Examples of some push mechanisms include product development public-private partnerships (PDPs), increased funding for basic research or product development, tax credits and strengthening prospective clinical trials sites. Interventions that reduce impediments or remove barriers in the R&D phase also fall into the "push" category. These include clarifying, expediting and harmonising different national regulatory pathways and assisting with testing protocols.

Push mechanisms are effective in pushing a particular line of research and can save time and avoid duplication. Some issues with push mechanisms include the fact that because they pay for research inputs rather than product output, funders must make decisions about where to commit funds before products are developed. Funders may not always have the expertise to judge which scientific approaches are most promising and as such have to depend on researchers to guide them. Another issue with push mechanisms is that while research can be spurred, this is not enough to produce a product and get it into the marketplace. That being said, push programmes have produced positive returns that would not have been

possible without the incentives to invest in research in the field of neglected infectious diseases (Annex C).

Pull mechanisms provide incentives for development and manufacture of useable technologies, usually towards the end of the innovation cycle. They provide motivation for product development and manufacture by creating a market, providing other economic rewards or removing economic deterrents. Pull mechanisms are most effective when there is no clear technological pathway for research and development (Annex C). The goal with pull mechanisms is to generate a wide variety of discovery efforts in a competitive process. Pull mechanisms are politically attractive because they address a specific need, are outcome-oriented and are bounded by time and expense (Callan and Gillespie, 2007).

Some pull mechanisms, such as other types of market assurances, can take various forms, including long-term purchase contracts. Some pull interventions include advance market commitments (AMCs), prizes of various types, market exclusivity (as used in US Orphan Drug legislation), patent extensions or expedited processing of regulatory applications.

Pull mechanisms, such as improved demand forecasting as recently addressed by the Washington-based Center for Global Development (2007) essentially operate by reducing the uncertainty in product demand that deters commercial engagement because of the risk of financial loss. Improved demand forecasting would also benefit purchasers in that there would be a more reliable supply and probably better prices – a "win-win" for both the public and private sectors.

Some issues with pull mechanisms are that there must be an ability to specify outcomes or describe a product beforehand. This is difficult to do with innovation and therefore pull products are not generally good at stimulating basic research. In addition, market pull alone does not appear to be enough to facilitate the timely uptake of new products in developing countries.

Examples of push mechanisms

Product development public-private partnerships

PDPs are used as financing mechanisms for targeted research and usually focus on a range of candidate products rather than a single product. Most PDPs make strategic and targeted investments in research centres (industry or academic) to develop a pipeline of drugs or vaccines. Different PDPs use different strategies for funding, managing and doing research

(Kettler and White, 2003). The necessary expertise and composition of teams to move candidates through different stages in the R&D process is large (Widdus and White, 2004) and, as such, most PDPs are usually organised on a virtual R&D model. In this model, the PDP manages the research and development process but funds external partners to do the work. PDPs involve a variety of arrangements and vary as to participants, legal arrangements and status, governance, management, how policy is set, operations and funding (Widdus, 2001). PDPs are models of co-ordination and integration that usually span multiple partners, including funders, pharmaceutical companies, academic research centres, laboratories, etc.

PDPs present a structure that harnesses the strengths of various sectors (public and private) and helps enable the crossing of traditional boundaries. The public sector brings access to public funding, researchers and academia. The private sector brings expertise in clinical trials, intellectual property, business expertise and best practices in quality management (*Médecins Sans Frontières*, 2005). PDPs are generally funded by private foundations and philanthropic or charitable trusts (*e.g.* Rockefeller Foundation, Bill and Melinda Gates Foundation).

While PDPs channel new funds to R&D, they also add other valuable contributions to the picture. In marshalling scientific expertise to manage portfolios rather than individual promising products, they assist in weeding out less useful investments and manage the risk of failure that accompanies individual projects. They also help in ensuring action to move the promising candidates along the R&D continuum. Many PDPs address the question of timely introduction of new products. Some, such as the Meningitis Vaccine Project (MVP), a partnership between the World Health Organization (WHO) and the Program for Appropriate Technology in Health (PATH),[1] also create markets for a defined period. Some PDPs probably could be considered as spanning push and pull types of intervention, as well as progressing candidate products.

With PDPs such as the Malaria Vaccine Initiative (MVI), the International AIDS Vaccine Initiative (IAVI), the Institute for OneWorld Health (IOWH) and the Global Alliance for Vaccine Initiative (GAVI), the prospects for producing products to address neglected diseases has been greatly improved. That being said, there are some issues with PDPs that prevent them from being considered as sole mechanisms for addressing the issue. Firstly, their financial resources are still too small to fund the development of the number of candidate medicines that are required. Secondly, most PDPs do not fund activities that translate basic ideas from research into products (Annex C). This type of activity is reliant on major biomedical research funders (Widdus and White, 2004) and speaks to a need

to continue to support, and adequately fund, basic research in the field of neglected and emerging infectious diseases.

Targeted R&D tax credits

This mechanism gives tax credits for research into neglected diseases (*e.g.* proposed US Vaccines for the New Millennium Act 2001, which proposed a 30% tax credit for R&D expenditures on vaccines for HIV, malaria and tuberculosis). Like most push mechanisms, R&D tax credits provide incentive for research inputs rather than the development of useable products. This mechanism does not help developing countries improve access to drugs or vaccines as it does nothing to control the price of the product or its affordability for poor populations. The tax credit also does not restrict the research into typology of diseases prevalent in developing countries (*e.g.* HIV, malaria and TB affect people in developed countries, but these strains can be different from the strains affecting developing world populations) and, as such, vaccines could be developed and marketed to populations in developed countries. As well, R&D tax credits are difficult to administer and complex to track for accounting purposes and do not help small biotechnology in the start-up phases as they usually have no current profits or tax liabilities.

Examples of pull mechanisms

Advance market commitments

AMCs seek to create incentives for R&D and ensure that prices are low enough to enable access to products for poor countries. With AMCs, donors commit to fully or partially financing the purchase of a product (vaccine, drug) targeted at developing countries, only when it is developed. Standards and criteria are set out which must be met, and the price of purchase is pre-set or guaranteed, as is the number of units to be purchased. If a product is developed, then poor countries decide whether to purchase the product and pay a low and affordable price for it. Sponsors of the AMC then top up this price to meet the guaranteed price specified to the developer. This provides market returns to the developer equal to sales revenues earned by average new medicines. In this agreement, once the number of guaranteed units is purchased, the manufacturer is obliged to sell any further products at low, affordable prices in the long term (Annex C).

With neglected infectious diseases that primarily affect developing countries, there is not a profitable market to provide incentive for private-

sector industry to transfer basic research into useable products. AMCs are an attempt to incentivise this part of the drug development pipeline. Some of the advantages of AMCs are that they reduce some of the risks of developing drugs specific to markets in developing countries, and if structured properly can ensure that vaccines and drugs, once developed, are made available to developing countries quickly and affordably. One of the major advantages of AMCs is that donor funds are only spent when the specified product is developed.

Some analysts believe that AMCs are an attractive tool as they could leverage the public financial commitment to attract additional private investment. Since AMCs are a market-based form of intervention that encourages entry, competition and continued motivation, it is theoretically market forces rather than donors that determine the allocation of investment (Annex C). Other analysts believe that the AMC is not like a market but is a long-term contract best aimed at late-stage and existing vaccines, not at research for development of new vaccines, and that it is a slower, less efficient way to incentivise research (Light, 2005). Other criticisms of the model say that the way it is set up would most probably lead to a vaccine being developed that would not be as high quality or effective, especially for early stage vaccines, as the model assumes that the science and business for developing vaccines is a fixed, linear model of innovation, whereas the innovation process is much more complex than the AMC assumes. There are also questions as to whether AMCs stifle innovation as they create a "winner takes all" solution (Farlow, 2006), making the development of incremental follow-on improvements to the product difficult (Farlow, 2005).

All commentators believe that AMCs are not an alternative to other pull mechanisms, but are complementary to other initiatives, especially when paired with push initiatives such as public and philanthropic financing of basic research through academia, PDPs and other bodies. These result in the formation of networks which increase the number of scientific researchers working on neglected diseases. In addition, AMCs could be a complement to public and charitable funding of basic research that could buy vaccines or drugs at lower prices.

AMCs have been gathering momentum and in December 2006, the G7 Finance Ministers announced an agreement to work on developing a pilot AMC. In February 2007, five countries (Canada, Italy, Norway, Russia and United Kingdom), along with the Bill and Melinda Gates Foundation, committed USD 1.5 billion to launch the first pilot AMC that targets the development of a vaccine for pneumococcal disease. A malaria-vaccine AMC is also being planned.

It is still too early to tell whether AMCs will demonstrate efficacy and cost effectiveness. Given the questions about some aspects of AMCs as they are presently constructed, it is imperative to have metrics to evaluate the pilot AMC on a number of fronts, including those set out in a report to the G8 Ministers on AMCs (Tremonti, 2005), which included the following elements:

- reliability in the eyes of industry,
- appropriate incentive structure,
- ability to spur innovation on subsequent improved vaccines,
- long-term sustainability,
- ability to create sufficient market size,
- effective access to those who need it,
- public health impact.

A number of other metrics should also be developed to measure cost effectiveness, quality of product, risk reduction, avoidance of duplication, comparison with other mechanisms, etc.

Fast-track regulatory approval

The priority review voucher is a mechanism that is included in the Neglected Diseases Amendment to the Food and Drug Administration (FDA) Revitalization Act that was signed into law in the United States on 27 September 2007. This amendment creates an incentive for pharmaceutical companies to invest in developing treatments for neglected diseases. The amendment provides a financial market incentive by rewarding pharmaceutical companies with a priority review voucher. The FDA is authorised to award a priority review voucher to the manufacturer of an approved drug or vaccine targeted to neglected infectious diseases (BIO Ventures for Global Health, 2007). The priority review voucher is transferable and can be applied to any drug in the company's production pipeline. It significantly reduces the FDA review time from approximately 18 months to 6 months. It has been estimated that the 12-month shorter review process would be worth more than USD 300 million if applied to the top 10% grossing drugs (Brownback, 2007). It is hoped that this amendment will spur pharmaceutical manufacturers to develop drugs and vaccines that will help the developing world treat, diagnose and prevent infectious diseases.

Patent extensions

Patent extensions compensate developers of products for neglected diseases by extending the patent rights on another product in their portfolio. This type of mechanism could be attractive to large pharmaceutical companies who have "blockbuster" products in their portfolio, where extending the patent rights on them could be very lucrative. This type of mechanism also potentially appeals to governments, who would not have to expend funding *per se*. This mechanism however, puts smaller companies and biotechnology start-ups at a disadvantage, as they do not in all likelihood have existing patents on useable products. This mechanism also places the burden of financing the scheme on consumers who would not have access to the cheaper, generic drug while the patent was extended. In countries with national health insurance systems, this mechanism may also create some burden on governments who usually pay for some drugs for certain populations.

Pharmaceutical industry involvement

The involvement of the pharmaceutical and biotechnology industry in the fight against neglected infectious diseases is crucial. Industry has the expertise, know-how and experience to develop the drugs, vaccines and diagnostics required. Industry is increasingly pursuing development or delivery of products to combat neglected diseases. Some companies have established research institutes dedicated to R&D of products for neglected diseases in collaboration with governments (*e.g.* Novartis and the Government of Singapore) or as in-house activities (GlaxoSmithKline, Novartis, AstraZeneca and Sanofi-Aventis). Some companies (*e.g.* Pfizer) have entered into agreements with the World Health Organization (WHO) for the screening of large compound libraries to discover drug leads; others partner with PDPs in drug development; and finally some companies collaborate with the governments of disease endemic countries (DECs) to control specific diseases (*e.g.* blinding trachoma).

Multinational drug companies conduct about half of the neglected drug development activity through collaborations. These companies work on a non-commercial basis and provide the final products to developing countries for not-for-profit prices (Moran *et al*., 2005). Multinational companies also donate existing products to patients in developing countries.

An International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) survey conducted in 2005, and verified by the London School of Economics and Political Science in 2006, reported 126 health partnerships providing up to 539 positive health interventions

with a value of USD 4.38 billion. The survey defined positive health intervention as the delivery of sufficient medicine to cure one person of one disease; the provision of a course of therapy sufficient to manage one disorder in one person for one year; the provision of sufficient vaccine to immunise one person against one disease for at least one year; and the delivery of a proven programme of health education to one person (Kanavos, Hockley and Rudisill, 2006).

When deciding to enter into partnerships in PDPs, multinational pharmaceutical companies are motivated by considerations such as: an opportunity to improve their reputation; social responsibility and humanitarian concerns; strategic business considerations such as the opportunity to get into developing country market; and the opportunity to experiment with the development of new business models. The model being used by the pharmaceutical companies in their involvement in PDPs is called "not-for-profit not-for-loss". This model allows commercial companies to be involved in activities that will not generate profits while protecting the interests of their shareholders. The advantages of this model is that it provides a source of high-quality innovative industry drug leads, sometimes uses developing country clinical trials, and provides developing countries with products at not-for-profit prices (Moran, 2005).

Financing mechanisms

Insufficient, short-term and unpredictable funding undermines the prospects for sustainable success of PDPs. There is a disconnect between the likely timeframes for pharmaceutical innovation and health system strengthening and the timing for development aid. This presents an issue for the development of new products. Pharmaceutical innovation typically takes well over a decade and a similar timeframe is likely necessary to achieve significant improvements in health systems delivery. However, the majority of relevant funding streams have at most a five-year limit and many are shorter. In addition, the level of funding is often unpredictable, year to year.

This situation creates a range of difficulties for various players contributing to neglected disease control. PDPs face uncertainty as to whether they will be able to complete development of promising new products, which in turn may discourage partners from entering collaborations. Uncertainty over the sustainability of funding, for example from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM),[2] may deter or delay introduction of new and better products, as was the case for artemisinin combination therapy (ACT) anti-malarials, even though old products were not effective for many patients. Unpredictability of funding makes incorporation of development aid into national budgets in developing

countries difficult, and planning to expand health services must therefore necessarily be under-ambitious.

It has been recognised that reliance on philanthropic and public funding is not sustainable as these sources can be endangered by a shift in priorities. To that end, new and innovative funding mechanisms have been put forward to help generate more sustainable and longer term resources. These are considered mostly as pull mechanisms, and include the following.

International Finance Facility

The International Finance Facility (IFF) is a UK-founded initiative that is based on government-backed securitisation. The IFF is built on long-term donor commitments, made up of pledges for a flow of annual payments to the IFF. On the basis of these commitments, the Facility leverages resources for aid by issuing bonds in international capital markets. In this way, there is a predictable and stable flow of aid to help finance investment in development. The IFF has been piloted (via the IFF for Immunization, IFFim) for long-term guaranteed vaccine purchase.

Currency transaction development levy

The currency transaction development levy (CTDL) (Brown, 2007) is a mechanism put forward by the Norwegian Ministry of Foreign Affairs' Stamp Out Poverty programme and proposes to introduce a small levy (less than 100^{th} of 1%) on currency transactions (Hillman, Kapoor and Spratt, 2006). By taking this small slice off the top of currency markets, it is postulated that there is the opportunity to generate billions of dollars that can be redirected to achieve sustainable development. The proposal suggests that such a levy is simple, inexpensive to apply and can be generalised to apply to other financial markets such as equity markets.

Airline tax

An airline tax was initiated by France with (approximately 19) other countries joining in 2006. This mechanism has governments levying a small tax on airline tickets and the proceeds from the tax are held by UNITAID (International Drug Purchase Facility). These funds are then used to accelerate access to high-quality drugs and diagnostics for HIV/AIDS, malaria and tuberculosis in countries with a high burden of these diseases.

Healthcare funding framework

The healthcare funding framework (HFF) is a mechanism put forward by SecureAid (Brown, 2007) and proposes to use the securitisation methods used by the IFF to manage portfolios of new medicines in order to remove funding bottlenecks for clinical development. This meets the needs of research and builds pipelines of new medicines and diagnostics for neglected infectious diseases.

These securitisation approaches can be applied to other long-term financing needs, such as product development and introduction, as well as to health system strengthening.

Conclusion

The push and pull mechanisms being experimented with to bring new health technologies on to the market are complementary models. Most commentators conclude that a combination of push, pull and PDP mechanisms is desirable and that the optimal mix may vary among different desired products and their stages of development. The consensus is that there is no single magic bullet. Variables such as the technology being used, the disease targeted market differential, type of firm involved, and cost differentials across diseases and technology make it is difficult to generalise as to what particular mechanism or combination of mechanisms will work in all circumstances. Also, since many different products are needed to combat neglected diseases, attempts to fine-tune interventions to specific products as problems arise would likely result in a burdensome product-by-product workload, delays and possibly escalating costs. The most promising strategy would appear to be to establish both broadly applicable push and pull mechanisms that can be utilised as necessary by PDPs as early as possible. From the experience of PDPs, it would appear that it is extremely critical and important that there be assurance of a market from the outset.

While their intent is to encourage the movement of candidate products through the innovation cycle, push and pull interventions do not do this *per se*: they must act through incentivising those capable of doing this. Many factors, both scientific and economic, go into decisions concerning where to engage. Thus, evaluation and examination of these mechanisms is necessary.

A combination of push and pull mechanisms, if designed and implemented correctly, should in theory facilitate the development of new vaccines and drugs for infectious diseases. As yet, these mechanisms are still too new to know what an optimal mix of mechanisms will be most effective and where best in the R&D innovation cycle they should be

positioned. As such, it is important that these mechanisms be evaluated against a set of agreed upon metrics so that the different incentives can be mixed and tailored for the broad range of diseases and treatments required. It is also important that these mechanisms be evaluated to show that they are a sound investment if they are to receive increased funding.

Push and pull policy mechanisms do little, however, to create efficiencies in the innovation cycle. Health innovation is an interactive and distributed process with many stages, including: identification of need, research and development, translational research/commercialisation, delivery and diffusion. These stages should be considered circular and iterative, rather than separate and linear.

The bio-medical research community, bio-pharmaceutical industry, and the medical service economy are closely linked. Health innovation is tightly connected to the provision, uptake and use of new treatments: feedback from purchasers, providers and patients is essential in shaping the innovation process. Feedback mechanisms are built in throughout this innovation cycle, and are the source of modifications that improve individual products and enhance innovative capacity as a whole.

Innovation needs to occur on the R&D side as well as bring together the processes and systems that facilitate getting technology to the patient. Not only should financing be aligned with demand, but there should be an understanding of how the supply chain works as well as a mechanism to encourage all the institutions, sectors and actors to work together (Grace, 2006).

In order to increase the availability of new medicines, participants at the High-Level Forum on Policy Coherence: Availability of Medicines for Neglected and Emerging Infectious Diseases agreed that there is a need to improve the efficiency of the innovation system, which at present fails to deliver a robust pipeline of new medicines, vaccines and diagnostics for the neglected diseases of the developing world. It was stressed that there was a need for innovation to occur throughout the product cycle, from basic research through to delivery to the patient.

Notes

1. See *www.meningitisvaccine.org*.
2. See *www.theglobalfund.org/en/*.

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Chapter 4

Moving Forward: Solutions and Next Steps

This chapter presents the Noordwijk Medicines Agenda (NMA), which puts forward a set of concrete actions and policy options to promote, in a coherent manner, an open innovation strategy that can deliver new generations of drugs, vaccines and diagnostics for neglected infectious diseases.

The chapter highlights what the OECD can bring to this issue and sets out the following areas for action: policy coherence; basic research; new models and policy mechanisms; more open innovation; collaborative mechanisms; global virtual collaborative drug development network; other areas requiring innovation, including regulatory approaches and new technologies and processes; building capacity in disease endemic countries; financing mechanisms; and delivery systems.

The message from the NMA is that no one can do this alone; there needs to be more partnerships, networks and policy coherence to achieve the common goals of developing an innovation system that can deal with today's challenges. This is an opportunity for governments to drive a health innovation strategy that is more efficient and responsive to global public health needs.

The Noordwijk Medicines Agenda

The Noordwijk Medicines Agenda (NMA) that was agreed by all participants and countries at the OECD High-Level Forum on Policy Coherence: Availability of Medicines for Neglected and Emerging Infectious Diseases (the "HLF") sets out specific actions for moving forward to build strong international support for accelerating the development and delivery of new medicines, vaccines and diagnostic tests for diseases that disproportionately affect developing countries. While participants at the forum agreed that many of the health issues affecting developing countries will not be solved by new medical technologies alone, they agreed that these are still crucial for attacking infectious diseases.

In order to improve the availability of new medicines, participants agreed that there is a need to improve the efficiency of the innovation system, which at present fails to deliver a robust pipeline of new medicines, vaccines and diagnostics for the neglected diseases of the developing world. Many of the suggested actions in the NMA are focussed on how to:

- make the health innovation system for infectious diseases more open;
- encourage more collaborative research;
- broaden the involvement of researchers, academic institutions, laboratories and companies globally in order to increase the efficiency and lower the costs of developing new, safe and effective medicines, vaccines and diagnostics.

The NMA calls for governments of OECD and developing countries to show political leadership and to join with a wide variety of stakeholders in multiple sectors to further intensify collaborative efforts and promote coherent policies to improve the availability of, and access to, medicines, vaccines and diagnostics for neglected and emerging infectious diseases. In particular, the NMA calls for

- prioritising research and development (R&D) needs and aligning research to a common purpose;
- pursuing the viability of a global virtual collaborative drug development network that draws on and scales up existing initiatives and is more open;.
- creating incentives for R&D through new alternative policy mechanisms to reward innovation;

- facilitating the development and operation of a sustainable architecture for sharing and exchanging knowledge, data and research tools;
- identifying infrastructure needs to underpin a global virtual collaborative network;
- exploring collaborative mechanisms for intellectual property (IP) management;
- promoting the transfer of technology, knowledge and technical skills to strengthen innovation systems in developing countries;
- forecasting accurate and effective demand of medical technologies for neglected and emerging infectious diseases;
- providing support and incentives to new for-profit and not-for-profit models of partnerships and networking among a variety of actors in developing and developed countries by building and sharing infrastructures and by encouraging more open innovation approaches in order to accelerate R&D for neglected infectious diseases.

The NMA recognises the importance of scaling up and expanding both for-profit and not-for-profit models of innovation that are coming out of the push and pull mechanisms being put forward to tackle neglected infectious diseases in the developing world. The NMA calls for changes in the way the present health innovation system is organised and carried out. It sets out some actions for driving a health innovation strategy that is more efficient and reactive to global public health needs. These actions have the potential to deliver a new generation of medicines for neglected diseases and will leave innovation systems in better shape to be able to deal with health challenges and continue to drive growth.

What the OECD can bring to this issue

Many of the actions contained in the NMA are aimed at the OECD, who in partnership with many other players (*e.g.* international organisations such as the World Health Organization [WHO], industry, non-governmental organisations, academia, etc.), has the expertise and experience to help to realise the actions set out in the NMA. The OECD can provide a strong foundation for evidence-based policy making. Its working methods encourage dialogue between different branches of government, a diverse set of industrial actors, and other parts of civil society including public research organisations, non-governmental organisations (NGOs) and philanthropies.

The added value that OECD brings to the issue of improving the availability of medicines for neglected and emerging infectious diseases is its:

- capacity for sound economic analysis and policy advice on the different policy options for action, including the scale up of R&D networks and the incentives necessary for bringing new products to market;
- understanding of the innovation system and groundbreaking work on new research models that could improve the efficiency of the discovery, development and delivery of new medicines by removing disincentives to sharing data and material and opening up innovation;
- ability to broker whole-of-government buy-in and build coherent policies, by virtue of the OECD organisational structure which includes cross-ministry representation (*i.e.* Health, Development and Aid, Finance, Innovation, Economic Development and Industry).

Areas for action

1. Policy coherence

Innovation is a multi-sectoral endeavour and speaks to a need for strong policy coherence. The issue of policy coherence is important in improving the availability of medicines since a number of policy areas need to be brought together in a coherent manner – including health, trade, science and technology, development co-operation and finance – in such a way as to create an environment that will spur both investments in, and efficiency of, research and product development. In turn, the availability of appropriate new health technologies could increase the effectiveness of development efforts for health.

Steps for control of infectious diseases would require a coherent, long-term policy for supporting control of neglected diseases that would include:

- delivery of existing products, but also attention to developing improved products for better disease control and replacement products, since the emergence of resistance is pretty much inevitable;
- support for strengthening developing country capacities for innovation since disease control is tied into a comprehensive and

coherent agenda through the commitment to ownership embodied in the Paris Declaration on Aid Effectiveness;[1]

- issues of international trade, domestic and foreign investment policies, technology transfer, taxation (*e.g.* R&D credits), etc.;
- consideration of private channels of drug distribution since so many people get their drugs through such systems but they are often ignored in public sector planning, (*e.g.* over 50% of malaria drugs are sought from private suppliers in many countries).

Any policy agenda designed to enhance control of neglected infectious diseases should logically be comprehensive if it is to be regarded as coherent since it is not rational to set goals and deliberately leave gaps in the way they are pursued. Further, such attention to improved and new products should probably include support for basic research as this is the foundation on which product innovation rests. Support for basic research as a contributor to combating neglected diseases is a policy coherence issue significantly removed in time from saving lives today, but is nonetheless a necessary part of the big picture.

Action

The OECD should consider commissioning the development of a conceptual framework for systematically identifying the spectrum of policy coherence issues relevant to control of neglected infectious diseases. This framework would need to take account of the lengthy time period required for product innovation and introduction, and would need to be broad in scope.

2. Basic research

As articulated in the NMA, there is a need to prioritise R&D and align research to a common purpose. With the increasing number of players, it is even more necessary to ensure that priorities in research are agreed upon and that research is organised toward a common goal. It was suggested that it was necessary for the WHO, along with other partners, to map the needs for neglected diseases innovation and provide information on what is being done so that R&D could be prioritised.

The HLF and the preparatory workshops noted that historically low levels of investment in basic research for certain neglected diseases is a problem and has led to a dearth of fundamentally new ideas for tackling these diseases. As well, translational research is difficult for neglected diseases and has also been underfunded by public sources and, until

recently, has not been of interest to commercial companies. Product development public-private partnerships (PDPs) typically do not undertake these activities, concentrating mostly on clinical phases for product development. While PDPs are important and need to be supported, they are not enough.

PDPs do not have large openings at the start of the pipeline where basic research takes place. Thus, there is a gap at the level of basic sciences and the point where PDPs might embrace science and take the risk of developing it further. While the pipeline feeding the PDPs has been transformed and there are drugs in the pipeline that were not there five years ago, given the attrition rate, the need for new compounds with new mechanisms of action, and the fact that resistance to available drugs is always an issue, new drugs are always required. As such, PDP pipeline feeding can still be considered weak and fragile.

With a weak pipeline, there is not an adequate and continuing supply of leads, which means that PDPs will not succeed in supplying new and replacement products. The HLF stressed the need for significantly increased attention to feeding the early pipeline of newly emerged PDPs. There was a consensus that basic research needed to be incentivised and that there was an important role for governments to play in this respect.

Therefore, there was a call for governments to strengthen the basic research base by continuing to support basic research at a substantial level and making basic research for neglected diseases a priority. There needs to be sustained efforts at the governmental level so that universities can have the resources to engage in basic research and develop it to a point where companies can take it and move it along the pipeline into products.

Academic institutions have an important role in the development of basic research and PDPs, which partner with academia and industry. PDPs help academics to tailor research to the needs of drug development for infectious diseases by bringing them in contact with industry scientists. This is needed since academic research rarely supports the kind of medicinal chemistry research that is required to produce a useable product (Butler, 2007).

In the early stages of research into medicines for neglected diseases, there is a need to share risk. Sustainable partnership may be part of the solution. A variety of approaches including ones based in or led by academia, pharmaceutical companies, "biotech" partnering, or international organisations need to be considered. Non-traditional partners such as patient groups, philanthropic organisations, small biotechnology and pharmaceutical companies should also be included.

Smaller companies may be more willing to explore innovative mechanisms to achieve the early funding they are dependent on. Further exploration of options (both for-profit and not-for-profit) is needed to assist the design of new and/or expanded systems to foster this type of innovation.

Action

OECD governments, along with their developing country partners, should strengthen the basic research base by providing substantial and continuous support for basic research. They should also make basic research for neglected diseases a priority by targeting funds to it.

3. New models and policy mechanisms

The NMA proposes that work be done to better understand and evaluate both for-profit and not-for-profit models of innovation in infectious diseases. In the past few years, various policy mechanisms and new models of R&D have been put in place to incentivise research and product development in infectious diseases (these include advance market commitments, prize fund models, different ways of valorising intellectual assets, public-private product development partnerships, etc.). Most of these assume a not-for-profit business model, but others could lead to new for-profit markets. Participants noted that more emphasis needs to be placed on for-profit incentive structures and R&D models because these could provide greater financial sustainability for R&D in infectious diseases.

There is a need to evaluate these new policy mechanisms in order to ascertain their strengths and limitations, evaluate how successful they are in practice, and understand what mix of mechanisms is necessary for what sorts of diseases or situations. It is hoped that a better understanding of the policies and incentives will lead to new R&D models, both on for-profit and not-for profit bases, that will accelerate the development of medicines, vaccines and diagnostics for neglected infectious diseases.

While participants in the High-Level Forum underscored the importance of the protection and use of intellectual property regimes (IPRs) for investment and research, they acknowledged that IPRs alone were not sufficient to stimulate innovation in infectious diseases and that complementary reward systems may play an important role as well.

Action

The OECD could play a role in the analysis and evaluation of these new policy mechanisms and research models. OECD contributions could include:

- evaluation and monitoring of alternative policy mechanisms to reward innovation (advance market commitments, prize fund models, valorisation of intellectual assets) in the development of health technologies for infectious diseases;
- identification of the strengths and limitations of alternative mechanisms to stimulate R&D in infectious diseases innovation, at different stages of the R&D cycle;
- monitoring of any pilot projects;
- development of metrics for social rates of return, in order to compare donor/philanthropy funding returns on investments in different initiatives including PDPs;
- identification and evaluation of for-profit and not-for profit models that promote innovation.

4. More open innovation

One of the NMA actions is the facilitation of partnerships and networking among a variety of actors by building and sharing infrastructures and by encouraging more open innovation approaches. The goal is to increase the number of industry and public laboratories involved in the research into and discovery of neglected diseases, and increase the efficiency and effectiveness of their efforts. If this is to be accomplished, a fundamental transformation of the innovation pathway is required (Callan and Gillespie, 2007).

During the past ten years, global R&D expenditures in pharmaceuticals and the biotechnology sector has steadily increased without a corresponding increase in the output of new medicines. This would indicate that the innovation system needs to be examined for new models (EFPIA, 2006). Partnerships and collaborations among players can help stimulate innovation and broader access to knowledge.

Changes in structure of the pharmaceutical industry have already occurred that encourage more open innovation. Pharmaceutical companies have been partnering with biotechnology companies to co-develop products. It is estimated that more than 50% of pharmaceutical revenues will come

from products that were discovered, researched and developed outside their organisation (Kettler and White, 2003).

A more open innovation system would provide a more open business environment for innovation that strikes a balance between stimulating innovation and providing broader access to knowledge. There are tools and networks that can promote easier, more open access to knowledge and innovative products and processes. Some of these tools are currently best known in the area of information and communications technologies.

PDPs operate on a more open innovation concept that they have combined with the outsourcing of knowledge, tools and compounds to create a relatively low-cost business model. PDPs increase the innovation pipeline by drawing on a wide range of expertise, know-how and capacity from industry as well as other sources like private laboratories. They generally use high, throughput screening of chemical compounds that come primarily from industrial libraries.

PDPs and other more open or networked innovation structures are transforming the supply side of drug development for neglected diseases by reducing the costs and increasing the global capacity for drug development. Taking PDPS as an example, the advantages of more open or networked structures are the ability to:

- co-ordinate and integrate multiple industry and academic partners along the drug development pipeline;
- allocate public and philanthropic funds to the right kind of R&D from a public health perspective;
- manage larger drug portfolios, including making decisions about the selection and termination of projects;
- use many different sources to develop compounds;
- foster a drug development pipeline that is far cheaper than a traditional commercial approach;
- build capacity scientific research and discovery and manufacturing in developing countries;
- yield more breakthrough innovation through the sharing and exchange of knowledge;
- integrate the development process across multiple partners;

- speed the discovery process (time metrics show that PDP drug development trajectories matched or exceeded industry standards and were significantly faster than public-alone drug development);
- produce cost savings and efficiency (Moran, 2005).

5. Collaborative mechanisms

To support new approaches to more open innovation and collaborative research, as well as access to knowledge, there is a need to improve the flow of information across organisations and accelerate learning in general, and in infectious diseases research enterprises in particular. To achieve this, collaborative mechanisms to facilitate broader access to and use of knowledge, data and inventions within a network need to be developed.

IP protections and IP management capacities

Open innovation systems are not intrinsically in conflict with IPRs. By far, the vast majority of participants at the HLF spoke of intellectual property protections as a potentially constructive tool in efforts to combat neglected diseases, if managed appropriately. As such, the NMA recognises that the protection and use of IPRs are important tools for fostering investment in R&D but that they may not be enough to stimulate innovation in the area of neglected infectious diseases. Most PDPs regarded the capacity for professional management of IP as a necessary asset in dealings with commercial companies and noted that companies had been willing to negotiate special arrangements for neglected diseases to promote access.

Some of the tools for managing the sharing of information include those discussed below.

Patent pools

Patent pools are an arrangement among multiple patent holders to aggregate their patents whereby all the pooled patents are available to each member of the network or pool. Where patent pools have been used successfully in other industries such as digital media, their use in the life sciences is relatively new. Patent pools could promote technology transfer and increase economic efficiencies. They might also provide a solution to multiple patent holders being able to block research or product development.

Information clearinghouses

Clearinghouses are central agencies that usually manage the collection, organisation, storage, and dissemination of information and resources for a particular group. Clearinghouses have also been used in the entertainment fields for the distribution of music, movies and software. Their main function is to serve as a link between creators and users of copyrighted works to ensure that the owners of rights receive payment for their works. Different types of clearinghouses need to be explored in terms of what would be most appropriate and work to stimulate more open innovation. At the Preparatory Workshop, it was felt that the creation of an information clearinghouse of ongoing R&D to reduce duplication of efforts in the field of neglected infectious diseases would be helpful.

Networks and consortia

Participants at the HLF and the Preparatory Workshops agreed that innovation was considered most likely to flourish when systems and processes:

- were more open in that they were specifically designed to foster access to, and exchange of, knowledge, data and research tools;
- maximised opportunities for all relevant intellectual inputs, whether from public or private sectors, developing or industrialised countries.

Such systems operating at the pre-competitive phase of commercial product development must include industry involvement. An example of a pre-competitive research project is one where research is aimed at providing the tools, information and data that enable competing companies to develop and register future products and services. Some examples of this type of consortia or network include the Protein Kinase Research Consortium,[2] the SNP consortium[3] and the Haplotype Consortium,[4] all of which serve a range of commercial companies.

For neglected infectious diseases, the NMA suggests pursuing the viability of a global virtual collaborative drug development network which draws on existing partnerships and consortia initiatives, and is more open**.** This virtual global network is explored in more detail in the next section.

Technology transfer offices

One of the issues that came up at both the Preparatory Workshops and the HLF concerning academic research was the focus that universities have on a reward culture that excessively stresses patents and publication. The emphasis that universities are putting on wealth creation by patenting everything that their researchers come across means that can make it unaffordable for groups wanting to translate this basic research into drugs or vaccines for neglected diseases. Researchers noted that technology-transfer offices in universities tend to measure the success of research by the number of patents, licenses and amount of revenue generated. This can pressure scientists into directions of research that are not conducive to improving neglected diseases. Universities, as has been demonstrated by University of California, Berkley in the United States, may need to look at measuring success by the social impacts of its intellectual property and not just the economic gains that can be realised (Butler, 2007).

Action

Participants in the High-Level Forum underscored the importance of fostering a more open environment for innovation. New approaches to more open innovation and collaborative research, as well as access to knowledge, were seen as important to further increase the efficiency and lower the costs of developing new, safe and effective health technologies. Participants agreed that work needs to be undertaken with regard to how collaborative mechanisms for access to, and use of, intellectual property improve the flow of information across organisations, and how to accelerate learning in general and in the infectious diseases research enterprise in particular.

What is needed is the development and operation of a sustainable architecture for the sharing knowledge, data and research tools. The OECD has already undertaken work on collaborative mechanisms and could expand this work to include the actions set out in the NMA with regard to the exploration and evaluation of for-profit and not-for profit models to promote more open innovation, in particular:

- exploring the potential value of sustainable collaborative mechanisms (such as patent pools or other IP and data management entities);
- identifying the potential use of existing flexibilities in multilateral agreements to foster innovation and access;

- strengthening the capability of developing countries to manage issues of intellectual property including outreach to developing countries on the lessons learned about IP management in a context of more open innovation.

In addition, during the preparatory Workshop on Accelerating Neglected Diseases Drug Discovery, participants suggested that OECD work in this area could also:

- identify the disincentives to sharing information and intellectual assets and suggest how to remove these disincentives;
- explain how voluntary knowledge markets and collaborative mechanisms can encourage the sharing of knowledge that might otherwise be kept secret;
- develop policy advice on how to improve the IP management practices of technology transfer offices;
- examine how funding bodies could encourage participation in more open innovation models or discovery networks, for example through grant criteria.

6. Global virtual collaborative drug development network

One key NMA action is to pursue the viability of a global virtual collaborative drug development network which draws on existing partnerships and consortia initiatives, and is more open**.** The purpose of such a network would be to rapidly and efficiently create a sustainable pipeline of innovative new drug candidates to enter development into medicines, vaccines and diagnostics for infectious diseases.

The idea would be to draw on existing initiatives (*e.g.* WHO Special Programme for Research and Training in Tropical Diseases [TDR], PDPs and regional [*e.g.* south-south and north-south] technology networks) and be more open and on a larger scale.

The TDR[5] is an independent global programme for scientific collaboration that aims to help co-ordinate, support and influence global efforts to combat a portfolio of major diseases of the poor and disadvantaged. TDR is developing virtual drug-discovery capacity by using a series of portfolio, screening and medicinal chemistry networks.

The TDR has two objectives:

- research and development to improve existing, and develop new, approaches to preventing, controlling, treating and diagnosing neglected infectious diseases;
- training and strengthening the capacity of developing endemic countries (DECs) so that they can undertake the research required to develop and implement new and improved disease control approaches.

The TDR works as a facilitator of global research and training by providing direction and resources for research priorities and opportunities. It works in partnership with other organisations such as government ministries, research institutions, academia, industry and non-governmental organisations in a virtual network.

Working in virtual R&D networks provides many opportunities, including the bringing together of specialist facilities and disease experts who are able to work in a co-ordinated manner to screen multiple drug-discovery groups and compounds (Hopkins, Witty and Nwaka, 2007). This increases the efficiency as well as the likelihood of identifying the right targets.

The virtual networks working in the area of neglected infectious diseases are functioning on a small scale. These networks need to be scaled up to make them sustainable and viable. This would lead to a co-ordinated effort that could leverage joint public and private investment to create synergies between scientific knowledge and capabilities. Bringing together many more partners from the pharmaceutical and biotechnology industries, non-governmental organisations and the public sector would allow everyone to contribute specific expertise and scale up the effort considerably.

A scaled-up network would mobilise resources and expertise from industry, academia and public and private research institutes globally. Specialists from different disciplines and institutions would work to a common mission through a virtual, voluntary collaborative framework. The network would scale up capacity in infectious diseases by:

- identifying priority research needs;
- facilitating participation by researchers world wide through discrete research modules;
- creating economies of scale by identifying common infrastructures, know-how, platforms and by building and sharing common research tools;

- exchanging data, knowledge and research outcomes so as to improve interdisciplinary and cumulative learning;
- creating a framework to facilitate voluntary contributions of advice, skills and infrastructure access from researchers in industry and the public sector;
- developing a portfolio of prioritised discovery projects that could identify a set of discrete research tasks for each project, which would help to match tasks to the competence of participants;
- using collaborative mechanisms to facilitate the flow of information within the network by simplifying access to, and use of intellectual property regimes.

Infrastructure requirements

A scaled-up initiative would require the identification of infrastructure needs required to underpin such a global virtual collaborative network. In order to scale up, there are a number of issues that would need to be addressed, including:

- managerial governance to agree on priorities and co-ordinate the various participants working at a distance;
- negotiated access to proprietary knowledge and infrastructures;
- standard collaboration and licensing agreements;
- interoperability of data to assure participant access and linkage from a common platform;
- sustainable financing;
- human capital, for example: sponsored researchers from industry, developing country researchers.

Participants at the HLF proposed that the viability of a global, virtual collaborative drug development network which draws on existing partnerships and consortia initiatives be explored. The purpose of such a network would be to rapidly and efficiently create a sustainable pipeline of innovative new medicines for infectious diseases (the scope is to be determined but might also include research on vaccines and diagnostics). The network would mobilise resources and expertise from industry, academia and public and private research institutes globally. These specialists from different disciplines and institutions would work to a common mission through a virtual, voluntary collaborative framework.

Action

Global virtual network

The OECD could play a critical role in elaborating how such a global, virtual network might function, identifying what infrastructures (scientific, regulatory, organisational) would be required to underpin its establishment; and canvassing the level of support across governments, industry, academia, and philanthropic groups for its creation. OECD contributions could include, as specified in the NMA:

- Facilitating the development and operation of a sustainable architecture for the sharing and exchange of knowledge, data and research tools necessary for the discovery of medicines, vaccines and diagnostics.
- Identifying the infrastructure needs to accelerate discovery through a drug development network. What infrastructures could be shared (e.g. compound libraries, information technology tools, databases, platforms)? How could a more open innovation network function, including issues of participation, governance, funding, knowledge sharing, IP and licensing agreements, etc.?
- Exploring mechanisms for identifying priorities for research in infectious diseases.
- Identifying incentives for partnerships and collaboration between developing and developed countries, and explaining how such a network could build capacity for research in developing countries.
- Identifying how the network and other mechanisms could promote the transfer of technology, knowledge and technical skills to strengthen developing countries innovation systems.

It is important to understand how to scale up and network the activities of public-private product development partnerships. For the moment these are relatively small and independent initiatives. A global network needs to learn from these initiatives and explore how they can be improved and scaled up. Any scale-up, however, has to be testable, its effectiveness measurable, and the process gradual.

"Big Tent" meeting

Participation in the conceptualisation and development of products to combat neglected diseases has been evolving over the last few years. Today, it is not limited to multinational pharmaceutical companies, which had been the targets of most interventions, but also includes PDPs, biotechnology companies and smaller pharmaceutical companies.

To take this work forward, it has been suggested the OECD facilitate the scale up of global virtual collaborative drug development R&D networks for neglected infectious disease by convening a large, inclusive meeting of all parties that would be involved in the creation and/or running of a global network for infectious disease drug development.

Participants at the meeting would discuss the desirability, feasibility, possible structures and governance of such a network or networks.

The meeting could focus parties on different aspects of networked health product development, including issues such as:

- how to expand or build off existing networks;
- what the infrastructure needs are;
- what the financing needs are;
- what the possible organisational structures, governance and rules of engagement are;
- how to build industrial, political and scientific support and where to take forward such a network.

7. Other areas requiring innovation

Combating neglected and emerging infectious diseases requires a complex, interlinked set of activities. These interlinked activities require various types of innovation. As such, discussions of innovation at the HLF covered not only the specific innovative step of developing new concepts into potential or candidate products, but also the possibility as well as the desirability of innovation in processes, systems and financing to achieve better control of neglected infectious diseases.

Regulatory approaches

Regulatory frameworks will need to reflect new ways of doing innovation that are more open. They will need to be developed and reassessed so that they support faster discovery and development of medicines. This would help to increase patient access to new medicines and help to decrease the costs of drug discovery and development.

It was made clear that standards and regulations should not be made easier for products for neglected diseases in developing countries; that there needed to be consistent high levels of standards across both developed and developing countries. But that being said, there was definite support for improving the drug, vaccine, diagnostic and medical device regulatory environment in order to achieve a more effective global system for assuring the safety, quality and effectiveness of pharmaceutical products, including, in particular, products to combat neglected diseases and counterfeit products.

Other pressing regulatory issues relating to neglected diseases that were discussed at the Forum, particularly by those involved in PDPS, included:

- clarifying regulatory pathways for products to be used mostly or exclusively in developing countries where development might be sponsored by industrialised countries;
- fast-tracking regulatory applications for life-threatening diseases;
- strengthening regulatory capacity as a way of suppressing counterfeit products in developing countries;
- ways to shorten the regulatory approval process, possibly using surrogate markers.

Many Forum participants from developing countries stressed the need to strengthen regulatory capacity as part of broader strengthening of their health systems, for example to counteract the problem of counterfeit pharmaceuticals. The strengthening of regulatory systems was also discussed in connection with collaboration with developing countries in product development and as part of a desired capacity in developing countries to house their own innovation systems.

Action

Since most regulatory expertise resides in OECD countries, they as a group may be better positioned than developing countries to initiate consideration of these issues, in collaboration with developing country representatives. As such, it was suggested that by drawing on expertise through the OECD regulatory community, the co-ordination of best practices and guidelines for regulatory processes could be created and adapted to the local needs of developing countries.

New technologies and processes

Recent breakthroughs in biomedical research do not appear to have influenced the ability to identify successful candidate drugs. There is thus a growing consensus that new tools and approaches are needed to facilitate more informed choices throughout the drug discovery and development process. This includes more robust development pathways that are efficient and predictable, and that lead to products that are safe, effective, and available to patients. Significant savings could be realised by identifying, as early as possible in the development process, those medicines that are likely to fail (OECD, forthcoming).

Some new processes and technologies show promise to improve the efficiency of the drug development process, to help identify targets more readily and to facilitate understanding of infectious organisms (Nwaka and Ridgley, 2003). These include:

- Pharmacogenetics and specifically genetic biomarkers – these could be used to reduce costs for clinical trials and improve the efficiency of the drug development process (OECD, forthcoming).
- Identification of new pharmaceutical targets through genomics.
- High-throughput screens to identify leads more efficiently.
- In silico modelling and screening.
- Synthetic biology which combines biology, genetics and engineering to create or alter organisms so that they can produce drugs or other compounds.6
- X-ray crystallography.
- Chemogenomics which uses both the chemical and genomic information about an organism and has the ability to link targets in parasites to likely chemical starting points. This enables the early

selection of potential targets before costly and time-consuming drug screening and optimisation studies (Hopkins, Witty and Nwaka, 2007).

- Combinatorial chemistry, which is the use of technologies designed to greatly accelerate the rate at which potential new drugs are produced. Using robots and other advanced techniques, hundreds or thousands of different candidate compounds can be produced simultaneously. This could help to diversify the number of agents available for screening.

This use of new technologies and innovative processes may help to identify leads as early as possible in the R&D cycle and in that way failure rates could be lowered along with the costs of research and discovery. These could also increase the efficiency and effectiveness of the innovation cycle.

Action

At present, TDR has access to the chemical compound libraries of Pfizer, Serono and Chemtura. Scaling up this initiative to increase access to pharmaceutical companies' chemical compound libraries to a network of researchers working on neglected infectious diseases would be a worthwhile step. Collaboration between the OECD, TDR and industry associations (*e.g.* International Federation of Pharmaceutical Manufacturers and Associations [IFPMA]) could examine what structure, governance and architecture would be required to underpin a network for compound libraries. This could link with a study of the collaborative mechanisms necessary for sharing this type of knowledge.

8. Building capacity in disease endemic countries

Almost universally, developing country participants in the Forum emphasised their strong desire for involvement in all aspects of efforts to control infectious diseases that were endemic in their countries, including at the R&D phase. They also emphasised the need to enhance indigenous innovation capacity.

Full involvement of researchers and health practitioners from disease endemic countries in pharmaceutical innovation for neglected diseases is warranted not only as a matter of principle, but also from a practical point of view. Such involvement can bring important contributions in:

- setting priorities to reflect developing country needs;
- establishing required target product profiles;

- ensuring that from the outset that product development considers that new products be appropriate for use in resource-constrained settings.

Inclusion of developing country scientists and other specialists in activities pursuing implementation of the Noordwijk Medicines Agenda was therefore seen as essential and an activity that would also contribute to some degree to strengthening innovation capacity.

A number of developing country participants spoke of their commitment and need to expand domestic investment in R&D. It was noted that some countries, particularly in Africa, currently have very little in the way of health research capacity, pharmaceutical innovation or manufacturing capacity. In these situations, strategies for strengthening capacity will likely need to be different from those countries where there is already some indigenous innovation for infectious disease control (*e.g.* Brazil, India).

Further work is required to identify the full range of necessary and existing activities to strengthen developing country innovation capacity (particularly African). Such an inventory would provide a basis for developing a comprehensive approach to this aspect of the NMA.

Action

The NMA recommends efforts to foster and strengthen innovation systems in developing countries. Such an effort would be facilitated by mapping existing activities and resource flows in: *(i)* strengthening health research capacity; *(ii)* other activities to strengthen science, technology and innovation; and *(iii)* strengthening capacity for intellectual property management.[7]

In order to establish and expand research capacity in DECs:

- Networks and global virtual collaborations should have built-in programmes where scientists from DECs do fellowships or placements in pharmaceutical companies and research facilities, as is currently the case with TDR.

- Research facilities and clinical trial sites should be established in DECs.

- It should be identified how the virtual global network and other mechanisms could promote the transfer of technology, knowledge and technical skills to strengthen developing countries innovation systems.

- DECs should be involved from the beginning in all research projects concerning neglected diseases.

9. Financing mechanisms

Many facets of the NMA are dependent on some expansion of financing, but more importantly on innovation in financing, for the range of activities entailed in combating infectious diseases in developing countries. Many new approaches to finance were outlined in Chapter 3.

While bilateral aid budgets are likely to remain subject to annual fluctuations, other government-backed funding vehicles, such as International Finance Facility-like schemes could offer advantages:

- They could be used to make funds from securitised pledges immediately available where earlier investment was justified to get benefits sooner (e.g. product development).
- They could put funds into the hands of intermediate funding agencies (e.g. the Global Fund to Fight AIDS, Tuberculosis and Malaria [GFATM]) so they could make long-term commitments.

Action

The OECD secretariat should collaborate with other groups in exploring recent proposals, in particular the possibility of using IFF-like mechanisms for product development and health services delivery, as one possibility to overcome the concerns that current funding is insufficient, short-term and unpredictable.

10. Delivery systems

Although the HLF did not focus on issues of access, it was recognised that access was a part of the innovation cycle and, as such, the issue of access was important. Forum discussions, particularly those referring to development of capacity in developing countries, emphasised that the innovation system for infectious disease control need to incorporate contributions from sectors beyond health. Comprehensive efforts in developing countries to strengthen or create systems for innovation will need to involve many sectors: education, science and technology, agriculture, commerce and trade, as well as health. Policies in these sectors will need to be aligned coherently to create a scientific and business environment that fosters innovation and its social, as well as commercial, application.

Strengthening delivery systems for existing products paves the way for more efficient delivery of new products that come from R&D; the two activities should not be seen as in competition. Some facets of delivery systems have received relatively little systematic attention, *e.g.* private sector distribution of drugs in poor countries, even though it is known that many persons obtain their care and drugs through such channels.

Action

Improvement of, and innovation in, efforts to ensure access to medicines would be facilitated by identifying, documenting, and sharing among OECD and development partners experiences in use of private sector delivery of health products and services.

Conclusion

The OECD High-Level Forum on Policy Coherence: Availability of Medicines for Neglected and Emerging Infectious Diseases represents a landmark among international attempts to forge a comprehensive approach to control of infectious diseases that predominantly affect poorer developing country populations. It brought together over 200 experts, drawn from a wide range of countries, responsibilities and disciplines within and beyond the health sector.

Dramatic changes have occurred in the last decade in the landscape surrounding neglected diseases. New organisations and new funding have emerged, and there has been a constructive shift to collaboration with, as well as greater engagement by, pharmaceutical companies.

Recent developments in the processes, systems, organisations and financing for ensuring research, development, and access to products to combat neglected diseases were welcomed. But these require financing at a higher level, especially from public sector sources as their support. Financing for these efforts and particularly for PDPs currently rests largely on philanthropy, in particular the Bill and Melinda Gates Foundation.

While some progress would most likely result from these recent developments, the general sentiment of presentations and discussions at the HLF was that new innovative approaches were needed to achieve the Millennium Development Goals (MDGs) and other targets for control of infectious diseases that predominantly burden developing country populations. Existing, and new resources, could be better organised to yield greater synergies and better prospects for success.

Participants concluded that dealing with infectious disease threats more effectively requires a spectrum of activities. Enhanced efforts to deploy existing pharmaceutical products (drugs, vaccines, diagnostics) were necessary not only to meet immediate health needs, but to also pave the way for better delivery of future products to those currently without access (up to half the population in some countries). In parallel, because of the length of time such activities require and the currently incomplete pharmaceutical armamentarium, work is required for new or improved products as well as replacement products to overcome drug resistance.

Participants agreed that there was a need to facilitate the scale up of a global virtual collaborative drug development R&D network for neglected infectious diseases. This virtual global network would implement more open methods of innovation all along the innovation cycle and include many more players. It was noted at the HLF that there was the need to particularly foster innovation in selected areas of the innovation cycle. Highest priority areas included:

- exploration of more open innovation systems and tools including the collaborative mechanisms for access and use of IPRs;
- evaluation of the effectiveness of new policies and research models for promoting R&D in infectious diseases (*e.g.* AMC, prizes, financing funds for R&D, etc.);
- innovation for feeding the product development pipeline for control of neglected infectious diseases through:
  - expanding basic research funding on neglected diseases which underpins all innovation;
  - exploring fresh approaches to identify new targets, concepts, candidates, and leads for products to combat infectious diseases;
  - incorporating into these activities inputs from disease endemic countries more extensively.
- ensuring the effectiveness of recent organisational innovations in neglected disease control by providing more adequate funding and other facilitating activities such as strengthening of sites for clinical trials;
- innovations in financing, to overcome currently insufficient, short-term and unpredictable funding;
- capacity strengthening for innovation systems (including intellectual property management) in developing countries;

- delivery innovations, including exploring private sector distribution channels and provision of care;
- innovative regulatory approaches to achieving a more effective global system for assuring the safety, quality and effectiveness of pharmaceutical products, including, in particular, products to combat neglected diseases and counterfeit products.

The Noordwijk Medicines Agenda puts forward a set of concrete actions and policy options to promote, in a coherent manner, an open innovation strategy that can deliver new generations of drugs, vaccines and diagnostics for neglected infectious diseases. These concrete actions have the ability to change innovation systems. While developed countries will benefit from a more efficient, more open innovation system, the top priority of doing this is to deliver medicines for infectious diseases to developing countries and to help them build capacity in line with their health priorities.

The message from the NMA is that no one can do this alone; there needs to be more partnerships, networks and policy coherence to achieve our common goals of developing an innovation system that can deal with today's challenges. This is an opportunity for governments to drive a health innovation strategy that is more efficient and responsive to global public health needs. This is an opportunity that must be seized.

Notes

1. See *www.oecd.org/dac/effectiveness/parisdeclaration*.
2. See *www.proteinkinase-research.org/*.
3. See *www.ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml#consortium.*
4. See *www.sanger.ac.uk/HGP/Chr6/MHC/consortium.shtml*.
5. See *www.who.int/tdr/*.
6. Synthetic biology was used by the company Amyris to produce a package of genes from three different organisms that when inserted into yeast will help make artemisinin, an effective malaria treatment. Currently artemisinin has to be extracted from the sweet-wormwood plant indigenous to China and Viet Nam and is difficult to manufacture in sufficient quantities at a cost low enough for the developing world.
7. Such work might be done in collaboration with the Global Forum for Health Research, Geneva, and the Center for Global Development's Global Health Resource Tracking Working Group. See *www.cgdev.org/files/13711_file_Resource_Tracking.pdf*.

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Annex A

Summaries of the High-Level Forum Preparatory Workshops

Summary of the Preparatory Workshop on Accelerating Neglected Diseases Drug Discovery, OECD, Paris, 2-3 May 2007

Background

Thirty-two experts participated in the Accelerating Neglected Diseases Drug Discovery workshop to discuss what OECD countries can do to improve the productivity and efficiency of the innovation system for drugs, vaccines and diagnostics for neglected and emerging infectious diseases. Neglected infectious diseases (such as African sleeping sickness, river blindness and Chagas disease) primarily affect people in developing countries. In general, the market for biomedical products that prevent, diagnose or treat such diseases is too small for pharmaceutical companies to recover their investments given the predominant innovation model. Most products for neglected infectious diseases are thus developed on a not-for-profit basis as a philanthropic endeavour.

The workshop first examined the current landscape of initiatives that aim to improve the availability of medicines for neglected and emerging infectious diseases. Over the past decade, a number of public-private product development partnerships (PDPs) have been established. What can be learned from the way PDPs create networks and the way they access expertise, data and resources? Can the working methods underlying these collaborations be expanded, improved or scaled up in order to accelerate the availability of treatments and preventive technologies for infectious diseases?

Indeed, while the focus of the workshop was on neglected and emerging infectious diseases, the applicability of more open or networked innovation

structures, such as those used by PDPs, could in fact be much broader and serve to accelerate, and make more efficient, the health innovation cycle.

The PDP and other innovative research and development models

Workshop participants discussed the strategies that PDPs use to develop leads for vaccines and drugs, and how they do so at relatively low cost. They also identified challenges facing PDPs.

Methods for PDPS to increase the pipeline

PDPs increase the pipeline by:

- drawing on a wide range of expertise, know-how and capacity including: volunteered scientific expertise, compound libraries, assays and computing capacity;
- high throughput screening of chemical compounds that come primarily from industrial libraries;
- leveraging industry in drug development capacity as a key to their success;
- using donated or off-patent molecules to develop new treatments.

Challenges facing PDPs and possible solutions

The challenges that PDPs face, and solutions to those challenges, include:

- Uncertain financial sustainability. PDPs' reliance on philanthropy and public funds could be endangered by a shift in priorities.
- To reduce reliance on donor funding it might help to:
  - Investigate how a for-profit model and the commercialisation of products could provide greater financial sustainability.
  - Encourage developing countries to participate in funding PDPs focused on discovery or product development for diseases endemic in their countries. This could be coupled with capacity building in the form of conducting more biomedical research and training clinical professionals in those developing countries.
  - Co-ordinate reciprocal policies for the recognition of tax exempt, non-profit institutes.

- Some PDPs began by cherry-picking the early development projects; now they are faced with doing more expensive early stage discovery, which may change the nature of the partnership.

How do PDPs define success?

Discussion regarding PDPs' definition of success touched on the following:

- The need to monitor and measure the success of different initiatives.
- At first success was thought to be registered products; increasingly ensuring access is the endgame.
- Do PDPs terminate activities when the disease is no longer neglected? When can the funding resource go elsewhere?

What is meant by "scale up" and how can we deliver it?

Workshop participants discussed how research capacity on infectious diseases could be scaled up, specifically what conditions are necessary to deliver one effective new medicine for each of the neglected tropical diseases.

The challenge

The cost of delivering at least one effective new medicine for each neglected infectious disease, using present industry cost structures, is enormous – on the order of over USD 1 billion.

The opportunity

PDPs and other more open or networked innovation structures are transforming the supply side of drug development for neglected diseases by reducing the costs and increasing the global capacity for drug development. This model should be improved and expanded to feed the pipeline of new health products for infectious diseases.

The suggestions

- Create an information clearinghouse of ongoing research and development (R&D) to reduce duplication of efforts. Participants wondered about the present division of labour among PDPs: should

they operate as one single entity or should they operate separately and specialise, for example in one particular disease?

- Enable virtual drug discovery networks of researchers, companies, laboratories, and PDPs.
- Use the networks to develop a portfolio of prioritised discovery projects that identifies a set of discrete research tasks for each project, and helps to match tasks to the competence of participating volunteer groups.
- Create a framework to facilitate voluntary contributions of advice, skills and infrastructure access from researchers in industry and the public sector.
- Exploit economies of scale. Identify common infrastructures, know-how and platforms that could be shared within networks.
- Agree on collaborative mechanisms to share knowledge within the networks.

What is needed to scale up?

- Managerial governance to agree on priorities and co-ordinate the various participants working at a distance.
- Negotiated access to proprietary knowledge and infrastructures.
- Standard collaboration and licensing agreements.
- Interoperability of data to assure participant access and linkage from a common platform.
- Sustainable financing.
- Human capital, for example: sponsored researchers from industry/in industry, developing country researchers.
- Scale up has to be testable, its effectiveness measurable, and the process gradual.

What can OECD do?

Advocacy and policy coherence

- Focus the donor community on the unprecedented opportunity in neglected infectious diseases to scale up product development and reduce costs through the use of new, more open innovation models.
- Encourage greater policy coherence amongst health, science, development, trade and industry policy makers, in both developed and developing countries.

Innovation policy

- Draw on OECD work on public-private partnerships to explore how PDPs in neglected diseases can be scaled up and improved.
- Identify disincentives to sharing of information and intellectual assets and suggest how to remove them. Investigate how voluntary knowledge markets and collaborative mechanisms can encourage the sharing of knowledge that might otherwise be kept secret.
- Improve the drug, vaccine, diagnostic and medical device regulatory environment by drawing on expertise through the OECD regulatory community to co-ordinate best practices and guidelines that are adapted to local needs of least developed countries.
- Develop policy advice on how to improve intellectual property management practices of technology transfer offices.
- Examine how funding bodies could encourage participation in more open innovation models or discovery networks for infectious diseases, for example through grant criteria.

Economic policy

- Develop metrics for social rates of return to compare donor/philanthropy returns on investment in PDPs. Without these metrics the decisions for funding are skewed.

Messages for governments

Participants at the preparatory workshop agreed the following messages for governments:

- A global, virtual collaborative drug development network drawing on existing initiatives and technology networks could increase the number of researchers involved in R&D for infectious diseases, their efficiency and their innovative output.
- Building capacity in developing countries and their institutions will increase their contribution to infectious disease R&D efforts, and improve the ability to deliver innovation to patients most in need.
- Greater policy coherence amongst health, science, development, trade and industry policy makers, in both developed and developing countries, may contribute to increasing the availability and accessibility of medicines for infectious disease that primarily affect developing countries.

Summary of the Preparatory Workshop on Policy Options and Policy Coherence to Enhance the Availability of Medicines for Neglected and Emerging Infectious Diseases, OECD, Paris, 3-4 May 2007

The economics of infectious diseases: what conclusions can be drawn?

Infectious diseases remain a major health problem in developing countries and account for most of the disease burden in Africa. Addressing infectious diseases that primarily affect developing countries is often seen as a moral or humanitarian obligation. This session considered whether it is also in the economic interest of OECD member countries to combat emerging and neglected infectious diseases and the consequences of not doing so. Participants made several points:

- **In poor countries, neglected infectious diseases have heavy human and economic costs. Globally they undermine long-term development and security.** About half of communicable disease deaths take place in sub-Saharan Africa. The annual costs of malaria in Africa have been estimated at a minimum of USD 12 billion; this resurgent disease alone may retard future African economic growth by 1.3 percentage points per year. Widespread infectious disease in Africa not only reduced output and incomes of Africans but also

reduced its contribution to growth in world trade and foreign investment. There are also security considerations as epidemics increase large-scale migration, undermine fragile states, and can increase the possibility of violent conflict.

- **In an interdependent global economy, emerging infectious diseases could have large health and economic consequences**. The rapid expansion in trade, foreign investment and international travel mean that infectious diseases can impact not only health but also the economic growth and security of OECD countries. As an example, severe acute respiratory syndrome (SARS), which was first detected in southern China, spread within five months to 28 countries with estimated costs of USD 10-30 billion. Estimates of the possible human and economic costs of new pandemics make SARS figures seem trivial.

- **Developing treatments and preventions for neglected infectious diseases yields innovation lessons relevant to all diseases**. Many of the policies and practices being put in place to enhance the availability of drugs, vaccines and diagnostics for neglected infectious diseases are also relevant to disease markets in advanced industrialised countries. A new infectious disease emerges every eight months and for many existing infectious diseases, drug resistance has become a serious problem. Creating efficiencies in the innovation cycle is key to quickly delivering new medicines to market at reduced costs. This is important for non-communicable diseases as well, where markets for medicines are shrinking and fragmenting due to genomics and targeted therapies.

- **Humanitarian, developmental and ethical reasons for addressing neglected infectious diseases in developing countries remain important.** OECD countries and multilateral institutions give USD 55 billion in overseas development aid. Policy coherence between science and technology (S&T) ministries and development assistance ministries as well as health ministries could enhance efficiency in research and product development of medicines to address neglected and emerging infectious diseases. These medicines could also help to increase the effectiveness of other forms of aid for health.

Stepping up research on neglected and emerging diseases: challenges and policy instruments

Research investment in neglected and emerging infectious diseases has been limited. Participants said that of all drugs licensed world wide between 1975 and 1997, less than 1% were for tropical diseases, of which one-third were discovered and developed by pharmaceutical firms. Though the situation is improving, this session considered policy mechanisms that could further increase investments, groups involved in, and innovation in, infectious diseases. Participants in this session noted:

- **Increased funding in itself is not sufficient**. **A better alignment between incentives and policy goals is needed**. In order to meet their health needs, developing countries should devote more attention and resources to the creation of more effective and equitable health systems. Adjustments in the policies of industrialised economies that shape incentives for addressing global health needs are also needed.

- **The "push" and "pull" mechanisms used to bring new health technologies on to the market are complementary, rather than competitive, models**. No individual mechanism (*e.g.* public-private product development partnership [PDP], advance market commitment [AMC]) is a panacea, nor does one over another replace traditional development programmes in health.

- **Public-private partnerships and networking are important tools** for enhancing health surveillance, sharing knowledge, accelerating research and development. The feasibility of developing enhanced international networks or an international "compact" for infectious diseases should be explored.

- **Developing countries need to be involved from the start**. Concerns about insufficient emphasis on the role of developing countries in all mechanisms must be addressed to ensure their priorities and needs are met.

Availability and accessibility: how can policy coherence deliver benefits from existing and newly developed medicines?

Increasing availability and accessibility to therapeutics, vaccines and diagnostics depends on many factors. Innovation itself encompasses access as well as availability. The emerging consensus is that both procurement and distribution costs in partner countries need to be reduced and aid effectiveness in health improved. Participants in this session discussed the

challenges to creating coherent solutions that would address the availability of, and access to, drugs.

- **The four legs that underpin "accessibility" include: evidence-based decision making; price; sustainable financing; and a functioning health system**. Weakness in any one of the four legs may create bottlenecks for the whole system.
- **An increase in developing country health budgets to cover improved access by the poor to essential drugs would be ideal**. But in many developing countries, suitable treatment and access to some essential medicines are hindered by lack or misallocation of resources, irrational selection of drugs, inefficient procurement procedures, corruption in distribution chains, lack of quality assurance, weak diagnostic capacity, unaffordable prices and lack of sustainable financing. **Development co-operation programmes should focus on capacity building and health policy reform.**
- **Many factors influence mark-ups on drugs in developing countries**. Further work is needed to ascertain which of these factors has the greatest impact on price as well as on the extent to which the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) influences prices in the least developed countries without pharmaceutical production capacity.
- **Prioritisation, in terms of choosing medicines which meet heavy disease burdens with high cost effectiveness, is key.** Even where cost-effective interventions exist, there is still a need to search for interventions that are far more cost effective, *e.g.* compare bed-nets with malaria vaccine.

The Noordwijk Medicines Agenda and the objective of the High-Level Forum: innovation as a complement to development

Two different possible objectives for the High-Level Forum emerged during the session discussion. Some participants suggested that a key objective is to improve the efficiency of **innovation**: policies should seek to create an environment that enables development of new drugs. Some emphasised the objective to **reduce poverty***:* policies must be assessed in terms of their expected impact on poverty reduction.

All participants agreed that innovation embraces the entire supply chain, from the laboratory to the patient. Innovations in product discovery and development for infectious diseases should be complemented by innovations in the way those products are delivered to, and diffused amongst, patients.

Non-aid policies – including S&T and health policies – can contribute substantially to meeting international poverty-reduction targets and the impact on development of such policies needs to be monitored and improved. Four levels of policy coherence are generally recognised. Within these, participants noted the following as important to improving policy coherence for medicine development and health delivery:

- The tension between the two objectives is more perceived than real, given that innovation is a weapon in the fight against poverty and has been the major driver of economic growth.
- At national level, the innovation cycle needs to be embedded in a supportive policy environment that enables innovation and knowledge sharing; promotes quality standards; ensures effective surveillance; and recognises the need to develop opportunities to address sustainable poverty reduction.
- Through whole-of-government approaches, the design of policy instruments available to advanced countries should take account of potential impacts on health development objectives.
- Efforts are needed to take note of developing-country-led priorities and to avoid aid fragmentation in line with the harmonisation and co-ordination provisions of the Paris Declaration on Aid Effectiveness.
- Alignment of policies with the needs of developing countries is fundamental.

Annex B

The Basic Economics of Scaling Up Healthcare in Low-Income Settings

By Professor Jeffrey Sachs[1] and Dr. Sonia Sachs[2]

The greatest challenge of global public health is to scale up the access of the world's poor to basic health services. An estimated 11 million children die each year of readily preventable and treatable conditions. Roughly half of these deaths occur in sub-Saharan Africa, though sub-Saharan Africa constitutes just 12% of the world's population. The over-arching problem is extreme poverty, and the over-arching solution is targeted assistance by the developed world to enable the poorest countries, and especially those in sub-Saharan Africa, to introduce basic health services with guaranteed availability to all.

It is often argued that the health crisis is much more complicated than a shortage of money, as health-sector shortfalls relate to governance, human skills, inadequate rates of research and development (R&D), barriers caused by patent rights, and more. Yet there is no contradiction here. Money from outside donors is a necessary, but surely not a sufficient condition. However, even where problems like "governance" are at the fore, money is usually critical for solving these "non-monetary" problems as well. Poor governance, insufficient human resources, brain drain, and profound under-investments in R&D are all related to the lack of purchasing power held by the poorest of the poor. Governments of the poorest countries lack the necessary budgetary revenues to fund an operational health system.

This annex lays out a basic framework for understanding the economics of the public health challenges, with a primary focus on the delivery of existing technologies. Annex D describes the challenges of R&D for diseases that affect the poor.

The 11 main conclusions of this annex are:

- The excess disease burden (morbidity and mortality) borne by the poor results from a small number of conditions: mainly infectious diseases, undernourishment, and unsafe childbirth (maternal and perinatal deaths).
- The excess disease burden creates an enormous social and economic cost that is several times greater than the cost of addressing it.
- There are proven, effective, and low-cost interventions to address the major sources of excess disease burden.
- Some of the interventions lie beyond the health sector, most notably safe drinking water and sanitation and nutritional supplementation.
- Essential interventions lie within the health sector, in a mix of preventative and curative public health services.
- The biggest challenge is that the poorest of the poor do not have access to these interventions. Public health systems are chronically underfinanced, and this in turn reflects the overall rate of extreme poverty. Under-financing is not a reflection in most cases of the lack of political will, but a reflection of the extreme poverty of the population.
- Private-sector provision of healthcare, paid for by the poor, cannot make up the difference, since the vulnerable population lacks the purchasing power to finance its own healthcare.
- What is required is a significant scaling up of basic health services, as well as selective interventions outside of the health sector. This scaling up is feasible and can be quickly accomplished.
- Various strategies are needed to address skill shortages, lack of working systems, and problems of governance. By addressing these challenges, a basic health system will be constructed.
- The argument between "vertical" and "horizontal" programmes is a straw man. Both kinds of programmes are needed. Moreover, vertical programmes help to build horizontal health systems.
- The costs of scaling up to ensure comprehensive coverage of basic health services fits within the promised aid levels promised by donor countries.

These points are now taken up in detail.

Excess disease burden

Excess disease burden is generally measured in disability adjusted life years (DALYs), which combine the years of life lost with a measure of year equivalents lost to severe disabilities (such as blindness or paralysis). The most recent comprehensive assessment of DALYs on a global comparative basis is the World Bank's *Disease Control Priorities in Developing Countries* (the "DCP") (Jamison *et al.*, 2006). The results of the DCP are clear and in line with earlier findings of the Commission on Macroeconomics and Health (CMH, 2001) and other similar efforts. The excess disease burden of the poorest countries relates to three classes of conditions: infectious diseases; nutritional deficiencies; and unsafe childbirth, both maternal mortality and neonatal mortality. Within these categories the following conditions are paramount:

- Infectious diseases:
  - AIDS,
  - tuberculosis,
  - malaria,
  - diarrhoea,
  - acute lower respiratory infection,
  - vaccine-preventable diseases,
  - tropical parasites,
- Nutritional deficiencies:
  - micronutrient deficiencies,
  - macronutrient deficiencies,
- Unsafe childbirth and other reproductive health conditions:
  - maternal mortality,
  - neonatal mortality,
  - sexual and reproductive health services.

These 12 conditions account for nearly all of the excess DALYs per capita of Africa.

There are several observations to be made about this list of disease burdens.

- First, many of these categories are syndromes (groups of diseases), rather than specific diseases.
- Second, most of the disease categories are virtually non-existent in rich countries, suggesting that comprehensive control of most of the diseases is possible.
- Third, the poor also suffer and die from the chronic "diseases of the rich" such as cardiovascular disease (CVD), cancer, metabolic disorders (adult-onset diabetes), mental health disorders, and so forth. The difference is that the poor suffer excessively from the former 12 conditions, but have age-adjusted mortality rates for the latter conditions that are roughly comparable with those of the rich world.
- Finally, note that the category of sexual and reproductive health services includes not only disease conditions, such as sexually transmitted diseases and complications in pregnancy, but also access to contraception and family planning.

Costs of disease are vastly greater than the costs of disease control

Every recent study that has examined the conditions of ill health in low-income countries has found that the cost-benefit ratio of disease control is enormously favourable. When the Copenhagen Consensus (2006) ranked 40 public policies for the world's poor, as just one recent example, it put health interventions and health-related interventions (safe drinking water) at the top of the list of priorities. Indeed, the top priority is "scale-up basic health services". The categories of health; sanitation and water; and malnutrition and hunger hold 10 of the top 15 positions in order of priority, as evaluated by a cost-benefit ranking, as shown in Table B.1.

The same findings were made earlier by the Commission on Macroeconomics and Health, where the cost-benefit ratio for introducing a functioning primary health system in low-income countries was put at roughly 1-to-6 (CMH, 2001). There is little further debate on this point, which helps explain the fact that 7 of the 18 Millennium Development Goal targets are health related. These involve the reduction of hunger, access to safe drinking water, control of infectious diseases, access to essential medicines, and reduced child and maternal mortality.

Table B.1. **The Copenhagen Consensus 2006 ranking**

	Challenge	Opportunity
1	Communicable diseases	Scaled-up basic health services
2	Sanitation and water	Community-managed water supply and sanitation
3	Education	Physical expansion
4	Malnutrition and hunger	Improving infant and child nutrition
5	Malnutrition and hunger	Investment in technology in developing country agriculture
6	Communicable diseases	Control of HIV/AIDS
7	Communicable diseases	Control of malaria
8	Malnutrition and hunger	Reducing micro nutrient deficiencies
9	Subsidies and trade barriers	Optimistic Doha: 50% liberalisation
10	Education	Improve quality / systemic reforms
11	Sanitation and water	Small-scale water technology for livelihoods
12	Education	Expand demand for schooling
13	Malnutrition and hunger	Reducing low birth weight for high-risk pregnancies
14	Education	Reductions in the cost of schooling to increase demand
15	Sanitation and water	Research to increase water productivity in food production
16	Migration	Migration for development
17	Corruption	Procurement reform
18	Conflicts	Aid post-conflict to reduce the risk of repeat conflict
19	Sanitation and water	Re-using waste water for agriculture
20	Migration	Guest worker policies
21	Sanitation and water	Sustainable food and fish production in wetlands
22	Corruption	Grassroots monitoring and service delivery
23	Corruption	Technical assistance to develop monitoring and transparency initiatives
24	Migration	Active immigration policies
25	Subsidies and trade barriers	Pessimistic Doha: 25% liberalisation
26	Corruption	Reduction in the state-imposed costs of business/government relations
27	Climate change	The Kyoto Protocol
28	Conflicts	Aid as conflict prevention
29	Corruption	Reform of revenue collection
30	Financial instability	International solution to the currency-mismatch problem
31	Conflicts	Transparency in natural resource rents as conflict prevention
32	Conflicts	Military spending post-conflict to reduce the risk of repeat conflict
33	Financial instability	Re-regulate domestic financial markets
34	Conflicts	Shortening conflicts: natural resource tracking
35	Financial instability	Re-impose capital controls
36	Financial instability	Adopt a common currency
37	Subsidies and trade barriers	Full reform: 100% liberalisation
38	Climate change	Optimal carbon tax
39	Climate change	Value-at-risk carbon tax
40	Climate change	A carbon tax starting at USD 2 and ending at USD 20

Source: Copenhagen Consensus Center (2006), "The CC06 Ranking", *www.copenhagenconsensus.com/Default.aspx?ID=783*.

There are multiple channels by which excess disease burden imposes enormous economic costs. These include: the direct economic costs of loss of life and loss of work time; reduced productivity due to disability, absenteeism, and insufficient physical endurance for productive work; loss of schooling and early dropouts; loss of on-the-job training; costs of orphanhood; reduced inflows of investments in disease-endemic communities; and direct extra healthcare costs.

One of the least recognised, but perhaps most important of all channels, is the fact that a high mortality rate among children delays or prevents the demographic transition, which is a crucial input to long-term economic development. In a nutshell, families facing a high risk of child mortality will tend to choose to have very large families. Total fertility rates in sub-Saharan Africa remain at rates of six or higher in rural areas. Much of this is a response to the very high child mortality rates. The result is that high child mortality leads to high total fertility, which in turn leads to low human capital investments per child, with regard to nutrition, education, and access to basic healthcare. By encouraging families to choose "quantity" over "quality" in childrearing, high child mortality stands as a fundamental obstacle to the inter-generational accumulation of human capital accumulation (Conley, McCord and Sachs, 2007).

Malaria, as one key example, has extremely harmful effects operating through all of these channels: increased under-five mortality; reduced adult productivity; reduced childhood schooling; adverse impacts on cognitive development; delayed demographic transition (to low fertility rates); reduced business investment in malaria-transmission regions; and more. The cost of comprehensive malaria control in Africa is currently around USD 3 billion per year (Teklehaimanot, McCord, Sachs, 2007), while the short-term losses due to malaria are at least USD 12 billion per year. The longer-term cumulative losses of African economies are an order of magnitude larger than the short-term losses. One estimate puts the loss of annual economic growth at around 1.3 percentage points per year (Gallup and Sachs, 2001; Sachs and Malaney, 2002). This suggests that Africa's current gross national product (GNP) per capita is most likely dozens of percent less than would be the case if comprehensive malaria control had been put into place several decades ago.

Low-cost, proven, effective interventions

The core reason for the enormous benefits relative to costs in primary health is that medical and public health sciences have identified effective, low-cost, and proven interventions for all 12 conditions that cause the excess disease burden. The very fact that these conditions are controlled in the rich

world is the simplest direct evidence that they can also be controlled in poor countries. We should also be aware, however, of the distinctive disease ecology in tropical countries, which increases the burden of tropical diseases such as malaria (Kiszewski *et al.*, 2004).

In each category of disease burden, the pathogenesis is reasonably well understood, and in almost all cases there are well-established protocols for prevention and treatment. In general, the high disease burden is a reflection of a combination of four factors:

- **Environmental conditions** related to poverty, most notably: unsafe drinking water, often linked to the lack of sanitary facilities; indoor air pollution related to the use of biomass in cooking; and dietary insufficiencies.
- **Tropical ecology**, which raises the force of transmission of certain diseases, most importantly malaria, but also helminthic infections and other eukaryotic parasites (lymphatic filariasis, leishmaniasis, Chagas' disease).
- **Lack of access to preventative and curative health services**, including the absence of facilities, shortages of equipment and medicines, the collection of user fees and charges for commodities (medicines, bed nets, contraceptives), the absence of trained health workers, and the absence of transportation to health facilities.
- **Social exclusion** of minorities, girls and women, widows, the extreme poor, low-caste households, orphans, particular professions (*e.g.* commercial sex workers), and may include social stigma (*e.g.* regarding HIV/AIDS), and the lack of household awareness of healthy behaviours and of the availability of social services Social exclusion is often most serious for women with regard to sexual and reproductive health.

Interventions outside the health sector

World health can be improved dramatically through support of interventions on safe drinking water and sanitation, indoor air pollution, and nutritional upgrading. Let us consider each of these in turn.

It is estimated that 1.7 million deaths per year are attributable to unsafe water, sanitation, and hygiene (WHO, 2002), especially diarrheal diseases transmitted by faecal-oral transmission, in which household water used for drinking, bathing, and food preparation is contaminated by human faeces. The solution in these cases includes environmental control of breeding sites (where this is feasible), and the protection of water used for human

consumption. Protected water sites might include: deep bore wells, sanitary facilities away from water points, protected springs and other natural water sites, piped water, and various water purification technologies, especially for institutional users such as schools and clinics.

Indoor air pollution is another major killer, resulting from burning of biomass (wood, dung, charcoal) on open stoves in household compounds without chimneys or other forms of ventilation. The resulting particulate pollution is abrasive to the lungs, and leads to acute lower respiratory infections and deaths. The solutions here involve upgrading stoves to reduce particulates, the introduction of ventilation and chimneys, and the transition from biomass-based cooking to alternatives (liquefied petroleum gas [LPG], solar concentrators, biogas, biofuels, and other technologies). In general, the poor cannot afford these improved cooking methods unless they are substantially subsidised.

Chronic under-nourishment is a third environmental risk factor. Macronutrient deficiencies involve insufficient daily intake of calories and proteins, and generally result from extreme poverty and an inability to afford an adequate basic diet. A significant proportion – perhaps two-thirds or more – of the world's chronically under-nourished people are smallholder subsistence farmers, who grow food for their own consumption. The yields of these farmers are too low to provide adequate nutrition. The key intervention here is agricultural – to raise the meagre productivity of subsistence farmers.

Micronutrient deficiencies involve chronic shortfalls in specific nutrients, including specific amino acids that may be lacking in local staples, vitamins, folate (for folic acid), and essential fatty acids (notably omega-3 fatty acids). Solutions here may include diversification of local food production, fortification of nutrients such as iodised salt, supplementation of vitamins and other micronutrients through special campaigns, and targeting of vulnerable groups (*e.g.* pregnant women, lactating mothers and small children).

Interventions within the health sector

There is, of course, no substitute for a functioning public health system, one that embraces preventative as well as curative interventions. Preventative interventions tend to be community-wide interventions based on community awareness, participation, and outreach by public health workers. Critical preventative interventions include the:

- Prevention of infectious disease transmission: bed nets and larvaciding of mosquito-breeding sites to fight malaria, mass

vaccination for all vaccine-preventable diseases, behavioural modification and use of condoms to prevent the transmission of AIDS and other sexually transmitted diseases.

- Presumptive treatment of helminth infections: regular de-worming of all school-aged children and adults in areas of high prevalence of soil-transmitted helminthes.
- Mass fortification of nutrients through iodised salt, vitamin D-enriched milk, and other means, as well as mass nutrient supplementation of vitamin A, folic acid, zinc, iron, and other micronutrients for vulnerable groups (*e.g.* pregnant women).
- Ante-natal and perinatal care, for safe pregnancy and safe delivery. There are several specific regimens that have been developed to protect pregnant women, infants, and lactating mothers, such as presumptive treatment against malaria, presumptive de-worming, iron and folate supplementation and prevention of mother-to-child transmission of HIV.

With regard to treatment, most of the major infectious disease categories mentioned earlier have well-established and effective interventions. To name a few:

- treatment of AIDS with anti-retroviral medicines (ARVs);
- treatment of tuberculosis (TB) with Directly Observed Therapy Short Course (DOTS) for regular TB, and special regimens for multi-drug resistant TB (MDR-TB);
- treatment of malaria through timely access to artemisin-based combination therapies (ACTs);
- symptomatic treatment of diarrhoea through administration of oral re-hydration solution (ORS) and antibiotics for underlying pathogens;
- antibiotic administration for acute lower respiratory infection (ALRI).
- treatment of several tropical parasites through de-worming, and occasionally through surgical interventions (*e.g.* for partial relief of distress from lymphatic filariasis or buruli ulcers).

Protocols for effective, safe newborn delivery, including comprehensive emergency obstetrical care, and the care of newborns, including premature and low birth-weight babies, have also been established for low-income settings. These protocols can be applied in a rudimentary healthcare system,

even one with very few doctors at hand. Health workers other than doctors can be trained in key procedures; basic facilities (*e.g.* an operating theatre) can be established in appropriate health units (*e.g.* a sub-district hospital), and local emergency referral systems can be designed using trained birth attendants, cell phones, and local transport (*e.g.* trucks and other vehicles available within a given area). Finally, with regard to other aspects of sexual and reproductive health, there is extensive demonstration of efficacy of family planning programmes focusing on expanded access to contraceptive services, birth spacing, and ante-natal care. Of course standard protocols also exist for the screening and treatment of sexually transmitted diseases.

Chronic under-financing of health services

Several recent cost analyses have been conducted to measure the operating costs of a basic health system that can manage the key conditions of infectious disease, under-nutrition, and childbirth. These include the Commission on Macroeconomics and Health (2001), the United Nations Millennium Project (2005), and the Disease Control Priorities in Development Countries (2006). The overwhelming point of these studies is that a basic health system designed to deliver key preventative and curative services can be funded at a remarkably low cost, around USD 40 per person per year. But this low cost is nonetheless beyond the reach of the poorest countries.

The USD 40-per-person paradox is the single most important fact about health financing in low-income countries. On the one hand, the cost of basic healthcare is amazingly low, considering that health spending per capita in rich countries is more than USD 2 000 per year. On the other hand, the cost is too high for the poorest countries, unless they get financial help from rich countries. Consider the case of Malawi, a landlocked tropical country in the south-eastern part of Africa. Per capita income is estimated to be USD 180 per person (2005). Government revenues are approximately 15% of GNP, about the maximum that can be collected in such a non-monetised and impoverished economy. This means that total government revenues per capita are on the order of USD 27 per person per year (= USD 180 x 0.15), and this amount must be distributed across every area of government consumption and investment: government ministries, Parliament, courts, schools, Presidency, police, defence, environment, education, roads, power, ports, and of course, health.

Even if 100% of government revenues were devoted to health, the revenues could not pay for a rudimentary health system. Of course it is difficult to imagine that even a quarter of domestic revenues, USD 7 per person per year, could be mustered, given the other urgent budgetary

demands. In most countries like Malawi, domestically financed healthcare spending very rarely reaches 20% of the budget, and more typically remains in the neighbourhood of 10-20% (Conroy *et al.*, 2006).

In the case of Malawi, healthcare spending has been on the order of USD 5-10 per person per year until the past couple of years, when healthcare spending finally exceeded USD 10 per capita on the basis of increased foreign assistance. Still, the healthcare system does not begin to meet basic needs. There is an estimated 1 doctor per 100 000 people; this means an even lower ratio of doctors to people in rural areas, since doctors tend to congregate disproportionately in urban centres. It is not surprising that life expectancy is 40 years, and under-five mortality is around 175 per 1 000 live births, one of the highest mortality rates in the world (World Bank, 2005).

Malawi's situation is not unique. Throughout Africa, there is a deep and chronic shortfall of financing for basic health services, and one that does not reflect the lack of African concern and prioritisation, but rather the lack of available resources in the context of extreme poverty. Tropical African incomes average around USD 350 per person per year, so that even if government raised 20% of GNP in tax collection (a very high ratio), total government revenues would amount to just USD 70 per person per year. Even if 15% were directed to health, the result would be USD 11 per person per year.

The fallacy of the private sector "escape valve"

The most common response to the limited resources of the public sector is to channel healthcare through the private sector. The World Bank has tried, for 20 years since the onset of the structural adjustment era, to champion every form of private sector health delivery: user fees, community health insurance, individual health insurance, regulation and liberalisation of private providers, and more. One regular motivation has been the observation that private spending on health in many poor countries is many times the rate of public spending. In India, for example, an estimated five-sixths of all health outlays are out-of-pocket spending by the private sector.

The results have been disastrous. The high proportion of private spending is no reflection of the quality of private care, or access to private care, but rather the paltry amounts spent in the public system. More importantly, the overwhelming share of private spending is attributable to the upper deciles of the income distribution. When the public sector is under-funded, the poorest half of the population inevitably lacks access to care. The private sector provides absolutely no alternative "safety net" for the bottom deciles of the income distribution. Survey after survey

demonstrates the lack of access of the poorest half of the population to basic services, even after liberalisation of private healthcare delivery. The lack of access to services is not the result of failures of public-sector governance *per se*, but rather the result of extreme poverty which leads to insufficient investment in the public health system.

Financial assistance for scaling up health services

The Commission on Macroeconomics and Health (2001) and the United Nations (UN) Millennium Project (2005) provided detailed estimates of the required levels of official development assistance (ODA) needed to achieve a basic functioning health system in the poorest countries. The ideas in both projects was to calculate the total costs of running a basic health system that could assure universal access to basic health services, and to allocate the financing of that system between domestic revenues and ODA. In both cases, it was presumed that the poor countries would make significant increased efforts on public health outlays, of about 2% of GNP per year, so that ODA would complement, not substitute, a considerable scaling up of national resource mobilisation.

While the estimates are necessarily approximate, and needs are likely to vary across countries, the very basic calculations are as follows. A core health system will require around USD 40 per person per year. The local resource mobilisation can cover perhaps USD 12 per person per year, if the domestic public sector makes a serious effort at raising domestic revenues and allocating those revenues to healthcare. The gap, of roughly USD 28 per person per year, would need to be financed by external assistance. This would apply to around 1 billion people, suggesting a need for donor financing on the order of USD 28 billion per year. If we add in another USD 6 billion or so for R&D directed at the needs of the poorest of the poor, we reach a total cost of some USD 34 billion per year, or roughly 0.1% of the income of donor countries.

The upshot is that a basic health system for all in the poorest countries requires roughly one-tenth of 1% of GNP in aid from the richest countries. Since those countries have already promised to deliver 0.7% of GNP in aid, the assistance needs to ensure that comprehensive healthcare falls squarely within the amounts that have already been promised.

Unfortunately, even after the massive expansion of health assistance in recent years, donors are still falling short of the required aid, and health systems in the poorest countries are still terribly underfinanced. Basic interventions to save millions of lives per year still fail to reach those who need them because the financing for scaling up has still not been mobilised. It is difficult to estimate the total amount of health-related aid, but it is much

closer to (and perhaps even less than) USD 10 billion per year than it is to USD 28 billion per year.

The UN Millennium Project also estimated the total ODA required to ensure universal access to basic needs outside of the health sector. The best estimate is that the health ODA would be roughly one-fourth of the total, with outlays on water and sanitation, other basic infrastructure (roads, power), education, and other sectors adding perhaps another USD 80 billion or so per year for low-income countries. This would mean that Millennium Development Goal (MDG)-related ODA would require perhaps 0.4-0.5% of GNP from the rich countries. Non-MDG-related aid would add another 0.2% of GNP (for disasters, post-war reconstruction, support for international institutions, and so forth). The total aid needs fall within the long-promised envelope of 0.7% of GNP, though most or all of that promised aid will indeed be required (UN Millennium Project, 2005).

Mechanisms for scaling up of basic health services

If the required ODA is indeed delivered, and recipient governments are enabled to make multi-year plans for scaling up their health sectors based on the delivery of that ODA, then the opportunities for effective and rapid expansion of primary healthcare are indeed available. Various techniques will be required to achieve the rapid scaling up. These include the following.

Campaigns

The International Red Cross, United Nations Children's Emergency Fund (UNICEF), the US Centers for Disease Control, Rotary International, and others have shown in recent years that it is possible to reach an enormous proportion of the population of low-income rural communities with key interventions through specialised "campaigns" and "child health days". The key interventions have traditionally focused on immunisations, but in the last couple of years, these campaigns have been expanded to include the delivery of many services at one time: immunisation, de-worming, mass distribution of anti-malaria bed nets, vitamin A supplementation and screening for various diseases (American Red Cross and CORE, 2004). Based on a campaign approach, it should be possible to ensure anti-malaria bed net availability for all of Africa's at-risk population, at least by 2010. (This would require the mass distribution of around 300 million bed nets).

Integration

Delivery of multiple, interconnected health services can dramatically lower the cost, and quickly raise the coverage, of the population. For example, there are natural synergies between the control of malaria (both preventative and curative) and the control of other "neglected tropical diseases" such as lymphatic filariasis, helminthic infections, onchocerciasis, and other diseases (Hotez *et al.*, 2006). These conditions occur in the same geographical setting, multiply infect the same individuals, lead to co-morbidity, and are often prevented by the same technologies (*e.g.* bed nets in the case of several of the insect-borne diseases).

Community health workers

It is widely appreciated that the intense shortage of African doctors and nurses cannot be immediately remedied. African medical schools and nursing schools train and graduate quality doctors who have no problems finding jobs anywhere in the world. Yet there are far too few graduates annually to fill the enormous needs, even were brain drain to be substantially reduced. Brain drain can be slowed by raising public-sector pay; HIV-infected health workers who would otherwise die of AIDS can be kept alive through access to ARVs; and of course, more doctors and nurses can be trained. Still, the training of high-skilled health workers will take five to ten years. In the meantime, there is widespread evidence of the enormous benefits of community health workers based in local communities, with training that lasts anywhere from three months to two years. Such village-based health workers, like China's "barefoot doctors" of the 1950s and 1960s, can perform vital basic public health services such as the provision of anti-malaria medicines, immunisations, antibiotics, and oral re-hydration solution, and can direct observe village-based treatments for TB and HIV under the supervision of doctors at more distant health facilities (*e.g.* district hospitals).

Close-to-client services

More generally, it is possible to construct, provision, and operate low-cost health posts for a catchment of 5 000 or so people (1 000 or so households). These close-to-client services make a life and death difference for infectious diseases and risky childbirth. They offer access within a short period of time, and through the use of cell phones and two-way radios, they offer a rudimentary system of referrals with more distant hospitals. Geographical proximity to health services is essential in the case of infectious diseases. Time saved translates directly to lives saved.

Pooled procurement

The international aid process can be streamlined through more effective procurement systems, especially those which minimise the chances for corruption, diversion, and delay of delivery of vital supplies. Countries that apply to the Global Fund for AIDS, TB and Malaria, for example, need commodities (bed nets, medicines, diagnostic kits, etc.) rather than the money for these interventions. Under current practices, however, the Global Fund typically approves country applications and then sends money to the recipient countries to support an international tender for the needed commodities. These tenders are often long delayed, because of local mismanagement and the complexity of organising such bids. It would be advisable for the Global Fund to forego this laborious process and instead to provide the necessary commodities directly to the applicant countries, with a pooled (and competitive) procurement process handled by the Global Fund (or its agent) at the international level rather than by dozens of individual, low-income countries. Pooled procurement has been successful in the case of TB drugs and diagnostics, and should now be extended to commodities related to AIDS and malaria.

Global targets

Scaling up will be greatly facilitated by shared international goals, expectations, and norms. For example, it is possible to ensure universal access to basic malaria control (bed nets, insecticidal spraying, and disease case management) by the year 2010, but these feasible goals have not been clearly adopted by the global community. The global community has enunciated the goal of universal access to anti-retroviral medicines for all who need them by 2010. The World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS), and the Global Fund should be harmonising efforts of all stakeholders to meet that commitment.

Fast-track financing

Financing remains the binding constraint for almost all low-income countries, despite occasional suggestions to the contrary. Sometimes it is claimed that the money is "at hand," in the recipient country but does not move. This is almost never the case on close inspection. The money may be "at hand", but is tied up in donor red tape, or the need for local counterpart funding which does not exist, or the need to combine commodity financing with increased financing for personnel. The closer one looks, the more one sees a cash-starved system. The problem, at the core, is extreme poverty, not lack of will or solutions. Another aspect of financing is the lack of reliable

and transparent scaling up of donor funds. While the G8 has promised to double donor funding for Africa by 2010, African countries have not been shown actual timelines or plans for that scale up. For this reason they are not yet able to plan ahead of time for increased aid inflows. Both the scale of aid and its multi-year predictability and reliability are needed. Dedicated funding through multilateral channels such as the Global Fund, the World Bank, and the European Commission funds would be an enormous help in systematising the scale up of health services.

The integration of vertical and horizontal health programmes

One of the red herrings in current debates is whether aid should be for "vertical" (disease-specific) programmes or "horizontal" (health system) programmes. All experts agree on this point: the right answer is "both." The dichotomy has been so persistent because health financing has been chronically insufficient. In the context of too little aid, there are incessant debates about how to spread paltry funding to the greatest effect. In a properly designed health system, however, both vertical and horizontal programmes should exist. Horizontal programmes are needed to mobilise expertise, establish national-based protocols and data reports, raise public awareness, and deliver effective health services. Vertical programmes, however, provide the basis for long-term and sustainable success. At USD 40 per person, it should not be difficult to fund both types of programmes at once.

Novel areas of health scale up

The most urgent priorities for scaling up are the disease burdens posed by infectious diseases, nutritional deficiencies, and safe childbirth and neonatal care. Yet there is an important challenge in expanding basic health services beyond that obvious and crucial core. Two kinds of expansion are important. First, the burden of chronic diseases in low-income settings is enormous, growing, and in need of a public health response. Thus, we need to more closely examine what can and should be done in response to cardiovascular disease; mental health disorders; adult-onset diabetes and other metabolic disorders; and cancer (*e.g.* prevention and screening). In addition, there are several crucial, yet often neglected, quality-of-life conditions that can be addressed in a low-cost setting, including eye care and correction, dental care, and trauma care. As just one example, remarkable recent innovations have reduced the cost of safe and successful cataract surgery to around USD 15 per operation, with the result of restoring eyesight to the blind. In the work in the Millennium Villages Project at the

Earth Institute at Columbia University, researchers are investigating the feasibility of low-cost healthcare in the following areas:

- eye care,
- mental health (mainly depression),
- trauma,
- undiagnosed hypertension,
- dental care (treatment of cavities and tooth extraction).

Proof of concept: the Millennium Villages Project

The key propositions stated in this paper, most importantly that morbidity and mortality can be reduced rapidly in low-income settings for a modest USD 40 per person per year, is being put to the test in the Millennium Villages Project (MVP), a joint venture of the Earth Institute at Columbia University, Millennium Promise (a non-governmental organisation dedicated to the MDGs), and the United Nations Development Programme. The MVP is a five-year village-based holistic poverty reduction effort, based on integrated investments in health, education, agriculture, and core infrastructure. The project now operates in 12 sites across 10 countries in Africa, covering roughly 400 000 people. The project began operations in most of the villages during 2006. The MVP is currently being expanded in scope to many additional countries and sites. The early results are enormously promising with regard to health outcomes. The combination of improvements in nutrition, malaria prevention (through insecticide-treated bed nets), de-worming, and clinical health services is demonstrating significant, rapid, and measurable reductions of disease burden and mortality, including sharply lower incidence of malaria and reduced prevalence of parasitemia and anaemia. The project will be publishing early quantitative results in the coming months (Sanchez, Palm and Sachs, 2007).

Systematic management of scaling up

One of the ironies of recent G8 commitments to double the aid to Africa by 2010 has been the reluctance of donors to commit to a specific time path to fulfil those commitments. Though recipient country governments have been told that aggregate aid to Africa will double, they have not been told when they themselves can expect those increases. The result is an inability to pursue a multi-year systematic strategy for investments in health. The donors have made commitments, but have not yet provided the modalities for recipient countries to benefit from those commitments.

To achieve the goals outlined in this annex, donors and recipients should agree on certain standard practices, including:

- a multi-year scenario for increases in donor support (consistent with overall promises to double aid by 2010, and to reach 0.7% of GNP in aid by 2015);
- a medium-term expenditure framework (MTEF) for using the additional aid;
- a specific health-sector plan for increased investments, which harmonises the flow of resources for human resources (doctors, nurses, community health workers), physical facilities (clinics, hospitals), and commodities (medicines, diagnostics, preventative technologies);
- training programmes for community health workers on a massive scale;
- systematic deliverables against time lines, supported by rigorous monitoring, evaluation, and audits.

Notes

1. Professor Jeffrey Sachs is the Director of the Earth Institute at Columbia University and Special Advisor to United Nations Secretary General Ban Ki-Moon on the Millennium Development Goals.
2. Dr. Sonia Sachs is the Director of Health Programs of the Millennium Village Project, Earth Institute at Columbia University.

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Annex C
OECD Country Policy Options for Increasing the Availability of Medicines for Neglected Diseases

By Michael Kremer[1] and Heidi Williams[2]

Executive summary

Together, malaria, tuberculosis, and the strains of HIV common in Africa kill 5 million people each year, almost all of them in poor countries. Yet research and development (R&D) on health technologies for these and other diseases concentrated in poor countries remains minimal.

What policy options are available to OECD country governments if they wish to improve the availability of medicines needed for diseases concentrated in poor countries? The focus here is on "availability" as referring to whether new medicines and vaccines are researched, developed and brought through clinical trials to the market.

This annex first discusses issues relevant to R&D on diseases concentrated in poor countries. The markets for diseases concentrated in poor countries are small, not only due to the poverty of the relevant populations, but also due to several severe market failures. Most notably, firms face a threat that once R&D costs have been sunk, governments and other large purchasers of products for poor countries will bargain down prices to levels which do not allow firms to recuperate their risk-adjusted R&D investments.

It then broadly reviews the R&D systems which currently exist for diseases in rich and (separately) poor countries. In markets for diseases prevalent in rich countries, direct "push" R&D financing and "pull" market incentives combine to spur innovation. While several push initiatives are in place for diseases concentrated in poor countries, there is a lack of complementary pull incentives to encourage the transformation of basic research into useable products.

This annex discusses several general design issues which arise and should be considered when evaluating "push" and "pull" initiatives. We also briefly review the rationale behind pull programmes and cite evidence suggesting that pull-like policies can spur R&D investments and innovation.

This annex then presents and critically reviews a number of policy options which have been proposed for improving the availability of medicines needed for diseases concentrated in poor countries.

Drawing on these discussions, the authors conclude by drawing some general lessons for thinking about policy options in this area. We argue that some combination of continued push financing and implementation of pull finance mechanisms provides the most promise for increasing the availability of medicines needed for diseases concentrated in poor countries. Push financing is likely best directed through existing product development public-private partnerships (PD-PPPs). Such efforts have greatly enhanced the prospects for finding medicines needed for neglected diseases, but on their own are likely to be insufficient in bringing products through the final stages of development, marketing, and delivery. This suggests that PD-PPPs would be fruitfully paired with a pull mechanism which would provide market incentives for private firms to become engaged in bringing products to market. A number of the pull mechanisms offer promise for providing such market incentives – including fast-track regulatory approval, patent buyouts, or transferable "wildcard" patent extensions. In the view of the authors, the advance market commitment (AMC) proposal is most promising in terms of providing a practical, effective, and cost-effective means of both pulling products through the late stages of clinical development and marketing, and assuring that individuals in low-income countries will have access to desired products if they are successfully developed.

Introduction

Our focus in this annex is on "availability", that is to say, whether new medicines and vaccines are researched, developed and brought through clinical trials to the market. To be clear, availability is also important in the sense of increasing access to existing health technologies for individuals in poor countries; for example, 3 million people die every year of diseases preventable with existing vaccines. However, the need for accelerated development of new health technologies targeted to, and appropriate for, the epidemiological conditions and health systems of poor countries cannot be understated. In recent decades much of the improved health in poor countries has been due to the widespread adoption of cheap, easy-to-use technologies that were developed in response to incentives provided by

prospective sales in rich country markets. Vaccines are perhaps the paradigmatic example: 74% of the world's children now receive a standard package of cheap, off-patent vaccines through the World Health Organization's (WHO) Expanded Programme on Immunization (EPI). These vaccines save some 3 million lives per year – almost 10 000 lives a day – and protect millions more from illness and permanent disability (Kim-Farley *et al.*, 1992).

Poor countries have benefited enormously from products such as the currently used EPI vaccines, but these benefits have been, for the most part, a fortunate by-product. Little public or private sector research and development (R&D) is targeted towards developing new health technologies for diseases concentrated in poor countries. One measure of this dearth of R&D on neglected diseases is in terms of inputs – in this case, spending on R&D. One commonly cited estimate is that while half of all global health R&D in 1992 was undertaken by private industry, less than 5% was spent on diseases specific to poor countries (WHO, 1996). Another measure of this dearth of R&D on neglected diseases is in terms of outputs – in this case, drugs that have been developed. Of the 1 233 drugs licensed world wide between 1975 and 1997, only 13 were for tropical diseases; of these 13, 5 came from veterinary research, 2 were modifications of existing medicines, and 2 were produced for the US military – only 4 were developed by commercial pharmaceutical firms specifically for human tropical diseases (Pecoul *et al.*, 1999).

Even for diseases that are major health issues in rich countries, R&D on these diseases may not result in products that easily spill over to the epidemiological conditions and health systems of poor countries. For example, in the case of HIV, most R&D is focused on the strain of the virus common in rich countries, and is on drug treatments rather than vaccines – treatments which are more difficult than vaccines to deliver in poor countries with weak healthcare infrastructures.

Background on R&D for diseases concentrated in poor countries

Market failures for R&D on medicines for neglected diseases

Biotechnology and pharmaceutical firms have little incentive to undertake R&D on diseases concentrated in poor countries. One reason is that the potential consumers (patients and their governments) are poor. This situation suggests a role for assistance from richer countries. But two major market distortions further reduce the incentives for R&D on new products for neglected diseases.

First, the scientific and technological advances generated by R&D on these diseases spill over to many nations, so none of the many small countries that would benefit from (for example) a malaria vaccine has an incentive to encourage R&D by unilaterally offering to fund R&D directly or to pay higher prices for new products.

Second, governments and other institutions that buy health technologies for these diseases face a "time inconsistency" problem. Once pharmaceutical companies have made the R&D investments necessary to develop health technologies, governments and aid institutions often use their powers as dominant purchasers and arbiters of intellectual property rights to keep prices close to marginal cost in the interest of using limited budgets to maximise access to life-saving products. Because, however, the largest part of the industry's expenditures lies in the initial R&D cost, prices that cover the (typically modest) variable costs of production will not allow companies to recover their R&D investment, thereby deterring industry from investing in such R&D in the first place.

Although the goals of creating incentives for R&D on new pharmaceuticals (which requires high prices) and ensuring wide access to pharmaceuticals once developed (where low prices enable budgets to go further) are often pitted against each other, well-designed incentive mechanisms can de-couple these goals and promote both effectively.

Existing R&D systems for medicines needed in rich and poor countries

For diseases prevalent in rich countries, a combination of "push" (reducing R&D cost and generating scientific leads) and "pull" (demand for the products that flow from the R&D) measures help to provide incentives for private sector R&D in biotechnology and pharmaceutical firms. Push funding from institutions such as the US National Institutes of Health and the Wellcome Trust supports basic scientific research and some clinical development, while the prospect of profits in rich country markets provide pull incentives for private sector firms to transfer basic research into useable products.

Applying the same principle to vaccines and drugs for poor countries would suggest using push programmes for basic research and clinical development and pull programmes to encourage biotech and pharmaceutical firms to turn this research into needed health technologies. For diseases concentrated in poor countries, push funding is currently being provided from a number of institutions, notably PD-PPPs such as the Malaria Vaccine Initiative (MVI) and the International AIDS Vaccine Initiative (IAVI), but

there is a dearth of complementary pull incentives to encourage private sector R&D into health technologies for these diseases. While more push funding is needed, some of which is used to fund private sector R&D, a major stumbling block remains the lack of a market pull incentive to turn basic R&D into useable products.

Policy options for financing R&D for neglected diseases

In this section, we present and critically review a number of policy options which have been proposed for improving the availability of medicines needed for diseases concentrated in poor countries.

Throughout, we attempt to highlight key issues which should be considered when evaluating these proposals. For example: can the mechanism encourage timely access to products, if and when they are developed, for individuals in poor countries? If the mechanism involves the private sector, will mechanisms be seen as credible by industry? Can the mechanism be structured so as to foster competition and follow-on, improved products?

We will first review two structures for "push" financing: PD-PPPs and targeted R&D tax credits. We will then review a number of "pull" mechanisms: patent extensions on existing pharmaceuticals; expanding markets for existing products needed in poor countries; patent buyouts; prizes or best-entry tournaments; AMCs; revenue (price and quantity) guarantees; and fast-track regulatory approval.

"Push" mechanisms

The canonical example of push funding is directly financed R&D as supported by institutions such as the Wellcome Trust and the US National Institutes of Health (NIH). Push funding can also be designed through PD-PPPs or through targeted R&D tax credits. Before discussing these two proposals in detail, we will first highlight several general issues which can arise with push programmes.

Design issues arising with push programmes

By design, push programmes pay for research inputs rather than results. While the R&D landscape which currently exists for medicines for diseases prevalent in rich countries suggests this type of push financing is critical for the development of successful pharmaceutical products, this design brings with it a number of potential problems.

Precisely because push programmes pay for research inputs rather than results, decisions must be made about where to commit funds before a product is actually developed. An obvious stumbling block is that administrators of healthcare R&D programmes may (understandably) have trouble deciding *ex ante* which scientific approaches are most promising and worth pursuing.

Even if programme administrators manage to choose wisely at the outset, they may develop a bureaucratic stake in their judgments and fail to revise them in light of subsequent evidence. In the case of R&D by a private firm, if results from a research project that initially appears promising turn out to be disappointing, the firm has bottom-line incentives to shut the project down. On the other hand, a public programme is arguably more likely to acquire its own bureaucratic momentum, which can lead governments to throw good money after bad.

A related problem is that authority about which research directions are most promising lies in the hands of administrators who must rely on information from those with vested interests in the decisions. Researchers funded on the basis of an outsiders' assessment of potential rather than for actual product delivery have incentives to exaggerate the prospects that their approach will succeed. These incentive problems occur regardless of whether aid comes in the form of grants or targeted R&D tax credits for research.

Finally, another potential problem with aid tied to research grants is that researchers often have incentives to stray from the task, devoting effort to preparing the next grant application or to work on unrelated projects that will advance their careers. As we will discuss below, this is in contrast to pull programmes which pay only if researchers successfully generate the desired product.

This being said, given the very large existing gap between private and social returns to research on medicines for neglected diseases, push programmes are, on average, likely to have strong positive returns even if they cannot realise the full potential return that would be theoretically possible in the absence of the inefficiencies detailed above.

Product development public-private partnerships

PD-PPPs emerged in the mid-1990s as a financing mechanism which focused not on a single candidate product but rather on developing a range, or portfolio of, several different candidate products – the idea being that management of such a portfolio is designed to manage the risk of failure which is associated with any individual candidate product (Widdus and White, 2004). Most PD-PPPs work in collaboration with numerous firms and laboratories, including smaller companies and groups in the developing world. A number of PD-PPPs now exist, and are primarily funded by private foundations and charitable trusts (such as the Rockefeller Foundation and the Bill & Melinda Gates Foundation).

The prospects for products addressing neglected diseases have been significantly improved in recent years by the establishment of PD-PPPs such as the MVI and the IAVI. However, although it is difficult to make generalisations about PD-PPPs, we argue that alone (that is, in the absence of partnership with a complementary pull financing mechanisms) such programmes encounter a number of stumbling blocks.

First, while PD-PPPs have greatly enhanced the prospects for finding medicines for neglected diseases, the financial resources are still too small to fund the development of more than a small number of candidate medicines.

Second, most PD-PPPs are not currently funding activities to translate research into ready-to-administer products (Nwaka and Widdus, 2004). This suggests that PD-PPPs may be fruitfully paired with another mechanism more oriented towards the later stages of development and delivery. We argue in this paper that a pull mechanism such as an advance market commitment may be a promising complement to PD-PPPs.

It is worth clarifying the potential role of advanced development and introduction plans (ADIPs) in this process. For late stage vaccines (those in Phase III trials and beyond), the Global Alliance for Vaccines and Immunization (GAVI) has suggested that public-private partnerships in the form of ADIPs can reduce the time lag between adoption of new vaccines in developed and developing countries by reducing demand uncertainty. ADIPs have been developed for the rotavirus and pneumococcal vaccines, and aim to speed uptake of vaccines by encouraging early communication between firms and major purchasers. They are intended to predict both demand and supply for a late stage vaccine, generate practical plans for vaccine delivery in developing countries, and assess the impact and cost-effectiveness of early introduction.

Relevant to this discussion, ADIPs are primarily applicable to vaccines that have already been developed, typically in response to incentives

provided by rich country markets. ADIPs play a valuable role in closing the gap between when vaccines are introduced in rich countries and when they are made available to poor countries, but arguably more substantive incentives are needed to spur R&D investments for products such as a malaria vaccine which would not be developed in response to rich country market incentives.

Targeted R&D tax credits

Some have proposed targeting R&D tax credits toward research for drugs and vaccines for neglected diseases such as malaria, tuberculosis (TB) and HIV. For example, in the United States the proposed Vaccines for the New Millennium Act of 2001 included a 30% tax credit on company R&D expenditures for vaccines for HIV, TB, and malaria. However, because these tax credits would reward research inputs and not results, they would likely be subject to many of the problems of other push programmes.

First, R&D tax credits do not improve access to products once they are developed. Patent rights for a malaria or HIV vaccine developed by a company that received the credit would remain with the company for the usual period of market exclusivity. And if intellectual property rights were respected, the price of the vaccine might well be high enough to deny the vast majority of residents of poor countries the benefit from the vaccine during the life of the patent.

Second, R&D tax credits may not create incentives to develop products appropriate for low-income countries because markets in rich countries are more likely to be profitable. Most new HIV infections occur in Africa, where clade C dominates. However, commercial vaccine development is largely currently focused on clade B, which is common in the United States and Europe. It is not known whether a vaccine designed to be effective against clade B would also be effective against clade C. An enhanced R&D tax credit for HIV vaccine research would not change the reality of where the commercial market lies.

Similar issues arise with malaria. A vaccine for travellers and military personnel would likely focus on the sporozoite-stage of malaria, which is the lifecycle stage of the parasite when it is first passed from a mosquito to its human host. But a vaccine focusing on sporozoites might provide only temporary protection, and thus not be useful for residents of poor regions where malaria is widespread. In fact, such a vaccine could even be contraindicated for residents because it could weaken the limited natural immunity built up by those who survived childhood.

Although one could attempt to overcome these problems simply by restricting the tax credits to particular forms of research — *e.g.* research on clade C HIV vaccines or malaria vaccines that target the parasite in the later merozoite stage – this might be counterproductive. For example, a vaccine designed for one HIV clade might prove to be effective against other clades, or research on the sporozoite stage of the malaria parasite's lifecycle might prove useful in creating a vaccine that would provide long-run protection. Instead of prejudging the scientific issues, it would be more effective to create rewards linked to the efficacy of a vaccine in the countries where the disease burden is greatest. Efficacy, of course, can only be assessed after a vaccine has been developed. This suggests explicitly linking rewards to final product through pull mechanisms. Restricting an enhanced R&D tax credit to the clinical stages of research might make it easier to target populations most in need, but would provide only a limited incentive as only a fraction of the capitalised cost of R&D is incurred in the clinical phase of pharmaceutical development.

A third problem with an enhanced R&D tax credit is that firms would have incentives to resort to creative accounting in order to maximise their claims. Determining expenses actually qualified for a targeted tax credit would be administratively complex at best. Expenses in vaccine research may be common to a number of research projects – not all of which should qualify.

Fourth, even a tax credit that could be administered effectively would only serve as an incentive for firms that have tax liabilities. Most biotechnology firms have no current profits or tax liability, and thus would not benefit unless they were permitted to pass their tax credits through to their investors – which itself would be problematic.

"Pull" mechanisms

In this section, we will critically review a number of proposed "pull" mechanisms: patent extensions on existing pharmaceuticals; expanding markets for existing products needed in poor countries; patent buyouts; prizes or best-entry tournaments; advance market commitments; revenue (price and quantity) guarantees; and fast-track regulatory approval. Before discussing these proposals in detail, we will first provide some background on the rationale behind pull mechanisms, and discuss several general issues which may potentially arise with pull programmes.

The rationale behind pull mechanisms

Sizeable academic literature as well as several historical precedents suggest that market-based pull incentives are effective in stimulating R&D investments and innovation in developed country markets. Specific to the pharmaceutical industry, Acemoglu and Linn (2004) analyse the effect of expected market size on the entry of new drugs through examining variations in market size for pharmaceuticals linked to demographic changes, and find that a 1% increase in the potential market size for a drug category leads to a 4-6% increase in the number of new drugs in that category.

Several historical examples reinforce the view that policies increasing the value of markets for pharmaceuticals can encourage R&D. For example, the US Orphan Drug Act, which went into effect in 1983, created a number of financial incentives for pharmaceutical companies to develop drugs for rare diseases like Huntington's, ALS (Lou Gehrig's disease), and muscular dystrophy – diseases which affect fewer than 200 000 people in the United States and therefore have a limited market. The primary attraction for companies is a promise of seven years of market exclusivity. Although before/after comparisons are difficult to make, over 200 orphan drugs have been developed since 1983, while fewer than 10 were introduced in the decade preceding passage of the act.

Another set of precedents for the case of vaccines are the recommendations from the US Advisory Committee on Immunization Practices (ACIP). ACIP's recommendations typically set policy for immunisation requirements in the United States, and hence if a vaccine is recommended by ACIP, the producers of that vaccine are assured of a reasonably large market. Finkelstein (2004) investigates the private sector response to health policies such as the ACIP recommendations that, in attempting to increase immunisation rates, also increased the expected profits from new vaccines. Her work estimates the change in investment in vaccines against those diseases, using changes in investment for vaccines against carefully selected diseases that were not affected by the policies to control for underlying secular trends in R&D in the vaccine market, and finds a strong positive impact of these policies on private sector R&D activity on affected vaccines.

Design issues arising with pull programmes

Pull programmes have a number of key benefits. With pull programmes money changes hands only when a successful product is developed – implying that sponsors need not worry that they will invest millions in a

project that ultimately fails. Pull programmes offer the opportunity to harness the same energy and creativity the private sector has shown in developing products for high-income countries toward the development of products for low-income countries in an open, transparent approach that is difficult for special interests to capture. Private sector R&D would be attracted to worthwhile products through a market-oriented approach, and donor dollars would reward success without micro-managing the research process.

Pull programmes are especially well suited for cases in which there exists a divergence of opinion on scientific prospects for a product – as is the case for the development of an effective malaria vaccine. The idea with pull is simply that if there are scientists who believe the development of a malaria vaccine is scientifically feasible, they should not be deterred or have insufficient resources just because the potential returns to investments are likely to be small. Individual scientists and firms working on a given problem are best placed to judge scientific prospects. If they judge scientific prospects worthwhile they can invest time and resources into pursuing projects; if not, they can invest their time and effort elsewhere. Pull programmes thus efficiently align incentives, with governments and other funders defining the problem and private developers competing to find the best solution.

Pull programmes do, however, have a number of limitations. In particular, they must specify the desired research outputs beforehand, and coming up with the right specifications and eligibility requirements may be difficult. For example, a pull programme could not have been used to spur the development of the Post-It Note® or the graphical user interface for computers because these products could not have been adequately described before they were invented. Similarly, it is usually difficult to stimulate basic research through pull programmes, since the output of basic research is often difficult to specify in advance. It would be easier (though still difficult) to define what is meant by a safe and efficacious vaccine, however, since existing institutions, such as the US Food and Drug Administration (FDA), are already charged with making these determinations.

One of the benefits of pull (that the sponsor does not have to pay unless and until a vaccine or drug is developed) is also one of the potential limitations as, without sufficient assurances, developers will be concerned that a sponsor will renege on the commitment and so not undertake the necessary research. This suggests that pull programmes should be designed carefully so as to create sufficient credibility. As discussed in Kremer and Glennerster (2004), the historical and legal record provides strong evidence that suitably designed pull programmes will be interpreted by courts as legally binding contracts (Morantz and Sloane, 2001).

Another issue is that pull programmes could potentially lead to duplication of research activities. Of course, it is often appropriate to pursue many different leads simultaneously in searching for solutions to important problems. Nonetheless, it is possible to construct examples in which pull could lead to excessive duplication of research. It is unclear whether replication of R&D would actually be a problem in practice, as at least in some cases it may make more sense for two teams to work on the most promising lead than for them to be directed to pursue different approaches. To the extent that policy makers are confident that promising approaches are being neglected under pull programmes, this limitation could be addressed through some combination of push and pull financing programmes.

Patent extensions on existing pharmaceuticals

One pull proposal is to compensate developers of (for example) an HIV vaccine with the right to extend patent rights on another pharmaceutical product in their portfolio. As an example, this proposal is currently applied selectively by the US FDA through the paediatric exclusivity rule – under which drug companies receive an extra size month's of patent protection if they test their product on children.

Such patent extensions may appeal to politicians because they do not show on the government budget as an expenditure and thus would need not run the gauntlet of the government budgeting process.

However, a potential drawback of this proposal is that patent extensions could unfairly – and inefficiently – place the entire burden of financing vaccine and drug development on patients who need the drug for which the patent has been extended. From a public finance perspective, patent extensions are economically equivalent to imposing a high tax on a narrow basis – which is an inefficient way of raising revenue since this would reduce consumption of the taxed good below the point where value at the margin equals production cost. In addition, if there are significant out-of-pocket payments by patients, patent extensions would also raise equity concerns. In practice, for countries such as the United Kingdom which have national health insurance systems, this may be a much smaller concern.

Another drawback of this proposal is that patent extensions would likely be a "winner takes all" mechanism and thus fail to provide incentives for competition and improved, follow-on products.

A general point is that transferring rights from one product to another eliminates a key advantage of patents – that is, that patents closely link the inventor's compensation to the value of the invention. If a vaccine is more effective, causes fewer side effects and is easier to administer, it will bring

in more revenue. By contrast, rewarding the inventor of an HIV vaccine with the extension of a different patent would break this link between the quality of the HIV vaccine and the magnitude of the compensation.

A potential downside of patent extensions is that the right to extend a patent would be worth the most to firms (usually larger pharmaceutical firms) already holding patents on commercially valuable pharmaceuticals. Smaller firms or firms located in developing countries may benefit less. Moreover, the patent-holding firms may not be the firms with the best opportunities for, for example, vaccine research. The problem would not be fully resolved by making patent extensions tradable, since firms holding patents on commercially valuable pharmaceuticals would presumably insist on some profit from such trades.

Expanding markets for existing products needed in poor countries

Some observers argue that by purchasing more of existing products at higher prices, policy makers could signal their intent to provide a market for future products – thereby encouraging research on desired technologies. There are, indeed, good reasons to increase purchases of existing vaccines; but we argue that such purchases would not be an efficient means toward the end of bringing new vaccines to market.

Although the standard EPI package of vaccines is widely distributed, a number of effective vaccines that are also available are not being fully utilised. Purchasing and distributing existing vaccines that are not widely used in low-income countries, such as the haemophilus influenzae b (Hib) vaccine, would be a cost-effective way to save lives and is justified in its own right, independent of any effect on research incentives. But stimulating research on new products will likely require more specific incentives. It could easily take a decade to develop malaria, tuberculosis or HIV vaccines, and developers would need to recuperate their investment through sales in as many years following the vaccine rollout. Since international interest in the health of poor countries is potentially fickle, firms might feel that the availability of funds to purchase vaccines now at a remunerative price would not say much about how much donors would be willing to pay for vaccines 15 years hence.

Moreover, paying higher prices from now onwards as a way to stimulate future research amounts to paying twice for the research. The Hib vaccine was developed on the basis of demand in rich countries and without any expectation of realising substantial profits in poor countries – thus, increasing the price paid now would generate a windfall for the developer. Providing these extra profits might be worthwhile if it were really the only way to ensure the credibility of donors down the road. However, if it were

possible to commit now to purchase future products at a remunerative price, there would be no reason to pay more for current products than developers had anticipated when they took the risk in pursuit of innovation.

Finally, some argue that increasing vaccine sales today would increase vaccine R&D budgets because pharmaceutical firms finance research on a division-by-division basis, as a percentage of current sales. While some drug makers may use such rules of thumb to make budgetary decisions within the current R&D system, they would have a clear incentive to adjust these rules if the environment changed. And if they did not, new biotech firms, which are more flexible in their budgetary decisions, would have incentives to enter the field in response to increased market sizes.

Patent buyouts

Another pull proposal would be for sponsors to offer to buy patent rights to a product meeting specified conditions, and then place the patent in the public domain and encourage competition in manufacturing the medicine. A historical example of this proposal was the *ex post* purchase, in 1839, by the French Government of Louis Jacques Mande Daguerre's patent for the photography process (see Kremer, 1998).

This mechanism overcomes many limitations encountered by other pull programmes. For example, by design, this mechanism attempts to improve access to products once they had been developed. The proposal might be attractive to individuals and companies which focus on basic and applied research but do not engage in product development.

Patent buyouts lead to free competition in manufacturing newly invented goods, whereas programmes designed to finance purchases (such as advance market commitments, as we will discuss below) require the sponsor to specify more details of the goods purchased. In many cases, this implies patent buyouts would have significant advantages over proposals such as purchase commitments. For example, if a sponsor committed to purchasing high-definition television sets as a way of encouraging research in the field, it would have to get involved in decisions about colour, style, reliability, screen size, and other issues best left to consumers. In the case of medicines, however, governments already purchase them and regulate their quality, and thus are, in effect, the consumers.

Moreover, in the case of vaccines, helping finance purchases of an actual product has significant advantages. First, because vaccines are difficult to produce, a patent buyout might leave the developer who has production know-how with an effective monopoly, anyway. Then the public

would effectively pay twice: once for the patent, and again for the product at a price far above manufacturing cost.

Second, product purchases would create a tighter link between payments and product quality. Suppose a vaccine received regulatory approval, but was later found to have harmful side effects – as was the case with the Wyeth-Ayerst rotavirus vaccine, which was withdrawn from the US market following evidence that in rare cases it caused intussusceptions (a form of intestinal blockage). If the patent had been bought out at the date of regulatory approval, a wasteful legal fight might have been needed to recover the money. Medicines purchases, on the other hand, could easily be suspended as soon as evidence of unacceptable side effects appeared.

Third, purchase commitments are likely to be more attractive politically than patent buyouts, and thus more credible to product developers. Developers are vulnerable to expropriation, even if the terms of the compensation programme legally obligate the sponsor to compensate them for qualifying products. For example, a pharmaceutical firm that had just earned a windfall on a malaria vaccine might be subjected to stiff price regulation on an unrelated product.

Prizes or best entry tournaments

In best entry research tournaments, a sponsor promises a reward to whoever has progressed the furthest in research by a specific date, whether or not the goal of a useful product has been reached. As an example, best entry tournaments are often used to select architects for large construction projects.

A vaccine or drug tournament would differ from an architecture tournament, however, because biomedical researchers could not promise a certain level of completion on a given date, whereas architects can generally submit completed designs by a deadline.

Best entry tournaments also have other limitations which make them ill-suited to encouraging vaccine and drug research. One drawback is that a payment would have to be made, no matter what amount of progress were achieved – implying that even if the target product proved impossible to develop – the same amount of money would be paid.

Perhaps the main concern with best entry tournament proposals is that it may be difficult to avoid a winner-take-all framework while maintaining credibility. For example, if committees evaluate the value of innovations *ex post*, they will be tempted to undervalue the innovations in order to reduce the payments to the developer, and hence free up sponsor resources for other public health expenditures. A related problem is that the subjective

aspects of judging progress would open decisions to bias. For example, the judges might decide to reward a firm with the most political clout, or perhaps the team that has done the most scientifically interesting work on other projects.

Best entry tournaments may also lead researchers to putting their efforts into looking good on the tournament completion date, rather than on positioning the project for a swift and successful conclusion. Firms that discover promising research leads that seem unlikely to yield solid results before the deadline might ignore these leads, while firms learning that the research lines they are pursuing are unlikely to yield a successful product might nonetheless continue their work in an attempt to hide their lack of progress.

Finally, best entry tournaments are also politically unattractive, as governments might be embarrassed paying large amounts for research that did not ultimately yield valuable medicines.

Advance market commitments

A working group convened by the Center for Global Development (CGD), with the support of the Bill and Melinda Gates Foundation, published a report recommending how a proposal called "advance market commitments" (AMCs) for vaccines could be implemented. We use the CGD proposal as the benchmark structure of an advance market commitment in this annex, and draw on the analysis set out in that report.

The idea behind an AMC as embodied in the CGD proposal is that sponsors would commit – in advance of product development and licensure – to fully or partially finance purchases of health technologies for poor countries at a pre-specified price. A financially (and otherwise) credible programme sponsor or coalition of sponsors would sign a contract underwriting a guaranteed price for the supplier. If a desired product is developed, poor countries would then decide whether to buy a product at a low and affordable price (say, USD 1 per treatment), and sponsors would guarantee to top up to a guaranteed price (say, USD 15 per treatment) – thus providing market returns for the developer which are comparable to other, average-revenue pharmaceutical products. Once the full number of treatments has been purchased at the guaranteed price, the supplier would, in return, be committed to selling further treatments at an affordable price in the long term. The sponsors could retain the right to seek alternative suppliers at the end of the guaranteed price contract period. Although not part of the contract, there would be nothing to stop the original sponsors or other donors from covering the USD 1 price on behalf of poor countries at

the time of purchase. The advance purchase commitment structure as recommended in the CGD report is presented in Table C.1.

Table C.1. **Example structure of an advance purchase commitment**

Advance market commitment	**Example for malaria vaccine**
Legally binding contracts, enforceable by law	Offer made by a group of sponsors
Total market value approximately equal to sales revenues earned by average new medicines	Total market size of USD 3 billion (net present value, 2004 dollars)
Sponsors under-write a specific price	USD 15 per treatment (*e.g.* USD 5 per dose for 3 doses)
Price guarantee applies to a maximum number of treatments	Guarantee for first 200 million treatments
Treatments sold in eligible countries	Vaccine Fund eligible countries
In return, the developer guarantees to sell subsequent treatments at a low price	USD 1 per treatment
Recipient country makes a co-payment for the products they buy (or asks a donor to do so)	USD 1 paid by recipient USD 14 paid by sponsors
Successful developers receive USD 15 per treatment sold.	
Subsequent products are also eligible for the guaranteed price, if superior to existing products – as developing countries can switch their demand to these subsequent, superior products.	
An Independent Adjudication Committee oversees the arrangement.	

Source: Barder, O., *et al.* (2005), *Making Markets for Vaccines*, Center for Global Development, Washington, DC.

This type of policy initiative has recently been gathering momentum. In November 2004, the UK Chancellor of the Exchequer, Gordon Brown, announced that the UK government, working in co-operation with other donors, would be willing to enter into an advance market commitment for a malaria vaccine (Brown, 2004); the Chancellor later announced that the United Kingdom will also explore the use of advance market commitments for HIV vaccines. In December 2005, the G7 finance ministers announced an agreement to work with others on developing a pilot advance market commitment (HM Treasury, 2005), and further statements of support were issued by several countries at the July 2006 G8 Summit in St. Petersburg, Russia (G8 Information Centre, 2006). The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA, an organisation representing the major global research-based pharmaceutical and vaccine companies) has also expressed support of the proposal (IFPMA, 2006). Kremer and Glennerster (2004) lay out the rationale for advance purchase

commitments and discuss design issues, and Berndt and Hurvitz (2005) discuss some of the legal and economic practicalities of structuring advance purchase commitments.

For firms, this type of advance purchase arrangement would reduce economic uncertainty and increase investor confidence about the returns they can expect if the relevant scientific challenges are overcome. To be clear, advance market commitments would not eliminate all risk to developers; the scientific challenge and risks, as in markets for diseases in rich countries, would be considerable and the risk of failure high, but AMCs would greatly reduce the risks specific to markets for diseases concentrated in poor countries.

If structured correctly, advance purchase commitments can also facilitate access to these technologies if and when they are developed. Consider the CGD proposal presented in Table C.1: in the short term, access is facilitated through donor purchasers at the higher, pre-specified purchase price. In the long term, financially sustainable access to these technologies is facilitated through the contract provision which requires developers to commit to dropping the price to a low level (close to marginal cost) after all high-price purchases have been made.

Several design issues are critical for AMCs. Commitments would need to cover the case in which more than one vaccine is developed, the rules for which should be set with several objectives in mind: first, fashioning incentives to appropriately reward development of the initial vaccine; second, creating incentives to improve on the original vaccine; and third, delivering the best available vaccines to patients. For example, from the standpoint of society as a whole, it is not a good use of resources to encourage development of second products that are different but not superior in use. The CGD proposal sets out one approach for dealing with this case (based on a "superiority clause" similar to a mechanism embodied in the US Orphan Drug Act), but others have suggested different approaches and this issue would need to be carefully considered in the design of an AMC.

Another key issue with AMCs is that the contracts must be credible. Kremer and Glennerster (2004) discuss how legal precedents suggest that such contracts are enforceable by contract law and existing legal institutions. The sponsors must have credible financial backing – such as developed country governments and well-endowed foundations.

A major advantage of AMCs is that donor funds are spent only if desired products are developed. If desired vaccines are developed, advance purchase commitments would be a very cost-effective expenditure from a public health perspective. Berndt *et al.* (2007) present a cost-effectiveness

analysis of advance market commitments; for the case of a malaria vaccine, the authors estimate that a purchase commitment of USD 3.1 billion (comparable to the average revenue for existing commercial products) would cost an estimated USD 15 per life-year saved – very cost effective compared to other health or development expenditures.

Revenue (price and quantity) guarantees

An advance contract mechanism closely related to that of advance market commitments is a revenue (or price and quantity) guarantee. That is, rather than simply committing to a guaranteed minimum price for a desired product, sponsors commit to how many treatments would be bought from each supplier at this price.

In a revenue guarantee scheme, manufacturers of qualifying products would be guaranteed all – or, if there are multiple qualifying products, a portion – of the sponsor's financial commitment, regardless of whether the products are actually used. This has the benefit of reducing the demand risk for manufacturers, which may be an important benefit for pharmaceutical companies in light of the existing deficiencies in the forecasting and procurement systems in many poor countries.

Arguably, however, a purchase commitment should pay for a product only if there is demand for that product. This requires manufacturers, sponsors and recipient countries to work together to take the steps necessary to ensure that the product is be delivered to those who need it, thus ensuring that sponsors do not find themselves legally obliged to purchase a product that no one wants.

The critical distinction between advance market commitments and revenue guarantees is who bears the risk: namely, in the case of revenue guarantees sponsors shoulder more risk than they do in the case of AMCs.

Fast-track regulatory approval

A final pull proposal is to reward pharmaceutical firms developing products for a neglected disease with "fast track" regulatory approval for an unrelated product in developed country markets. As an example, this mechanism is currently selectively applied by the US FDA.

As a general point, one could argue that if there are positive health impacts of fast-track approvals then, arguably, they should be used for all products, and not used as a reward; if there are negative health impacts then fast-track approvals are inappropriate and should not be used.

One potential challenge with this proposal is that the value of transferable fast-track licensing approvals could vary over time, thus creating a substantial amount of uncertainty for companies.

This proposal would need to be carefully designed so as not to be equivalent to a "winner-takes-all" situation (which would fail to provide incentives for competition and subsequent improved, follow-on products).

Table C.2 summarises the advantages and challenges of the pull proposals discussed in this section.

Table C.2. **Alternative forms of "pull" incentives for commercial R&D**

Approach	Description	Advantages	Risks and challenges
Patent extensions on existing pharmaceuticals ("wildcard" or transferable patents) *Example:* Currently applied selectively by the US FDA (paediatric exclusivity rule)	Give a manufacturer the right to extend the patent on any product in an industrial market	Attractive to larger pharmaceutical companies Potential political appeal because would not be shown as an expenditure on government budgets	Favours big companies and those with existing patents (unless transferable) Breaks link between compensation and value of product Places cost of development on users of drugs whose patent is extended; may impede access to that drug Winner takes all – does not foster competition for subsequent improvements
Expanding markets for existing products needed in poor countries	Purchase more of existing medicines for neglected diseases at higher prices as a way of signalling a market for future products	Justified on its own as a cost-effective way of saving lives, independent of any effect on R&D incentives	Provides no binding commitment, hence unlikely to spur risky or long-term investments Amounts to "paying twice" for existing products which would be purchased at a higher price but would have been developed anyway
Patent buyouts *Example: Ex post* purchase, in 1839, by the French Government of Louis Jacques Mande Daguerre's patent for photography process	Sponsor offers to buy patent rights to a product meeting specified conditions, then puts the patent in the public domain and encourages competition in manufacturing the product	Allows competition among manufacturers May reduce prices and thus increase access	Promises must be credible Must be designed to cover appropriate products No tight link between payments and product quality Challenge of judging value of inventions Likely to be winner takes all

Table C.2. **Alternative forms of "pull" incentives for commercial R&D** (continued)

Approach	Description	Advantages	Risks and challenges
Prizes or best entry tournaments *Example:* USD 10 million X-prize for non-government human spaceflight[1]	Offer cash or other reward to whoever achieves a certain, pre-specified goal	Immediate upfront payment; no need for long-term contract	Industry may not be enthusiastic about competing for prizes Does not address access Winner takes all – does not foster competition for subsequent improvements
Advance market commitment *Example:* As proposed for vaccines by the Center for Global Development	Sponsor promises to fully or partially fund purchases of products meeting specified conditions	Creates link between payment and product quality Creates market for improvements Ensures access in short and long run Sponsors only pay if a desired product is developed	Promises must be credible Must be designed to accommodate the case of multiple qualifying products Must be designed to cover appropriate products
Revenue (price and quantity guarantees)	Sponsor promises to finance the purchase of a specified number of treatments for each supplier at a guaranteed price	Reduces demand risk facing manufacturers	Increases demand risk facing sponsors May lead to the purchase of products which are not usable or not desired
Fast-track regulatory approval *Example:* Currently applied selectively by the US FDA	Rewarding pharmaceutical companies by fast-tracking regulator approval for them or for other, more profitable medicines	Benefits to pharmaceutical companies at little cost Complement other approaches	Reward insufficiently large and insufficiently certain Only benefits firms with other profitable products (unless transferable) Unless carefully designed, would be comparable to winner takes all – and hence not foster competition for subsequent improvements

1. See *www.xprizefoundation.com/* for more details. The X-prize was modelled after a long history of aviation prizes, and was intended to spur the first non-government human spaceflight. On 4 October 2004, "SpaceShipOne'"(the winning entry) became the first private manned spacecraft to exceed an altitude of 100 km twice in as many weeks, thus claiming the USD 10 million prize.

Source: Adapted from Barder, O., *et al.* (2005), *Making Markets for Vaccines*, Center for Global Development, Washington, DC.; Kremer, M. and R. Glennerster (2004), *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases*, Princeton University Press, Princeton; and Kremer, M., A. Towse and H. Williams (2005), "Briefing Note on Advance Purchase Commitments," paper prepared for the UK Department for International Development (DFID).

Looking ahead

Some combination of continued push financing and implementation of pull finance mechanisms provides the most promise for increasing the availability of medicines needed for diseases concentrated in poor countries.

Push financing is likely best directed through existing PD-PPPs. Such efforts have greatly enhanced the prospects for finding medicines needed for neglected diseases, but on their own are likely to be insufficient in bringing products through the final stages of development, marketing, and delivery. This suggests that PD-PPPs would be fruitfully paired with a pull mechanism which would provide market incentives for private firms to become engaged in bringing products to market. A number of the pull mechanisms we discuss offer promise for providing such market incentives – including fast-track regulatory approval, patent buyouts, or transferable "wildcard" patent extensions. In our view, the advance market commitment proposal is most promising in terms of providing a practical, effective, and cost-effective means of both pulling products through the late stages of clinical development and marketing, and ensuring that individuals in low-income countries will have access to desired products if they are successfully developed.

Notes

1. Michael Kremer is with Harvard University, the Brookings Institution, the Center for Global Development (CGD) and the National Bureau of Economic Research (NBER).
2. Heidi Williams is with Harvard University.

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Annex D

Improving the Access to Essential Medicines in Low-Income Countries

By Professor Jeffrey D. Sachs[1]

An estimated 10.8 million people died from infectious diseases in 2001. Of those deaths, 98.6% (10.6 million) occurred in the developing world, while only 1.4% (150 000) occurred in high-income countries (Jamison *et al.*, 2006, Chapter 3). Around half of all deaths from infectious diseases occur in sub-Saharan Africa. Indeed, as seen in Table D.1, the top four killers in sub-Saharan Africa are infectious diseases, and the fifth is perinatal deaths, while in rich countries, the top five killers are non-communicable diseases. The vast majority of deaths from infectious diseases, maternal mortality, and perinatal deaths are preventable or controllable. The core problem is that existing, highly effective, and low-cost interventions to control these diseases simply do not reach the poor. The root cause of this massive failure is extreme poverty itself: health systems barely function in the rural areas of the poorest countries (Sachs and Sachs, 2007). Rich countries can afford to fight infectious diseases, while the poor cannot. Increased donor resources, directed at the poorest of the poor, could save millions of lives each year and would achieve vast economic benefits many times larger than the costs (CMH, 2001).

Table D.1. **Leading causes of the disease burden by region, 2001**

Rank	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa	High-income countries
1	Cerebrovascular diseases	Ischemic heart disease	Perinatal conditions[1]	Ischemic heart disease	Perinatal conditions[1]	HIV/AIDS	Ischemic heart disease
2	Perinatal conditions[1]	Cerebrovascular diseases	Unipolar depressive disorders	Perinatal conditions[1]	Lower respiratory infections	Malaria	Cerebrovascular diseases
3	Chronic obstructive pulmonary disease	Unipolar depressive disorders	Homicide and violence	Traffic accidents	Ischemic heart disease	Lower respiratory infections	Unipolar depressive disorders
4	Ischemic heart disease	Self-inflicted injuries	Ischemic heart disease	Lower respiratory infections	Diarrheal diseases	Diarrheal diseases	Alzheimer's disease and other dementias
5	Unipolar depressive disorders	Chronic obstructive pulmonary disease	Cerebrovascular diseases	Diarrheal diseases	Unipolar depressive disorders	Perinatal conditions[1]	Tracheal and lung cancer

1. Perinatal conditions include low birthweight, asphyxia and birth trauma.

Source: Jamison, D.T, *et al.* (eds.) (2006), *Disease Control Priorities in Developing Countries*, 2nd Edition, World Bank and Oxford University Press, Washington, DC and New York.

While it is true that most deaths from infectious disease could be averted using existing technologies, it is also true that many of the existing technologies are inadequate, in that they are less than fully effective, or are difficult to use, or are too costly in time and money. Most importantly, there are no vaccines available for a wide range of major killers, including HIV/AIDS, tuberculosis (TB), malaria and other tropical diseases. Also, for many diseases the pathogens have developed resistance to the low-cost first-line medicines, leading to the rapid spread of drug-resistant varieties. This has contributed to the resurgence of malaria in many parts of Africa and Asia as a result of resistance to chloroquine and sulfadoxine-pyrimethamine, and to the spread of multi-drug resistant TB (MDR-TB) in many parts of the world. Even where drugs remain effective, clinical regimens are often burdensome and difficult to implement; for example, standard TB treatment requires six months' delivery of directly observed therapy (DOT).

The inadequacy of existing technologies also relates indirectly to extreme poverty, just as the failure to use those technologies does. When diseases afflict mainly the poor, private-sector research and development (R&D) outlays will tend to be low, since there will be few prospects for recovering R&D outlays through commercial sales of new products. The limited R&D that does exist will be motivated mainly by corporate social

responsibility, or the scientific curiosity of individual researchers, or contracts with funding agencies, such as not-for-profit foundations, the military, or governmental science programmes in high-income countries.

The extent of market-based R&D for a particular disease category therefore depends enormously on whether the disease afflicts both rich and poor (such as HIV/AIDS and cardiovascular diseases), or whether the disease is concentrated in poor countries, as with tropical diseases such as malaria, schistosomiasis, onchocerciasis, and filariasis, to give just a few of the relevant examples. For diseases that afflict both rich and poor, private-sector R&D will be stimulated by the prospect of profits in the rich-country markets; products successfully developed for rich-country markets can then be adopted in the poor countries as well. Also, public institutions in the rich countries will contribute public-sector funding. In the case of the "diseases of the poor" however, there will generally be very little R&D unless governments and not-for-profit institutions (such as private foundations) create special incentives. This is evident in Table D.2.

Table D.2. **Relationship between research funding and burden of disease**

Condition	Global BoD (million DALYs)	% of total global BoD	R&D funding (USD millions)	R&D funding (USD per DALY)
All BoD[1]	1 470	100	105 900	72
HIV/AIDS + TB + malaria[1]	167	11.4	1 400	8.4
CVD[2]	148.19	9.9	9 402	63.45
Diabetes[2]	16.19	1.1	1 653	102.07
HIV/AIDS[2]	84.46	5.7	2 049	24.26
Malaria[2]	46.49	3.1	288	6.2
TB[2]	34.74	2.3	378	10.88

1. Financial data for 2001 from *Monitoring Financial Flows for Health Research*, Volume 2, Global Forum for Health Research, 2004; BoD data from WHO Global Burden of Disease, World Health Organization, 2002.

2. Based on bibliometric assessment of R&D spending presented by G. Lewinson *et al.* (Forum 8, Mexico City, November 2004) and work by the Malaria R&D Alliance.

Source: Global Forum for Health Research (2006), *Monitoring Financial Flows for Health Research 2006: The Changing Landscape of Health Research for Development, www.globalforumhealth.org*.

The 10/90 gap

The severe under-financing of "diseases of the poor" has been recognised at least since 1990, when the Commission on Health Research for Development identified the very small proportion of global health R&D that was being directed to diseases of the poor. This became known as the 10/90 gap, on the rough assessment that 10% of the world's biomedical research funding was being directed to problems that afflicted 90% of the world population, while 90% of the R&D funding was directed to diseases that were concentrated on only 10% of the world (the rich). This 10/90 gap is only metaphorical, however, since much of the research for "rich country" diseases also potentially spills over to the poor (for cardiovascular disease, cancer, HIV/AIDS, metabolic disorders, and other non-communicable conditions). The real problem is that R&D funding is extremely deficient for the infectious diseases that are overwhelmingly or exclusively concentrated in the poorest countries. When we compare R&D spending on a particular disease category to the disability adjusted life years (DALYs) caused by the disease, we see which disease categories are well funded or poorly funded in R&D relative to the disease burden that they cause. The average R&D spending on all diseases worldwide is USD 72 per DALY, but only USD 6.20 per DALY for malaria (a disease of the poor), compared with USD 102 for diabetes (a disease that disproportionately affects the rich). Cardiovascular diseases in total receive approximately USD 63 per DALY, compared with USD 8 per DALY for the combination of HIV/AIDS, TB, and malaria.

Various follow-up studies, including a 1996 World Health Organization (WHO) *Ad Hoc* Committee on Health Research, reached a similar conclusion about the shortfall of R&D for major disease categories afflicting the poor. In 1998, the Global Forum for Health Research was established, with the motto "Helping Correct the 10/90 Gap". In 2001, the Commission on Macroeconomics and Health called for R&D for specific diseases of the poor on the scale of USD 3 billion per year, up from less than USD 0.5 billion in 2001. The Gates Foundation has begun to narrow the research gap, with generous outlays of several hundred million dollars per year (less than USD 1 billion), but with the major scaling up of R&D for diseases of the poor still lying ahead.

The issue of patents

Patent protection complicates this story. Patent protection is a major spur to private-sector R&D in the rich countries, and as such, patents offer crucial incentives for the discovery of new drugs that can eventually be of great benefit for the poor. Anti-retroviral medicines (ARVs) against HIV/AIDS offer a clear example of patents in rich-country markets helping to create incentives that generated life-saving medicines of importance to the poorest of the poor. Yet, when drugs are discovered through private-sector R&D, patents can become a serious obstacle to the uptake of those products in poor countries. Consider the case of the anti-retroviral medicines. Patent-protected ARVs sell for around USD 10 000 per treatment course per year in rich countries even though the marginal production cost is around USD 100 per year.[2] The spread between the USD 100 marginal production cost and the USD 10 000 market price is sustained, of course, because the pharmaceutical company holding the ARV patent has exclusive rights to sell the product during the life of the patent. It is indeed the anticipation of profits that result from such monopoly rights that spur the private-sector R&D in the first place. The problem though is that a price of USD 10 000 per year would put the ARVs completely out of the reach of poor countries, even with substantial support from official donors.

A simple and practicable solution is to enforce patent rights in rich-country markets, but to ease or remove patent protection for essential medicines in low-income markets. In that way, the medicines can be provided to poor countries at the marginal production cost rather than the market prices of rich countries. In the case of ARVs, for example, the result is two prices for the same medicine: USD 10 000 per year in patent-protected rich-country markets, and USD 100 per year in poor countries. The strategy is known as "tiered pricing" or "market segmentation". This approach provides an acceptable solution that combines the benefits of patent-based incentives in the rich-country markets and access of the poor to the life-saving drugs in low-income countries.

Major pharmaceutical companies have by now widely accepted this compromise, though with long delays during the 1990s and with a fair bit of kicking and screaming along the way. Most of the major pharmaceutical companies that produce ARVs have made their products available to the poorest countries at their marginal production cost, either through special discounts set by the companies, or by licensing the products to generic producers. Low-income countries, for their part, have exercised their clear rights under international trade law to override patent protection in the case of public health needs. Countries can set aside patents in their home markets

by enforcing a "compulsory license" *vis-à-vis* a patent holder. Moreover, they can make contracts directly with third-country generics producers of the needed products.

Tiered pricing or market segmentation solves some problems but not others. In the case of ARVs, for example, the poorest of the poor (and their governments) are still unable to afford them, even at USD 100 per treatment per year. International donor assistance is still vital, therefore, even when patents no longer stand in the way. Moreover, tiered pricing will create a mechanism for the poor to get access to new products only when those products exist in the first place, *i.e.* only for diseases for which the rich-country markets provide an incentive for private-sector R&D.

Development of new technologies: push and pull mechanisms

The simple reality is that market forces alone will not lead to the development of new technologies for the "diseases of the poor". R&D will have to be supported by donor governments and private foundations. The most direct approach for supporting R&D is **direct financing of R&D** by such donors, often working through specialised intermediaries that are established specifically to foster drug discovery for particular research targets. This is the approach that the Gates Foundation has taken in establishing public-private partnerships (PPPs) for the discovery of new drugs, vaccines, and diagnostics. The Gates initiatives include R&D for malaria medicines (MMV), malaria vaccines (MVI), TB medicines (GATBDD/TB Alliance), TB vaccines (Aeras/TB), AIDS vaccines (IAVI), TB diagnostics (TBDI), Hookworm vaccines (HHVI), and Dengue vaccines (PDVI), among others. These PPPs use Gates Foundation and other funding to contract with private pharmaceutical companies, biotech start-ups, academic laboratories, and other institutions to undertake targeted R&D on a contract basis.

Another major Gates Foundation initiative that provides direct financing of R&D is the Grand Challenges in Global Health Program. In the first stage of this programme in 2003, the Gates Foundation, in partnership with the National Institutes of Health, the Canadian Institutes for Health Research, and the Wellcome Trust, canvassed the world's scientific and policy communities to identify the priorities for R&D for public health in the developing world. Approximately 1 500 suggestions were received from an estimated 10 000 scientists in 75 countries. A high-level Science Board selected 14 Grand Challenges from among the submissions. In the second step, the Program solicited proposals for R&D projects to address the 14 Grand Challenges. The Grand Challenges project then made awards of

USD 450 million to support 43 of the submitted R&D projects during 2004-05 (*www.gcgh.org*).

A second approach that has been proposed to spur R&D for diseases of the poor is for the donors to create a **donor-driven market** for specific new products, by committing in advance to purchase targeted new products at pre-set prices if and when the products are successfully developed by the private sector. For example, donors might try to spur the development of a malaria vaccine by promising to purchase 10 million doses of a new malaria vaccine per year at USD 10 per vaccine, whenever a qualifying vaccine is successfully brought to market. Such a promise would ensure a USD 100 million per year "market" for malaria vaccines, albeit a market funded entirely by donors rather than by end-users. This promised market would then provide a spur for private companies to invest in R&D, as long as a vaccine developer has the confidence that the USD 100 million per year in committed purchases will indeed be honoured, and that the right to sell the USD 100 million of vaccines will not be transferred to a generics producer after the R&D is undertaken. The overall approach has been termed an "advance market commitment" (AMC), and was first proposed by Professor Michael Kremer and myself (Sachs, Kremer and Hamoudi, 1999). It looks likely to be adopted, on a trial basis, by donors during 2007, though there are still debates as to the right first candidates, with consideration being given either to pneumococcal vaccines or malaria vaccines.

The advance market commitment approach must overcome two major incentive challenges to be successful. The first involves pricing. The advanced commitment must include not only a commitment on quantities to be purchased but also on the price per unit. Otherwise, once a new product is brought to market, the donor-purchaser will try to negotiate a low purchase price for the new product, one that covers the marginal production costs but not the sunk costs of R&D. In that case, the preceding R&D investments would not be recuperated. Firms would recognise that risk ahead of time, and would not undertake the R&D in the first place. Thus, a price adequate to elicit R&D must be set beforehand. Yet once a purchase price has been committed in advance, the product developers may lack the incentive to deliver a high-quality product. Therefore, an advanced purchase commitment should include not only a guaranteed price and quantity, but a clear specification of the required quality (or qualities) as well. Ideally, the advanced commitment would provide for a set of contingencies, with higher prices for more effective products. Yet such complicated contracts would be difficult to write, and even more difficult to enforce.

The second challenge for an AMC, and one that remains unsolved in practice, is the organisational structure of the financial pre-commitment. When the AMC was first proposed in 2000, many donor governments

decided that they would be unable to pre-commit to purchase a product in a future year, since such a financial commitment would impermissibly bind a future parliament to honour the financial commitments made by an earlier parliament. In a related way, the US Treasury decided that it would have to appropriate money immediately to cover potential commitments in the future, rather than simply committing today and appropriating the funding as needed once the products come to market. In short, it proved difficult for many potential donors to find a workable institutional vehicle to make a credible and legally enforceable pre-commitment. More recently discussion has turned to the feasibility of using the Global Fund to Fight AIDS, TB, and Malaria (GFATM), or the Global Vaccine Fund (GVF), as the vehicles for such advance market commitments. These funds could potentially make credible commitments of future purchases backed by the credibility of their boards (which include donor governments, foundations, and civil-society and private-sector institutions), without necessarily having the funding already in hand to honour those future commitments.

A third approach for spurring R&D is the use of **prizes**. In this case, the donors announce that they will offer prizes for breakthroughs in new drug discovery. The prizes might relate to specific targets announced in advance (*e.g.* vaccines for specific diseases) or might be general prizes in broad categories of work, as is the case with the Nobel Prizes. Either way, in the case of prizes the donors do not seek to choose specific strategies of R&D (as do the PPPs when they extend contracts to research organisations), but rather leave the choice of research strategies to individual researchers who are seeking the prize. In this way, prizes and advance market commitments are similar, in that they promote end goals, but not specific R&D strategies, which are left to a decentralised and competitive process.

Targeted R&D, for example through PPPs and Grand Challenges awards, is known as a "push" mechanism, since the direct financing of R&D is used to "push" a particular line of research and development. AMCs and prizes are known as "pull" mechanisms, since they create the pull of a financial reward (either through a prize or a guaranteed level of product sales) that is obtained at the end of the R&D process. Push mechanisms are most effective when there is a clear technological path to success. In that case, push mechanisms economise on time and avoid a duplication of scarce R&D resources. Pull mechanisms, on the other hand, are most effective when there is no clear favoured pathway for R&D. The goal is to generate a wide variety of discovery efforts, in a competitive race to the finish line.

In any model, however, great care must be taken to ensure that financial incentives are put in place to cover every step of the R&D chain, which is long, complicated and expensive. From "start to finish" the R&D chain includes basic scientific discovery, identification of potential targets, testing

in animals, Phase 1, 2, and 3 clinical trials in humans, applied engineering research for mass production, epidemiological studies for the identification of potential end-users, and operational research on drug delivery and medical protocols. And once this R&D supply chain is complete, donor agencies will still have to buy the product on behalf of the poor countries, and help to facilitate its delivery to those in need. A whole additional supply chain from the factory gate to the end user in a rural village must also be constructed, managed, and financed. Too many R&D schemes consider just a few steps in the R&D supply chain, and too many donors neglect the drug delivery that must be promoted once the R&D is successfully completed. The failure to conceptualise the drug access problem from start to finish leads to many half-completed ventures, in which medicines are delivered but not used, or are half-developed, but then languish in the laboratory without seeing the light of day.

Promoting uptake once a medicine is developed

As noted earlier, the over-arching problem of low uptake of *existing technologies* is extreme poverty. Almost everything wrong with health systems in poor countries reflects the shockingly low levels of public health expenditures per person in those systems. External donors such as the World Bank often demand superb performance of public health systems that spend as little as USD 10 per person per year, compared with the thousands of dollars per person per year spent in high-income countries. Without greater financial resources, the health systems of the poorest countries will continue to fail. Drug supplies will be erratic; brain drain will continue; supply chains of medicines will break down; laboratories, and even running water, will be out of reach.

The central challenge of scaling up financial resources for healthcare systems, especially in Africa, is covered in a companion paper (Sachs and Sachs, 2007). There are three specific points that should be mentioned here.

First, the attempt to recover costs at the point of service, by charging the poor for medicines, has been a cruel disaster for the poor. So too has been the resort by donors to "social marketing" of medicines and other health products (*e.g.* contraceptives and anti-malaria bed nets) at subsidised prices. Even a slight charge for medicines and other commodities prevents their uptake by the poorest of the poor, who lack the money even for food, much less for medicine. Realistic health policies should insist that essential health services be made available to the poor without co-payments or user fees. International donors should provide the financing necessary to make a reality of such commitments.

Second, all low-income countries should create "close-to-client" services within villages in order to ensure timely access to lifesaving technologies (anti-malarials, oral re-hydration solution, antibiotics for respiratory infection, etc.). Every village needs a health post with trained staff, and with a regular flow of commodities, and a drug dispensary (for free for essential medicines). Community health workers should be trained by the thousands to deliver the most basic technologies. Each village of 5 000 people (1 000 households) should have at least 5 trained community health workers, who visit the households and help to connect them to the health facilities.

Third, international donors (such as the Global Fund) should strive to deliver commodities directly to the poor countries rather than to leave the procurement to the countries themselves. Pooled procurement at the global level, rather than individual procurement by each low-income country, will lead to less corruption and more speed and reliability in the drug supply chain. In the case of tuberculosis, a TB Green Light Committee is supporting global procurement services for low-income countries. Similar arrangements at the global level should be undertaken with regard to AIDS, malaria, and other diseases.

Some policy recommendations on R&D

Led by the Gates Foundation, there has been a recent burgeoning of new R&D for diseases of the poor, but much more still needs to be done. In closing, we offer four specific recommendations.

1. Systematic monitoring of the levels of R&D

Even with the renewed focus on R&D for the poor, it remains extremely difficult to collect up-to-date and authoritative information on actual R&D outlays according to category of disease and type of product (*e.g.* medicines, preventative technologies such as bed nets, vaccines, diagnostics, medical instruments, etc.). At least one of the lead organisations involved in spurring the new R&D, whether the Global Forum for Health Research, the Gates Foundation, and/or the World Health Organization, should take the lead in systematic monitoring and reporting of R&D outlays. An annual R&D report should provide policy makers, the private sector, the foundations, and the scientific community with a clear road map of R&D programmes for diseases of the poor.

2. Scientific committees to assess priorities

For each major disease category (*e.g.* HIV/AIDS, malaria, TB, diarrhoea, tropical parasites, nutritional disorders, safe childbirth), a standing committee of scientists and public health specialists should provide regular assessments of R&D priorities. Malariologists, for example, would monitor the spread of drug resistance and hence the need for new medicines, the efficacy of diagnostic tools, the various best options on vector control, the onset of resistance to pesticides used in bed nets and indoor residual spraying, the changing epidemiology of malaria as a result of climate change or land use change, and other relevant factors that should shape priorities for malaria research and development. To some extent, the existing PPPs already do this, but their efforts are not sufficiently systematic, and their concerns are rightly addressed to their own funding portfolios than to the "big picture" of needs in their respective disease categories. The World Health Organization, perhaps in partnership with the Gates Foundation and the Global Forum for Health Research, would be the logical home for such standing committees.

3. Launch of AMCs on a trial basis

After more than five years of discussion, it is time to try an advance market commitment for at least one significant drug or vaccine target. A promising area would be malaria vaccines, since the disease is of first-order importance, the need for a vaccine is great, and the relevant science is advancing rapidly. Yet there is no consensus on the best path forward. There are indeed several vaccines entering into clinical trials right now, usually being funded by one or more of the "push" mechanisms. In such a setting, an AMC would offer a powerful additional incentive for a "race to the finish line". Probably the most practical way to implement such an AMC would be through the Global Fund to Fight AIDS, TB, and Malaria. The Global Fund would identify several possible candidate vaccines, and then enter into advanced purchase commitments with those candidates. Other candidates might come forward to negotiate a similar arrangement. The contracts would specify quantities, prices, quality, and the terms for selecting among candidate vaccines that might be brought to the market in a given period.

4. Overall donor commitment to increased funding

Perhaps most importantly, there is the need for an increase in the overall scale of R&D financing for the diseases of the poor. The Gates Foundation has played a heroic role in initiating this needed scale up, but it should be not alone in the task. Government donors, multilateral institutions (*e.g.* the

World Bank), national research labs (*e.g.* National Institutes of Health), private companies, and other foundations should pledge increased resources as well. The scale of the needed effort should be guided by the ongoing work of the scientific advisory committees recommended earlier.

Notes

1. Professor Jeffrey D. Sachs is the Director of the Earth Institute at Columbia University and Special Advisor to United Nations Secretary General Ban Ki-Moon on the Millennium Development Goals.

2. The marginal production cost means the cost of producing one additional unit of the product. By definition, it does not include the sunk costs of the R&D that went into the discovery and development of the product in the first place, but only the cost of producing an extra unit once the R&D has been successfully undertaken. Marginal production costs signify the true social costs that society must bear to make an existing drug available for additional users, *e.g.* for extending the use of a medicine from rich countries to poor countries.

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