

# Research and Development

Coordination and Financing

**Report of the  
Expert Working Group**



**World Health  
Organization**

**RESEARCH AND DEVELOPMENT  
COORDINATION AND FINANCING  
REPORT OF THE EXPERT WORKING GROUP**

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Printed in Switzerland

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## **ABBREVIATIONS**

OECD	Organisation for Economic Co-operation and Development
R&D	Research and Development
TDR	UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
WHO	World Health Organization

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## **ACKNOWLEDGEMENTS**

The Expert Working Group acknowledges the contributions to this report of WHO Member States, academic and research institutions, civil society groups, funding institutions, health-related industry, international intergovernmental organizations and other stakeholders. These groups provided input at two web-based public hearings on new financing proposals and also to the framework for evaluation.

This report is the product of extensive consultations. It benefited from reports prepared by Pedro Conceição, Sania Nishtar and Mary Moran with the assistance of colleagues at the George Institute for International Health (Australia). Additional support was provided by the Global Forum for Health Research (Switzerland). The Expert Working Group also thanks Dr Ok Pannenberg for technical support.



## **1. INTRODUCTION**

As this is a report to the Director-General of WHO, it is framed within the possibilities of action of that Organization. WHO, as mandated by its constitution, has been central to or an active participant in all debates on the changing panorama of health, particularly that in developing countries, and on health inequities. Several commissions and working groups were established in recent years to examine one or other facet of the difficult problem of how to change this scenario for the better. The problem is bedevilled by the fact that much of the improvement in health that has occurred has been in areas that are not usually considered to be within the health sector. In spite of the evidence of an inseparable bidirectional link between health and all facets of human development, galvanizing global attention to the fundamental problem and possible solutions has been slow. A global approach to the needs of countries is required, and many of the new challenges are blurring the differences between developed and developing countries.

“Innovative developing countries” are now considered to have requirements and strengths that are different from those of both the developing and the developed world. One issue that is assuming increasing prominence is the cost of and lack of access to essential health products in the context of global financial constraints and domestic fiscal space issues, and the extent to which these problems are linked to current technological innovation. Many technological developments have come from developed countries and have numerous restrictions that place them beyond the reach of the world’s poor countries, adding to the plethora of existing restrictions inherent to institutions and health systems.

This report was written by a time-limited expert working group established by the Director-General of WHO in response to the request of the Health Assembly in resolution WHA61.21, with specific, limited responsibilities to sift the enormous amount that has recently been written about the subject and related areas. The work of the Expert Working Group builds on the earlier work of the Commission on Intellectual Property Rights, Innovation and Public Health and the Intergovernmental Working Group. The interrelations between intellectual property, innovation and public health have been discussed extensively in those forums. The Intergovernmental Working Group in particular noted that intellectual property rights are important incentives for the development of new health-care products but that these incentives alone are not sufficient for finding new products to fight diseases when the paying market is small or uncertain. A key element of the Global strategy and plan of action on public health, innovation and intellectual property adopted by the Sixty-first World Health Assembly is to encourage and support the application and management of intellectual property in a manner that maximizes health-related innovation, especially to meet the research and development needs of developing countries, protect public health and promote access to medicines. Another aim is to explore and implement, where appropriate, new incentive schemes for research and development.

The Working Group decided from the beginning to adhere strictly to its mandate and not to address the issues that remained unresolved from the work of other groups. Thus, the report is structured to address current financing of research and development, coordination of research and development and proposals for new, innovative sources of financing to stimulate research and development. The Group had to complete its work within 1 year. It held three face-to-face meetings in Geneva in January, June–July and November–December 2009, but much of its work was done by soliciting public comment and electronic submissions, as appropriate.

The Working Group commissioned several background papers for its work. At the first meeting, presentations were made by groups and organizations that have interest or expertise in the area. All the

presentations, the background papers and individual submissions to the Working Group are available on the WHO web site. At subsequent meetings, the extensive material presented was discussed and evaluated. Most of the work on various proposals and report drafts between meetings was conducted by virtual consultations. The extensive comment at public hearings was gratifying and an indication of interest. The membership of the Expert Working Group on Research and Development Financing<sup>1</sup> represented a wide cross-section of countries and disciplines.

The Working Group is grateful to those who made submissions and contributed to our work, but special thanks must be given to the WHO Secretariat for intellectual and logistics support to this effort.

## **1.1 Background**

The taxonomy of diseases has changed with time. In an earlier classification, diseases were classified into types I, II and III. Subsequently, data on burden of disease led to a clear distinction between communicable and noncommunicable diseases; now, a separate class of diseases is designated as “neglected”, almost all of which are communicable. None of these classifications is rigid, and there is overlap and movement from one to the other. Growing emphasis is also being placed on the social determinants of disease, another dimension of neglect in health, and the role of gender in determining disease outcomes.

There is abundant, incontrovertible evidence that developing countries bear a double burden of disease. Furthermore, many large countries are virtual spaces, with significant differences in health status within them. The tyranny of the averages hides much of the ill health that affects the world’s poor. The old paradigm that infectious diseases affect developing countries and the poor and that chronic noncommunicable diseases affect only the rich has been put to rest.

Since the 1980s, the burden of noncommunicable diseases has been increasing rapidly in low- and middle-income countries. Whereas these diseases accounted for 47% of the disease burden in 1990, the proportion is projected to increase to 69% by 2020.<sup>2</sup> Conversely, whereas communicable diseases accounted for 42% of the disease burden in 1990, the proportion is expected to decrease to about 17% by 2020.<sup>2</sup> Noncommunicable diseases are now the leading cause of morbidity and mortality in every region of the world except sub-Saharan Africa, where they are prominent but overshadowed by communicable diseases and by maternal, perinatal and nutritional conditions.

Of the global deaths in 2005, 60% were due principally to cardiovascular disease and diabetes (32%), cancers (13%) and chronic respiratory diseases (7%). The burden of noncommunicable diseases is felt especially in low- and middle-income countries, of which 23 countries<sup>3</sup> account for 80% of deaths from noncommunicable diseases worldwide.<sup>4</sup> Noncommunicable

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<sup>1</sup> See page vi.

<sup>2</sup> Boutayeb A. The double burden of communicable and non-communicable diseases in developing countries. *Royal Society of Tropical Medicine and Hygiene*, 2006, 100:191–199.

<sup>3</sup> Argentina, Bangladesh, Brazil, China, Colombia, Democratic Republic of the Congo, Egypt, Ethiopia, India, Indonesia, Islamic Republic of Iran, Mexico, Myanmar, Nigeria, Pakistan, Poland, Philippines, Russian Federation, South Africa, Thailand, Turkey, Ukraine and Viet Nam.

<sup>4</sup> Abegunde DO et al. The burden and costs of chronic diseases in low-income and middle-income countries. *Lancet*, 2007, 370:1929–1938.

diseases were responsible for an estimated 49% of the worldwide burden of disease in 2005 and 46% of the disease burden in low- and middle-income countries. Coronary heart disease and stroke accounted for 21% of disability-adjusted life-years in this group, cancer for 12% and respiratory diseases for 8%.<sup>1</sup> Endocrine disorders (primarily diabetes) accounted for 3.7% of the disability-adjusted life-years attributed to noncommunicable diseases, but this proportion is predicted to rise sharply to 5.4% by 2030, with much of the increase in low-income countries.<sup>2</sup> Neuropsychiatric conditions account for up to one third (28%) of disability-adjusted life-years attributed to noncommunicable diseases, although the size of this contribution varies between countries and according to income level.<sup>1</sup>

Although the burden of communicable diseases per person fell by 20% between 1990 and 2001, HIV/AIDS, tuberculosis, malaria and neglected diseases remain significant causes of morbidity and mortality.<sup>3</sup> Particularly in low- and middle-income countries, HIV/AIDS, tuberculosis, malaria and diarrhoea caused by communicable diseases are among the leading 10 causes of death, accounting for a combined 14.8% of deaths in 2001.

The rapidly increasing burden of these diseases is affecting poor and disadvantaged populations disproportionately, contributing to widening health gaps between and within countries. Young people aged 15–19 years in low- and middle-income countries have a 30% greater risk of death from noncommunicable diseases than their counterparts in high-income countries. Just under half of all deaths from these diseases in low- and middle-income countries and only 27% in high-income countries occurred in people younger than 70 years.<sup>4</sup> The contributions of conditions such as cardiovascular and chronic respiratory diseases to disability and the long-term consequences of communicable diseases and nutritional deficiencies are also higher in low- and middle-income countries.<sup>8</sup> In these countries, moreover, communicable diseases still cause many deaths and disabilities. In 56 of the 58 countries in which the bottom billion live, virtually every person has at least one neglected tropical disease.<sup>5</sup> According to the Global Fund to Fight AIDS, Tuberculosis and Malaria,<sup>6</sup> 95% of the estimated 33 million people living with HIV are in low- and middle-income countries (68% in sub-Saharan Africa), and 27% of new cases and 31% of registered deaths from tuberculosis were in Africa.<sup>7</sup>

The cost of disease to societies, particularly in low- and middle-income countries, has serious implications for poverty reduction and economic development. People who are already poor are the most likely to suffer financially from chronic diseases, which often deepen poverty and damage long-

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<sup>1</sup> Prince M et al. No health without mental health. *Lancet*, 370:859–877.

<sup>2</sup> Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine*, 2006, 3:e442. Doi: 10.1371/journal.pmed.00304424.

<sup>3</sup> Lopez AD et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*, 2006, 367:1747–1757.

<sup>4</sup> Taskforce on Innovative International Financing for Health Systems. *Constraints to scaling up and costs, Working Group 1 Report*. Geneva, World Health Organization, 2009.

<sup>5</sup> Hotez PJ et al. Rescuing the bottom billion through control of neglected tropical diseases. *Lancet*, 2009, 373:1570–1575.

<sup>6</sup> The Global Fund to Fight AIDS, Tuberculosis and Malaria. *Fighting HIV/AIDS*. Geneva, 2009. Available from: [www.theglobalfund.org/en/hivaids/](http://www.theglobalfund.org/en/hivaids/) Accessed 11 October 2009.

<sup>7</sup> *Preventing chronic diseases: a vital investment*. Geneva, World Health Organization, 2005.

term economic prospects.<sup>1</sup> Abegunde and colleagues estimated that US\$ 84 billion of national income will be lost from heart disease, stroke and diabetes alone in 23 low- and middle-income countries between 2006 and 2015, if nothing is done to reduce the risks for noncommunicable diseases.<sup>2</sup> Achievement of the global goal of preventing and controlling chronic diseases would avert 36 million deaths by 2015 and would have major economic benefits. Furthermore, because most of the averted deaths would be in low- and middle-income countries and about half would be those of people under 70 years, it would have major economic benefits, including extension of productive life and reduction in the need for expensive care,<sup>3</sup> much of which involves the use of technology. Adopting preventive and cure-related technologies for use in resource-poor countries should be emphasized.

The first of the recent WHO commissions on global health concerns was the Commission on Macroeconomics and Health, which adduced data showing the link between health and economic growth.<sup>4</sup> The Commission emphasized the need for global knowledge to fight disease, which is of particular relevance to the work of this Expert Working Group. The report stated:

“The fight against disease requires important investments in global public goods, beyond the means or incentives of any single government and beyond the sum total of national level programmes. One of the most important kinds of public goods is those that involve the production of new knowledge, especially through the investments in research and development. We believe that at least US\$ 3.0 billion per year should be allocated toward research and development directed at the health priorities of the world’s poor. Of that amount, US\$ 1.5 billion per year should be allocated toward targeted research and development for new drugs, vaccines, diagnostics and intervention strategies towards HIV/AIDS, malaria, tuberculosis, reproductive health and other priority conditions of the poor.”

The Commission went on to explore various mechanisms for mobilizing resources and the institutional framework for dispensing and monitoring their use.

The promotion of health and the promotion of development beyond economic growth go hand-in-hand. This was acknowledged by Member States when they met in 2000 and committed to addressing a series of development challenges known as the United Nations Millennium Development Goals, which provide a timeframe for addressing challenges, such as poverty, illiteracy, child and maternal mortality, HIV/AIDS, malaria and other diseases. It is important that the current concern about research and development with respect to the health components of the Millennium Development Goals and its implementation extend beyond 2015.

Governments have recognized the moral and legal issues involved in ensuring general access to drugs for people in need and those who also have limited means to combat burdensome diseases, such

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<sup>1</sup> Taskforce on Innovative International Financing for Health Systems. *Constraints to scaling up and costs, Working Group 1 Report*. Geneva, World Health Organization, 2009.

<sup>2</sup> Abegunde DO et al. The burden and costs of chronic diseases in low-income and middle-income countries. *Lancet*, 2007, 370:1929–1938.

<sup>3</sup> Beaglehole R et al. Prevention of chronic diseases: a call for action. *Lancet*, 2007, 370:2152–2157.

<sup>4</sup> Commission on Macroeconomics and Health. *Macroeconomics and health: investing in health for economic development*. Geneva, World Health Organization, 2001. [www.cid.harvard.edu/archive/cmhl/](http://www.cid.harvard.edu/archive/cmhl/). Accessed 9 November 2009.

as HIV/AIDS. Their needs are related closely to socioeconomic inequalities and imbalances with regard to both the demand and supply of new drugs and vaccines.<sup>1</sup>

### **1.1.1 The Commission on Intellectual Property Rights, Innovation and Public Health**

With increasing awareness of the global disease situation and the importance of reducing poverty and addressing the social determinants of ill health, an international debate has been taking place on the relations between intellectual property rights, innovation and public health. The emphasis has been on the contribution that innovation in public health can make to improving human health in developing countries, especially for the poorer and more vulnerable segments of the population. Ensuring research and development that responds to the needs of these populations is crucial, as the contribution that innovation can make will be meaningful only if products are acceptable, affordable and accessible.<sup>2</sup>

In response to this public concern, the Fifty-sixth World Health Assembly in May 2003 established an independent, time-limited body, the Commission on Public Health, Innovation and Intellectual Property Rights, to collect data and proposals from the people and institutions involved and present an analysis of intellectual property rights, innovation and public health, including appropriate funding and incentive mechanisms for the creation of new medicines and other products against diseases that disproportionately affect developing countries.<sup>3</sup> The report that the Commission submitted to Member States in April 2006 contained 60 recommendations grouped into five categories: discovery, development, delivery, fostering innovation in developing countries and supporting a sustainable global effort.

The Commission concluded that intellectual property rights provide important incentives for the development of new medicines and medical technologies. Those rights are not, however, an effective incentive when patients are either too few or poor. As a result, there is a gap in the innovation cycle: in some cases no product exists to address the health needs of the poor, and, in other cases, products exist, but little effort is made to ensure that they are affordable for poor communities.<sup>4</sup> Other incentives, financial mechanisms and coordination among stakeholders are needed. Defining the conditions necessary for products to be accessible is, therefore, an important part of the report.<sup>5</sup>

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<sup>1</sup> Commission on Macroeconomics and Health. *Macroeconomics and health: investing in health for economic development*. Geneva, World Health Organization, 2001. [www.cid.harvard.edu/archive/cmhl/](http://www.cid.harvard.edu/archive/cmhl/). Accessed 9 November 2009, Figures 4.1 and 4.2. Mortality from AIDS in the United States of America (Figure 4.1) fell from 17 per 100 000 to 5 per 100 000 between 1995 and 1998, due to treatment and less infection. In most developing countries during the same period, the epidemic continued unabated, rising from over 1 million deaths to about 1.75 million, due to the lack of availability of drugs that are found in developed countries (Figure 4.2).

<sup>2</sup> *Ibid.*, pp. 97, 98.

<sup>3</sup> Resolution WHA56.27. Increasing access to essential medicines. In: *Fifty-sixth World Health Assembly, Geneva, 19–28 May 2003. Volume 1. Resolutions and decisions*. Geneva, World Health Organization, 2003 (document WHA56/2003/REC/1).

<sup>4</sup> Commission on Macroeconomics and Health. *Macroeconomics and health: investing in health for economic development*. Geneva, World Health Organization, 2001, Figure 1.4, p. 23. Available at: [www.cid.harvard.edu/archive/cmhl/](http://www.cid.harvard.edu/archive/cmhl/). Accessed 9 November 2009.

<sup>5</sup> Türmen T, Clift C. Public health, innovation and intellectual property rights: unfinished business. *Bulletin of the World Health Organization*, 2006, 84:338.

### **1.1.2 Recommendations of the Commission and follow-up**

#### ***Discovery***

With regard to the discovery of new health-care products, the Commission reviewed some of the science of disease control and the economic and policy choices facing countries, in particular the scientific, institutional and financial issues arising between carrying out basic research and identifying a lead compound. The Commission sought to determine the gaps in this process for diseases that principally affect developing countries and policy measures that might be appropriate to fill those gaps. It concluded that it is in the interests of all countries to promote health research that addresses the needs of developing countries and to set specific, measurable targets in that regard.

#### ***Development***

The most expensive part of the process is development: taking the candidate product through all the required stages of preclinical and clinical research and meeting regulatory requirements. The Commission recognized that increasing attention is being given to drug development and regulation but stressed that clinical trials and regulatory frameworks should be strengthened in all countries. It also recognized the role of new players and public–private partnerships. It examined the range of activities, from optimization of a lead compound through to regulatory review of the safety, efficacy and quality of a new product, and identified several issues that require careful consideration.

#### ***Delivery***

Successful efforts to develop new products will be of no value if the products are not available and accessible to those who need them. The Commission examined the factors affecting the introduction of new and existing products into developing countries, including health delivery systems, regulation, pricing, intellectual property and policies to promote competition.

#### ***Fostering innovation in developing countries***

The Commission observed that lessons can be learnt from those countries that have made significant progress in innovative capacity for health research. It also affirmed the significant contribution of the most scientifically and technologically advanced developing countries to biomedical R&D. It recognized the massive indigenous resources in developing countries in the form of traditional medicine, which could be used better by making it more widely available and applying knowledge to accelerate the development of new treatments. The Commission's recommendations focused on building capacity in developing countries in the fields of science and technology, regulation, clinical trials, the transfer of technology and traditional medicine, as well as intellectual property.<sup>1</sup>

#### ***Supporting a sustainable global effort***

The Commission defined the role and responsibilities of WHO as the lead international agency for public health, including devising a global plan of action to secure more and sustainable funding for

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<sup>1</sup> Intergovernmental Working Group on Public Health, Innovation and Intellectual Property. *Review of recommendations of the Commission on Intellectual Property Rights, Innovation and Public Health*. Geneva, World Health Organization, 2006 (document A/PHI/IGWG/1/2), p. 2.

developing and making available products to address diseases that disproportionately affect developing countries. More sustainable financing must be ensured for innovation and access and to promote synergy between partners. Ultimately, it is the responsibility of governments to see that these objectives are achieved; however, it is appropriate that WHO take the lead in promoting a more sustainable, better-funded effort.<sup>1</sup>

The Fifty-ninth World Health Assembly welcomed the report of the Commission on Intellectual Property Rights, Innovation and Public Health and, as a follow-up, adopted resolution WHA 59.24 on “Public health, innovation, essential health research and intellectual property rights: towards a global strategy and plan of action”.<sup>2</sup> The resolution requested the Director-General of WHO to establish an intergovernmental working group, open to all interested Member States, to draw up a global strategy and plan of action for a medium-term framework, based on the recommendations of the Commission.<sup>3</sup>

### **1.1.3 Preparation of a global strategy and plan of action**

The Intergovernmental Working Group was mandated to develop a global strategy and plan of action aimed at, inter alia, securing an enhanced, sustainable basis for needs-driven, essential health research and development relevant to diseases that disproportionately affect developing countries, proposing clear objectives and priorities for research and development and estimated funding.<sup>3</sup> The Intergovernmental Working Group thus became the first forum to address the issues of innovation and access simultaneously.

In May 2008, the World Health Assembly adopted resolution WHA61.21,<sup>3</sup> approving the global strategy and most parts of the plan of action on public health, innovation and intellectual property; the remaining actions were adopted in resolution WHA62.16.<sup>4</sup>

The global strategy proposes that WHO play a strategic, central role in the relations between public health and innovation and intellectual property. To achieve this, Member States endorsed by consensus a strategy designed to promote a new approach to innovation and access to medicines, which would encourage needs-driven rather than market-driven research to target diseases that disproportionately affect people in developing countries.

The global strategy comprises eight elements, which are based on a set of principles agreed upon by Member States to promote innovation, build capacity, improve access and mobilize resources and will. The elements are to:

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<sup>1</sup> Türmen T, Clift C. Public health, innovation and intellectual property rights: unfinished business. *Bulletin of the World Health Organization*, 2006, 84:338.

<sup>2</sup> Resolution WHA59.24. Public health, innovation, essential health research and intellectual property rights: towards a global strategy and plan of action. In: *Fifty-ninth World Health Assembly, Geneva, 22–27 May 2006. Volume 1. Resolutions and decisions*. Geneva, World Health Organization, 2006 (document WHA59/2006/REC/1).

<sup>3</sup> Resolution WHA61.21. Global strategy and plan of action on public health, innovation and intellectual property. In: *Sixty-first World Health Assembly, Geneva, 19–24 May 2008. Volume 1. Resolutions and decisions*. Geneva, World Health Organization, 2008 (document WHA61/2008/REC/1);

<sup>4</sup> Resolution WHA62.16. Global strategy and plan of action on public health, innovation and intellectual property. In: *Sixty-second World Health Assembly, Geneva, 18–22 May 2009. Volume 1. Resolutions and decisions*. Geneva, World Health Organization, 2009 (document WHA62/2009/REC/1).

- to assess the public health needs of developing countries with respect to diseases that disproportionately affect them and identify their research and development priorities at national, regional and international levels;
- to promote research and development on types II and III diseases and assess the research and development needs of developing countries in relation to Type I diseases;
- to build and improve innovative capacity for research and development, particularly in developing countries;
- to improve, promote and accelerate transfer of technology between developed and developing countries as well as among developing countries;
- to encourage and support the application and management of intellectual property in a manner that maximizes health-related innovation, especially to meet the research and development needs of developing countries, protects public health and promotes access to medicines for all, as well as explore and implement, where appropriate, possible incentive schemes for research and development;
- to improve delivery of and access to all health products and medical devices by effectively overcoming barriers to access;
- to secure and enhance sustainable financing mechanisms for research and development and develop and deliver health products and medical devices to address the health needs of developing countries; and
- to design mechanisms to monitor and evaluate implementation of the strategy and plan of action, including reporting systems.

The plan of action linked to the global strategy identifies stakeholders, leaders and timeframes for implementation.

#### **1.1.4 The Expert Working Group on Research and Development Financing**

In recent years, donors have provided additional funding to promote access to diagnosis and treatment and Research and Development relevant to diseases affecting developing countries. Nevertheless, further sustainable funding is essential to support the long-term efforts that are required to meet the health needs of developing countries.<sup>1</sup> The global strategy therefore called on WHO to establish a results-oriented, time-limited expert working group that would link with other relevant groups to examine current financing and coordination of research and development and proposals for new and innovative sources of financing, to stimulate research and development related to types II and III diseases and the research and development needs of developing countries in relation to Type I diseases.<sup>2</sup> In response to this request, the Director-General established the present Expert Working Group, which comprises internationally recognized policy-makers and technical experts in the fields of

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<sup>1</sup> Resolution WHA61.21. *Global strategy and plan of action on public health, innovation and intellectual property*. In: *Sixty-first World Health Assembly, Geneva, 19–24 May 2008. Volume 1. Resolutions and decisions*. Geneva, World Health Organization, 2008 (document WHA61/2008/REC/1), Annex, paragraph 40.

<sup>2</sup> *Ibid*, Annex, paragraph 42.

public health, biomedical science, finance and economy. The members of the group participated in their personal capacity, providing technical expertise and strategic guidance to take forward this component of the global strategy. The Working Group debated whether the classification of diseases into types I, II and III, formulated by the Commission on Macroeconomics and Health, was still valid and decided to be less rigid in separating diseases into those categories in some of its work.

The establishment of the Expert Working Group raised considerable debate and discussion in various forums. The Group was expected to consolidate and clarify the various proposals on research and development and financing recommended by various previous commissions and groups.

This report draws on three sources of evidence. The analysis of financing, with regard to the volume, efficiency and effectiveness of allocation, is based partly on published literature. The coordination of research and development financing and research was assessed by qualitative research methods, comprising a review of published and “grey” literature, consultation of archives and interviews. To evaluate innovative health research and development financing proposals, an evaluation tool was used, with agreed criteria, in order to choose proposals from an extensive inventory. The method used by the Expert Working Group to assess the various proposals on research and development and financing is outlined in Annex 1.

## **2. FINANCING RESEARCH AND DEVELOPMENT<sup>1</sup>**

### **2.1 Context**

The adoption of the Millennium Declaration in 2000<sup>2</sup> and the subsequent mobilization of multilateral and bilateral development agencies around the Millennium Development Goals renewed focus on the resources required to advance development. The question of how to mobilize the required resources led to a number of studies and initiatives, which gave rise to ideas for “innovative sources of financing for development”. These continue to be discussed in debates on how to finance the Millennium Development Goals and promote development. Although public sources of financing for health care in general and research and development in particular are important, they are not adequate, and the gap must be bridged from other sources. Some of the ideas that are called “innovative” are actually quite old and are re-emerging, including the “Tobin tax”, a levy on certain financial transactions (such as foreign exchange).<sup>3</sup>

Kaul and Conceição<sup>4</sup> expanded the analysis of financing beyond resource mobilization, to consider a range of options, both to promote development and to enhance the provision of global public goods. This broadened perspective led to consideration of a number of possible mechanisms to increase not only the volume of resources but also the efficiency and effectiveness of their allocation. Various risk management tools must be considered in order to optimize the intertemporal allocation of

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<sup>1</sup> Much of this section was drawn from a paper prepared for the Expert Working Group on R&D Financing by Pedro Conceição, *Financing for health R&D that address challenges of the poor: context, analytical framework, and initial compilation of options*.

<sup>2</sup> Resolution A/RES/55/2. *United Nations Millennium Declaration*. In: *Fifty-fifth United Nations General Assembly, New York City, 5–28 September 2000*. New York City, United Nations.

<sup>3</sup> Tobin J. A proposal for international monetary reform. *Eastern Economic Journal*, 1978, 4:153–159.

<sup>4</sup> Kaul I, Conceição P. *The new public finance: responding to global challenges*. New York, Oxford University Press, 2006.

resources and to enhance the predictability and stability of financing. The International Finance Facility was proposed to meet the target dates of the Millennium Development Goals and because of the potentially high returns of frontloading certain investments. Donor countries have promised to increase official development assistance over time. It was considered that if it were possible to “advance” these commitments in order to take advantage of high returns from frontloading, there would be potential gains in efficiency and effectiveness. The International Finance Facility would mobilize financing from capital markets by selling bonds backed by commitments from governments of future financial flows that would service the debt linked to the bonds over time. Initially, this was an open-ended proposal, intended to mobilize significant resources to frontload investments to meet the Millennium Development Goals.

A more modest proposal, the International Finance Facility for Immunization has been implemented, which placed bonds backed by long-term, legally binding commitments from seven countries: France, Italy, Norway, South Africa, Spain, Sweden and the United Kingdom. Backed by these commitments, the Facility sold bonds (borrowed) from international capital markets and has been able to raise US\$ 2 billion since it was launched at the end of 2006; it is expected to raise approximately US\$ 3.3 billion by 2015. The resources from the International Finance Facility for Immunization are channelled to the GAVI Alliance to fund vaccines and other health interventions. The potential of this type of innovative financing to generate additional resources is limited, as it is intended mainly to frontload commitments. It is also costly, because of the administrative and debt servicing costs. It would be cheaper to channel funds directly from participating countries to the GAVI Alliance; however, given the practical reality that such funds are not always forthcoming, the costs must be weighed against the benefits of frontloading and predictable financing, which may result, for example, in cost saving by the establishment of long-term purchase agreements with vaccine manufacturers.

One set of market failures is due to inadequate risk management. For example, one of the challenges of development is that technology specifically designed to address the problems of poor countries is not developed, both because the public interest of rich countries in subsidizing such technology is low or heavily discounted and because there are no private incentives, given that the markets in which the technology would be sold are thin and small. This has long been recognized as a problem in terms of health interventions, especially medicines and vaccines for diseases that affect developing countries almost exclusively, but it also exists in other areas, like agriculture.

One idea for mitigating these problems in the case of vaccines is to establish “advance market commitments”. The idea is that a group of donors makes a binding commitment to buy a vaccine only if that vaccine is developed. The commitment ‘creates a market’ for the vaccine that is expected to encourage private investment into its development. This is essentially a “risk management” tool, as an advance market commitment moves the market risk away from private developers, given that market demand is guaranteed by the public or philanthropic sector. The market risk is not entirely removed, as the vaccine is not free; the market is subject to a “demand test”, which implies that part of the cost must be supported by the developing country, albeit heavily subsidized. From the point of view of the private developer, however, the market risk is substantially reduced. In June 2009, a pilot advance market commitment for vaccines against pneumococcal diseases was launched, with pledges amounting to US\$ 1.5 billion from Canada, Italy, Norway, the Russian Federation, the United Kingdom and the Bill & Melinda Gates Foundation. This advance market commitment backs commitments to purchase new pneumococcal vaccines that meet criteria to ensure their effectiveness and safety. While the pilot commitment is an important step, it is uncertain how effective it will be in stimulating investment in vaccines and other technology that require longer, more substantial investment than for pneumococcal diseases.

The Taskforce on Innovative Financing for Health Systems considered the proposals outlined above and identified measures to catalyse private voluntary giving.<sup>1</sup> New ideas are emerging in this area, including voluntary donations linked to air travel or mobile telephone use (as proposed by the Millennium Foundation for Innovative Financing for Health, established by UNITAID). The idea is to obtain small individual contributions in very large volume, where the providers of goods or services are concentrated to minimize the transaction costs of the initiative.

## **2.2 Incentives to stimulate research and development in the light of market and policy failures in the production and diffusion of knowledge**

Public policy is important to stimulate research and development. Without direct public subsidies or incentives for private engagement in research, the public (more precisely, non-rival) nature of knowledge implies that it will be undersupplied in decentralized markets. The current arrangements could be improved to enhance efficiency and equity in the global production and diffusion of health-related knowledge. The incentive structures that encourage health-related research and development which benefits developing countries have practical implications.

It is puzzling that current incentives for the production of knowledge may have resulted in underprovision at the global level. The nature of knowledge is such that any innovation, wherever produced, could in principle be made available immediately and easily to the whole world. According to the taxonomy proposed by Sandler,<sup>2</sup> the production of knowledge follows a “best-shot” aggregation technology. In principle (if restrictions to access to knowledge are ignored for the moment), therefore, it is enough for a single country to contribute to knowledge generation for that knowledge to be fully provided.

Knowledge is, however, underprovided, access to existing knowledge is widely asymmetrical, and engagement in research and development is uneven in different countries. One hypothesis is that both the underprovision of knowledge and problems of access result in part from the fact that not enough consideration has been given to global asymmetry in the supply and diffusion of knowledge in policies and activities for the development of science and technology. As knowledge-generating activities are costly and rely on scientific and technological capability, most poor countries cannot afford and do not have the ability to generate knowledge specific to their contexts. In addition, a national focus limits incentives for producing technology with a large global spillover or that would bring benefits to poor countries.

Lack of consideration of the global dimension has also created problems of access to existing knowledge, often as a result of intellectual property rights. Intellectual property rights, designed to stimulate innovation in rich countries, often affect the price and the variety of goods available in developing countries for consumption and for production. Yet, even knowledge that is not formally restricted in this way fails to be diffused.<sup>3</sup> Quah noted: “... one of the most significant aspects in

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<sup>1</sup> Taskforce on Innovative International Financing for Health Systems. *Raising and channelling funds, Working Group 2 Report*. Geneva, World Health Organization, 2009. Available at: [www.internationalhealthpartnership.net/pdf/IHP%20Update%2013/Taskforce/Johansbourg/Taskforce%20Working%0Group%202%20Report.pdf](http://www.internationalhealthpartnership.net/pdf/IHP%20Update%2013/Taskforce/Johansbourg/Taskforce%20Working%0Group%202%20Report.pdf). Accessed 17 July 2009.

<sup>2</sup> Sandler T. Assessing the optimal provision of public goods: in search of the holy grail. In: Kaul I et al., eds. *Providing global public goods: managing globalization*. New York, Oxford University Press, 2003.

<sup>3</sup> For example, poliomyelitis vaccines were never patented. The incidence of poliomyelitis was reduced by 86% in developed countries between 1955 and 1957, while a comparable reduction was achieved in poor countries only after an

economic development is not knowledge's over-dissemination, but instead the opposite, even in the absence of explicit intellectual property rights. Knowledge – something economists have expended so much effort studying how to restrict – turns out, puzzlingly, to be one of the most difficult things to disseminate.”<sup>1</sup> National incentive structures may often be insufficient to provide knowledge efficiently and equitably at global level; therefore, international collective action might be needed to provide incentive structures for global knowledge generation and diffusion

### **2.2.1 Implications of the public nature of knowledge**

The “public good” nature of knowledge implies that, as Arrow indicated,<sup>2</sup> it will be undersupplied in decentralized markets. The reason for undersupply in competitive markets is simple: the costs of production are decoupled from the benefits of consumption. This is true also for knowledge embodied in tangible goods. The lack of incentives for knowledge production in competitive markets does not mean that it cannot be supplied privately, nor that it must necessarily be produced by the State. Rather, it implies that some type of incentive structure must be put in place to reward the efforts of creation. The argument is not that in the absence of these incentive structures no knowledge would be produced but that the amount of knowledge supplied would not be as abundant as with institutionalized incentive mechanisms to compensate creative efforts.

### **2.2.2 Evolution of incentives to stimulate research and development**

Two main incentives structures – the establishment of intellectual property rights and public support – are available to stimulate the production of knowledge. According to David,<sup>3</sup> the objective of the mediaeval and Renaissance traditions of alchemy was to discover formulae that would confer power over material things. These formulae would be kept secret and would be used only for the benefit of the discoverer. Geographical knowledge (trade routes, more accurate maps) would be kept from the public domain, to be used only by the merchants or rulers who had discovered this new knowledge, from which military or mercantile gains could be extracted. Craftsmen kept close watch over the techniques used in their trades, even when no formal guild restrictions applied.

In the private sector, trade secrecy continues to be used as a means to protect commercial knowledge. It is somewhat limited as a means of restricting others from using knowledge, as it may be possible to understand the information embodied in a product or associated with a certain production process. Commercial processes used in the development and manufacture of a product – that is, “know-how” – are, however, often not apparent from an examination of the final product and may be kept secret. The principle of attributing to the discoverer the power to exclude others from using new inventions for commercial purposes has been institutionalized in the incentive structure of the patent system. The outcomes of basic research conducted in universities, government laboratories and

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eradication effort was launched in 1988. See Arhin-Tenkorang D, Conceição P. Beyond communicable disease control: health in the age of globalization. In: Kaul I et al., eds. *Providing global public goods: managing globalization*. New York, Oxford University Press, 2003.

<sup>1</sup> Quah DT. *Demand-driven knowledge clusters in a weightless economy*. London, Centre for Economic Performance, London School of Economics, 2001 (London School of Economics Department Working Paper).

<sup>2</sup> Arrow KJ. Economic welfare and the allocation of resources for inventions. In: Nelson RR, ed. *The rate and direction of inventive activity. Economic and social factors*. Princeton, New Jersey, Princeton University Press, 1962.

<sup>3</sup> David PA. From keeping ‘nature’s secrets’ to the institutionalization of ‘open science’. *University of Siena Lectures on Science as an Institution and the Institutions of Science*, 2001.

research institutions that is funded by governments and foundations are made public in scientific articles even when patents are being sought. Patent documents also make public the inherent knowledge of an invention, but the use of the invention may be excludable, as the creator has the right to exclude others from its commercial use. In this case, private market incentives work: the creator provides access to the invention only to those who are willing to pay for access or use (see Global strategy and plan of action on public health, innovation and intellectual property, sub-elements 2.2 and 2.4).<sup>1</sup>

At the same time that intellectual property rights were taking hold in the United States, another institutionalized way of providing incentives for knowledge generation was emerging in Europe. In post-Renaissance Europe, a system of aristocratic patronage by rulers and nobles (both lay and ecclesiastical) concerned with the “ornamental” benefits of the discoveries of the philosophers and savants they sponsored planted the seeds for a research culture of open science.<sup>1</sup> Rather than keeping the discoveries private, incentives were oriented towards rapid, wide dissemination of the new achievements to enhance the prestige and power of the patron. Savants sponsored by others scrutinized these discoveries, to make sure that the claims to grandeur were legitimate. Philosophers who consistently showed their ability to make important discoveries gained a reputation that was based on wide dissemination and scrutiny of their discoveries. Today, the rules of engagement of the scientific community are based on this second incentive structure.

### **2.2.3 Incentives for the provision of knowledge at national level**

These two incentive mechanisms tend to separate knowledge into two categories. People and firms are willing to pay for knowledge for which substantial private benefits exist or are perceived to exist, as these private benefits create market demand for knowledge, making it attractive to attempt to produce that knowledge, so that it can be sold after intellectual property rights have been awarded to the innovator. For other types of knowledge, the benefits are so widespread, uncertain or long-term that no one will pay enough for having it produced. Thus, the two institutional mechanisms tend to create knowledge of two types: one that remains in the public domain (which is paid for by the public or, sometimes, provided voluntarily) and one that is private (protected by intellectual property rights or by secret). This dichotomy can be identified, in a very crude way, as a distinction between ‘science’ and “technology”.<sup>2</sup> The national structuring of public support for science and technology introduces imbalances in the global production of knowledge that are of real consequence. The imbalance in the global production of science has direct consequences for the welfare of countries. The issues that receive public support are those of more relevance to national concerns. research and development to produce knowledge that addresses problems in poor countries is underfunded, and knowledge specific to their needs is underprovided.

This balance between intellectual property rights and public support should not be confused with other, different issues associated with the interaction of public and private actors in the production of knowledge. In particular, public support does not have to be provided exclusively by the State. Clearly, resources must be mobilized from agents that are willing for knowledge to remain largely in the public sector. For example, private philanthropic organizations – especially foundations in Europe and the United States – have played important roles in supporting health-related research and development for a long time and continue to do so.

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<sup>1</sup> Resolution WHA61.21.

<sup>2</sup> Dasgupta P, David P. Toward a new economics of science. *Research Policy*, 1994, 23:487–521.

## **2.2.4 Mechanisms to provide public support for research and development**

Direct public support for science and technology can be given in various ways, including three mechanisms used frequently individually or in combinations: grants, procurement contracts and prizes. Grants are usually given as a result of a competitive process of proposal submission, and proposals are judged on the basis of their scientific merits. Funding is allocated with few strings attached, as long as the scientific programme of the proposal has been complied with. Procurement for a specific technology or scientific solution for a national problem entails contracting with an research and development producer. Depending on the goal of public procurement, however, access to knowledge may sometimes be restricted, so public support to research and development does not always mean that the knowledge is made public. Prizes are a combination of the grant and the procurement approach. The government or another funder decides which problem it wants to have addressed (as in procurement) but, instead of a procurement contract, commits to pay a prize to whoever solves the scientific or technological problem.

Indirect public support to increase the overall level of research and development has also been provided, often through incentives oriented towards the private sector. The rationale behind public support for privately executed research and development is the large spillovers that are presumed to be associated with research and development. Although the evidence for the existence of spillovers at the micro or industry level is controversial at the aggregate country level,<sup>1</sup> the existence of spillovers is well established.<sup>2</sup> Indirect support is often provided through tax exemptions or tax credits on private expenditure on research and development. No single mechanism is superior in every circumstance to the others.

Lack of access is not the only issue associated with overreliance on intellectual property rights. If the concern about access to existing knowledge is deep-seated, there is also the solution of public buying out of patents<sup>3</sup> and even of compulsory licensing. The issue, rather, is that without “push” and, specifically, without grants, fundamental knowledge for the overall progress of science and technology may never or may take much longer to be found.

## **2.3 Possible framework for considering financing options**

Health research and development for the problems of the poor is deficient because the current (public and private) incentives to produce and diffuse the innovations required by the poor are inadequate:

- Private incentives, associated with intellectual property rights, are of limited effectiveness because the markets in developing countries are small and “thin”.
- As developing countries are severely resource constrained, they devote limited resources, in a sustained way, to research and to technological innovation.

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<sup>1</sup> David PA, Hall BH, Toole AA. Is public R&D a complement or substitute for private R&D? A review of the econometric evidence. *Research Policy*, 2000, 29:497–529.

<sup>2</sup> Jones CI, Williams JC. Too much of a good thing? The economics of investment in R&D. *Journal of Economic Growth*, 2000, 5:65–85.

<sup>3</sup> Kremer M. Patent buy-outs: a mechanism for encouraging innovation. *Quarterly Journal of Economics*, 1998, 113:1137–1167.

- The contributions of industrial countries to research on problems specific to poor countries have been inadequate due to a mismatch between the costs of the research and the scope of the benefits, as elaborated upon above.

The diseases faced by developing countries are different from those in developed countries. Infectious and parasitic diseases account for one third of the burden of disease in developing countries but only 3% in high-income countries. Noncommunicable conditions, such as cancer and cardiovascular disease, account for more than 80% of the burden of disease in developed countries and are now assuming greater importance in developing countries. The last year in which communicable diseases caused more deaths than noncommunicable diseases globally was 1998, and, in low- and middle-income countries, noncommunicable diseases now account for more than 50% of all deaths.

Two questions to be considered in designing an analytical framework with which to analyse financing options for health research and development are:

- whether the knowledge required by the poor already exists. If it does, the main challenge is ensuring the diffusion of that knowledge. If it does not yet exist, the challenge is to ensure that it is generated;
- whether the innovations (knowledge) are relevant only for the poor or are relevant for both developing and industrialized countries.

Consideration of these two dimensions indicates that the gap in health research and development results from four sets of challenges, each set belonging to one of the four quadrants shown in Figure 1. The concrete challenges can be summarized as follows:

(a) When knowledge exists and is relevant mainly to poor countries, the challenges are predominantly associated with the nature of the demand. It may be that, very simply, developing countries do not have the resources to acquire the knowledge, or volatile demand may dissuade public and private agents from investing in production of the goods and services that would permit the deployment of knowledge. This is particularly relevant in the case of time-tested, evidence-based strategies for the prevention and control of neglected infectious diseases in poor countries, such as tropical parasitic diseases, diarrhoea and pneumonia, which continue to attract inadequate investment due to lack of demand. Challenges associated with intellectual property rights may also exist but may have less impact.

(b) When knowledge exists but is relevant to both industrialized and developing countries, the same challenges related to demand contribute to impede the access of the poor to this type of knowledge. In this case, however, there is probably an additional barrier: prices driven by intellectual property, i.e. market-based pricing aimed at maximizing profits when patent rights covering the product make it possible. Knowledge in this quadrant is likely to be protected, the rights to access and use of the knowledge being held mainly by private agents (but also in some cases by public entities) that seek to be compensated for the investments made to generate the knowledge by charging intellectual property-driven prices, which prevent the poor from accessing the knowledge.

(c) When knowledge does not yet exist that is relevant to both poor and industrialized countries, the challenges are a combination of technical and scientific issues and demand. Additionally, issues of intellectual property may play a role, in that rights may impede access to existing knowledge. Moreover, such issues must be considered in order to avoid or limit the

possibility that intellectual property prices will not exclude the poor once the knowledge has been generated (moving to quadrant 2).

(d) Perhaps the most vulnerable situation is that depicted in quadrant 4, when knowledge relevant only to the poor does not exist. In this case, not only is there an almost absolute lack of incentive but there is no capacity in developing countries to develop the knowledge required by either private or public agents.

**Figure 1. Framework to identify missing incentive structures for the production and distribution of knowledge**

Knowledge exists	<ul style="list-style-type: none"> <li>• “Demand” challenges</li> </ul> <p style="text-align: center;"><b>1</b></p>	<ul style="list-style-type: none"> <li>• IP-driven prices*</li> <li>• “Demand” challenges</li> </ul> <p style="text-align: center;"><b>2</b></p>
	<ul style="list-style-type: none"> <li>• No incentives</li> <li>• No capacity</li> <li>BUT, urgent need and potential high social benefits</li> </ul> <p style="text-align: center;"><b>4</b></p>	<ul style="list-style-type: none"> <li>• Scientific and technical development</li> <li>• IP-driven prices</li> <li>• “Demand” challenges</li> </ul> <p style="text-align: center;"><b>3</b></p>
Knowledge does not exist	Knowledge applicable only in poor countries	Knowledge applicable both in poor and other countries

\* IP = Intellectual property

Figure 2 illustrates the generic situations described above. There is now sufficient knowledge for use of a combination of therapeutic drugs and preventive measures (including insecticide-impregnated nets) to control malaria, but this knowledge fails to be used effectively in poor countries. Lack of resources and volatile demand for the goods and services needed to use this knowledge obviate application of the knowledge.

Many childhood vaccines are no longer subject to patent protection. Although they are relevant in both developed and developing countries, they are still not used effectively in developing countries. Challenges associated with demand (especially its volatility) impede access. Access to antiretroviral drugs for HIV/AIDS has been limited by intellectual property pricing barriers, in addition to the demand challenges that affect childhood vaccines.

**Figure 2. Framework to identify missing incentive structures for health research and development, with examples**

Knowledge exists	<ul style="list-style-type: none"> <li>• Malaria control</li> </ul> <p style="text-align: center;"><b>1</b></p>	<ul style="list-style-type: none"> <li>• Childhood vaccines</li> <li>• ARVs*</li> </ul> <p style="text-align: center;"><b>2</b></p>
	<ul style="list-style-type: none"> <li>• Malaria vaccine</li> <li>• TB vaccine (effective)</li> <li>• HIV/AIDS vaccine (?)</li> </ul> <p style="text-align: center;"><b>4</b></p>	<ul style="list-style-type: none"> <li>• Cancer treatment</li> <li>• HIV/AIDS vaccine (?)</li> </ul> <p style="text-align: center;"><b>3</b></p>
Knowledge does not exist	Knowledge applicable only in poor countries	Knowledge applicable both in poor and other countries

\* Antiretroviral therapy

The cures for many types of cancer and an HIV/AIDS vaccine are examples of knowledge that does not yet exist but would be relevant throughout the world. It is not certain that an HIV/AIDS vaccine that stimulates an immunological response against the strain of HIV prevalent in Europe and North America would also do so against the strain of the virus that is prevalent in Africa, and there are questions about whether an HIV/AIDS vaccine would be equally effective everywhere (thus, the question mark). The constraints in this case are mostly scientific and technical.

Examples of knowledge that is completely absent include that on vaccines against malaria and an effective vaccine against tuberculosis for developing countries. Perhaps, as indicated above, an HIV/AIDS vaccine for the strains of HIV that are prevalent in Africa and vaccines against neglected diseases are also needed.

## 2.4 Applying the framework to financing options

The framework described above includes a number of concrete initiatives, proposals and ideas for closing the knowledge gap.

In quadrant 1, the main task is to meet the challenges associated with demand. Options to improve access to knowledge by the poor usually include generating reliable demand on a scale that is commensurate with the requirements of those who produce the goods and services that are needed to use the knowledge. One way is to pool purchasing funds for medicines, so that not only are the

medicines made available in developing countries but at lower price, due to economies of scale in consumption and enhanced bargaining power, in a cycle of enhanced access. Resource pooling and bulk purchasing have been used by initiatives such as the GAVI Alliance, the Global Fund, and the Global Tuberculosis Drug Facility. An excellent example of pooled purchasing by small countries is the Drug Facility in the eastern Caribbean.

When knowledge is relevant to both the poor and others (quadrants 2 and 3), the challenges may be intellectual property-driven prices or to demand. The options for meeting demand are similar to those described above. When the challenges are intellectual property-driven prices, the options to overcome restrictions to access include segmentation and differentiation of the markets for the poor and for others. If the knowledge exists, access can be improved by adopting differential pricing for patented technologies. This option is efficient (Pareto improving), as developed countries will not be worse off (they would pay the same they pay now or even slightly less), and developing countries would pay a substantially reduced price (based on the ability to pay and marginal costs of production). Differential pricing for some critical technologies has come up against the decision by some groups of low- and lower-middle-income countries to obtain a single price.

Deficiencies in the application of existing knowledge for the improvement of health may also lie in the weaknesses of existing health systems.

**Health systems: a critical element**

Increasing emphasis is placed on the critical role of health systems in achieving the Millennium Development Goals. Building strong health systems and the relevant infrastructure will require substantially more resources internally and from the international community. New and innovative sources of financing will be needed to improve health systems, particularly those in the least-developed countries, which bear the heaviest burden of disease. The critical deficiencies of health systems include failure to maximize the benefits of current interventions and those that may be derived from new research; physical and financial inaccessibility; problems of human resources and weaknesses in planning and management. Ineffective or inefficient application of existing knowledge about appropriate interventions is a reflection of the inadequacy of health systems. In addition, research on health systems is needed to derive new, contextually appropriate knowledge. It is of particular relevance to the work of the Expert Working Group on R&D Financing that such research has traditionally been underfunded. Recommendations for the mobilization of new resources must take account of the needs of health systems.

If knowledge does not exist, differential patenting<sup>1</sup> is an option, taking into account the flexibilities of the Agreement on Trade-related Aspects of Intellectual Property Rights (the TRIPS agreement). Basically, firms accept advance licensing of their technologies to the poor while retaining the usual property rights in developed countries. This proposal has been advanced to solve problems of access to pharmaceuticals but could be extended to other types of innovation. It could be implemented within the current system of intellectual property protection if firms were to file foreign licence statements at the same time as their patent application.

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<sup>1</sup> Lanjouw JO. *Intellectual property and the availability of pharmaceuticals in poor countries*. Washington DC, Center for Global Development, 2002 (Working Paper No. 5).

As mentioned above, quadrant 4 represents perhaps the most vulnerable situation. The options highlighted indicate how the scientific power and technological capacity of private and public institutions in developed countries could be mobilized to focus on the problems of the poor. They do not address the longer-term need to build endogenous capacity to allow the poor to become fully active participants in the knowledge economy. Several options have been considered to meet these challenges. One is advance market commitments by developed countries to purchase vaccines for neglected diseases, as discussed above.

Basic research and efforts to obtain new, fundamental scientific results upon which later technological developments can be built require different incentives, “push” incentives probably being more effective for this purpose. One possibility, based on the scientific capability of the private sector in developed countries, is to offer tax credits on expenditure associated with research and development oriented towards the diseases that affect predominantly developing countries; such legislation has been proposed in the United Kingdom and in the United States. Another possibility is to offer tax credits to pharmaceutical firms in developed countries for sales of new vaccines against conditions specific to developing countries, which provides an incentive not only for vaccine discovery but also for its distribution and sales to those in need. A pharmaceutical company in a rich country could receive US\$ 1 in tax credits for each US\$ 1 of sales to a poor country, which would correspond roughly to giving the government half the burden of the cost. This burden would be incurred, however, not only if the vaccine is discovered but also if it is sold, which, in principle, would happen only if it was used effectively. For a more detailed discussion, see Attaran et al.<sup>1</sup>

Of course, incentives such as a purchase commitment do not pay for opportunity costs. Why should a firm that has limited resources and time engage in research and development for a vaccine, even if there is a purchase commitment, when it could invest in more rewarding projects? The size of the purchasing commitment may be important to overcome the opportunity cost, but grants may also be needed for clinical trials or even research and development. “Orphan drug legislation” combines marketing exclusivity with clinical trial grants. Thus, government funding (through direct grants or tax credits) for research and development may often be required as a “push” mechanism.

Another possibility, still oriented to private firms, is to extend national orphan drug legislation to the international level. National orphan drug legislation gives access to special public funds for research on diseases that affect only a minority of the population, with special treatment in the regulatory drug approval process and other benefits once a medicine actually exists. Applying the same principle to diseases that have been neglected in developing countries would provide added incentives for research.

Yet another possibility is to use the research capacity of national laboratories and universities by establishing at the international level an equivalent to the Medical Research Council in the United Kingdom or the National Institutes of Health in the United States.

Perhaps the most promising approach for linking the capacity of public and private sectors to address the problem shown in quadrant 4 is product development partnerships.

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<sup>1</sup> Attaran A et al. *A tax credit for sales of HIV, tuberculosis, and malaria vaccines*. Cambridge, Massachusetts, Harvard University, Center for International Development, 2000.

## **2.5 Partnerships for product development**

Product development partnerships are a type of public–private partnership in which a government service or private business venture is funded and operated through a partnership between the government and the private sector. They typically involve a contract between a public sector authority and a private party, in which the private party provides a public service or project and assumes substantial financial, technical and operational risk in the project, with the guarantee of adequate return on the private investment.

Successful product development partnerships include the Medicines for Malaria Venture, a Swiss foundation with the mission of bringing together public, private and philanthropic sectors to fund and manage the discovery, development and delivery of new medicines for the treatment and prevention of malaria in endemic countries. Another example is the International Aids Vaccine Initiative, an ambitious non-profit entity with truly global reach, which works to accelerate the development of an AIDS vaccine in addition to promoting expansion of universal access to prevention, treatment and support in HIV infection. The Initiative implements most of its research, policy and advocacy programmes in developing countries, where 95% of new HIV infections occur.<sup>1</sup>

Another product development partnership, the Donor Coordination Group, comprising Irish Aid, the Department for International Development (United Kingdom), the Wellcome Trust, the World Bank, the Directorate General for International Cooperation of the Netherlands, the Bill & Melinda Gates Foundation, the Swiss Agency for Development and Cooperation, the Rockefeller Foundation, the Canadian International Development Agency, the Norwegian Agency for Development Cooperation, the United States Agency for International Development and the United States National Institutes of Health, was established in April 2004 to help donors in supporting and monitoring the performance of product development partnerships through information sharing, policy analysis and advocacy. An additional rationale for the Donor Coordination Group was that donors and representatives of the partnership could reduce the costs of transaction costs of monitoring and engagement on both sides, through coordinated initiatives. Three years later, Irish Aid highlighted what it saw as the advantages of the Donor Coordination Group: (i) improved decision-making, (ii) influence on policy as part of a large group of donors, (iii) reduced transaction costs and (iv) increased capacity to oversee and monitor the product development partnership field. Irish Aid also noted, however, that work to date had not resulted in criteria or clarified for donors how they could judge and choose between different partnership options. They considered that WHO and other relevant normative multilateral agencies should be included as full partners in product development partnerships, to avoid addressing the upstream–downstream interface for each product or only by individual partnerships, with the risk of product or disease-specific verticalization.<sup>2</sup>

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<sup>1</sup> [www.iavi.org/about-IAVI/PAGES/what-we-do.aspx/](http://www.iavi.org/about-IAVI/PAGES/what-we-do.aspx/) Accessed 2 October 2009.

<sup>2</sup> Irish Aid. *Strategy for supporting global health partnerships 2006–2010*. Dublin, 2007. [www.irishaid.gov.ie/hivandaids/downloads/Irish\\_Aid\\_GHP\\_Strategy.doc](http://www.irishaid.gov.ie/hivandaids/downloads/Irish_Aid_GHP_Strategy.doc). Accessed 18 October 2009.

### 3. COORDINATION OF FINANCING FOR RESEARCH AND DEVELOPMENT

There are presently no good sources of information on investments in research on communicable or noncommunicable diseases.<sup>1</sup> Total global financing for health research and development exceeded US\$ 160 billion in 2005, the private for-profit sector accounting for 51% of this amount, the public sector for 41% and the private not-for-profit sector for 8%.<sup>2</sup> Lack of reporting mechanisms, inconsistent data, lack of publicly available information and lack of resources for examining reports in other languages posed significant challenges to data collection. Advances have, however, been made in identifying investments by disease category and by region, such as the work of G-Finder on neglected diseases<sup>3</sup> and the HIV Vaccines and Microbicides Resource Tracking Group.<sup>4</sup> Nevertheless, there is no global understanding of investments in communicable and noncommunicable diseases. In addition, research and development must be coordinated to address the problems faced by many developing countries in achieving the Millennium Development Goals.

#### 3.1 Main sources of funding

The Working Group prepared an overview of the largest government, pharmaceutical and not-for-profit sources of funding for research on communicable and noncommunicable diseases in the world during 2008 from publicly available sources. Relevant funding was tracked in: France, Germany, Japan, the United Kingdom and the United States, which collectively contributed 80% of global public spending on health research and development; the 10 pharmaceutical firms with the highest revenue, which collectively contributed over 60% of all industry spending on research and development; and the largest private international foundations and charitable organizations in the five high-income countries listed above. Inclusion of other research portfolios would add to the overall view of global research on noncommunicable and communicable diseases, such as the important, growing contributions of private sector research and development in innovative developing countries; however, it was not possible to obtain these data in the short time and with the resources available. Further research is desirable to broaden the scope of this exercise.

While no communicable diseases were excluded from the analysis, the focus is on those noncommunicable diseases that make the largest contribution to mortality in most low- and middle-income countries: cardiovascular disease, cancers, chronic respiratory diseases and diabetes. These diseases share the characteristic of being largely preventable by effective interventions against shared risk factors.<sup>5</sup> Mental and neurological disorders, important chronic conditions with a unique set of features, the diagnosis of which with other health conditions is inadequately appreciated, were also

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<sup>1</sup> Many of the data in this section were collated by Marta Feletto as a part of a report to the Expert Working Group on R&D Financing. Feletto M, Matlin S. *Global R&D financing for communicable and noncommunicable diseases*.

<sup>2</sup> Global Forum for Health Research. *Monitoring financial flows for health research 2008. Prioritizing health research for health equity*. Washington DC, 2009. Available from [www.globalforumhealth.org/layout/set/print/Media-Publications/Publications/Monitoring-Financial-Flows-for-Health-Research-2008-Prioritizing-research-for-health-equity](http://www.globalforumhealth.org/layout/set/print/Media-Publications/Publications/Monitoring-Financial-Flows-for-Health-Research-2008-Prioritizing-research-for-health-equity).

<sup>3</sup> Moran M et al. Neglected disease research and development: How much are we really spending? *PLoS Medicine*, 2009, 6:e1000030.

<sup>4</sup> HIV Vaccines and Microbicides Resource Tracking Group. *Report archive, 2009*. Available from: [www.hivresourcetracking.org/resources/report\\_archive](http://www.hivresourcetracking.org/resources/report_archive). Accessed 14 September 2009.

<sup>5</sup> Taskforce on Innovative International Financing for Health Systems. *Constraints to scaling up and costs, Working Group 1 Report*. Geneva, World Health Organization, 2009.

included in the analysis.<sup>1</sup> The study therefore focused on cardiovascular disease, chronic respiratory diseases, cancer, diabetes and mental health, and the figures refer only to these categories.

All financial figures are expressed in 2008 international US dollars.<sup>2</sup> Absolute figures for research and development funding and the relative proportions of research and development for specific diseases are reported for the public and the not-for-profit sector. These figures should be interpreted with caution, as only a share of total public and private not-for-profit spending on communicable and noncommunicable disease research could be tracked from publicly available sources. More importantly, the size of this share varied by country, and it is not known how untracked funds are distributed to different disease areas. The absolute figures do not cover all national public and private not-for-profit spending, and the relative share allocated to research on specific diseases might change substantially if the overall spending in these sectors was to be tracked.

### **3.1.1 Public funding**

To estimate the breadth of research funded by the public sector, the Committee analysed data for five high-income countries – France, Germany, Japan, the United Kingdom and the United States – that accounted for 80% of global public spending on health research and development, according to the latest information from the OECD.<sup>3</sup> The largest public funders of health research and development in each of the five countries were identified. To avoid constraining or biasing the analysis, budgets and reports were accessed in the original languages on public portals. The lack of standardization in research and development reporting between and within countries and the absence of disaggregation of research information by disease posed significant challenges.

A total public research and development budget envelope is provided for each country, when available, as well as the share that could be classified as earmarked for communicable and noncommunicable disease-related research. A detailed review of the way in which funding was identified and categorized is given for the United States, to serve as an example. The amounts are given in figures converted by purchasing power parity (2008 international US dollars).

Financial research and development figures are shown in Table 1. The United States is the largest public funder. Germany's and Japan's absolute figures are understated, as these are the two countries for which the lowest portion of public funding was tracked. Moreover, the United Kingdom figures include the R&D budgets of the three most important philanthropic organizations, and public funding in the United Kingdom would be substantially lower if the relative contribution of not-for-profit organizations (as estimated from their annual research and development budgets) had been

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<sup>1</sup> Rezaie R et al. Brazilian health biotechnology—fostering crosstalk between public and private sectors. *Nature Biotechnology*, 2008, 26:627–644. [www.nature.com/nbt/journal/v26/n6/pdf/nbt0608-627.pdf](http://www.nature.com/nbt/journal/v26/n6/pdf/nbt0608-627.pdf).

<sup>2</sup> As it is unlikely that the recent trend in dollar exchange rates bears much resemblance to trends in the price of carrying out R&D, we used purchasing power parity rates against the US dollar, as they are adjusted for general internal price levels between countries and reflect the opportunity cost of committing funds to R&D. Figures are first converted from local currencies into constant 2008 values (Kumaranayake L. The real and the nominal? Making inflationary adjustments to cost and other economic data. *Health policy and Planning*, 2000; 15:230–234 and [www.imf.org/external/pubs/ft/weo/2009/01/weodata/weoselgr.aspx](http://www.imf.org/external/pubs/ft/weo/2009/01/weodata/weoselgr.aspx)) and then into international dollars by applying purchasing power parity conversion rates ([www.oecd.org/dataoecd/61/54/18598754.pdf](http://www.oecd.org/dataoecd/61/54/18598754.pdf)).

<sup>3</sup> Burke MA, Matlin SA, eds. *Monitoring financial flows for health research, 2008: prioritizing research for health equity*. Geneva, Global Forum for Health Research. Available from [www.globalforumhealth.org/layout/set/print/Media-Publications/Publications/Monitoring-Financial-Flows-for-Health-Research-2008-Prioritizing-research-for-health-equity](http://www.globalforumhealth.org/layout/set/print/Media-Publications/Publications/Monitoring-Financial-Flows-for-Health-Research-2008-Prioritizing-research-for-health-equity).

subtracted. Public institutions in France receive a mix of funds from public and private donors, and public funding would be lower if solely the portion allocated by the public sector had been estimated.

### **3.1.2 Industry funding**

To broaden its search on noncommunicable and communicable diseases funded by the private sector, the Committee analysed data for the 10 pharmaceutical companies with the highest revenues in 2008.<sup>1</sup> The collective investments of these companies for R&D accounted for 62.4% of that made by the entire pharmaceutical industry in 2008 (US\$ 90.5 billion).<sup>2</sup> Each firm's "pipeline" was retrieved from the company's web site, and compounds under active development, either in clinical trials or at the registration stage, were grouped into drugs for communicable or noncommunicable diseases on the basis of the product's primary therapeutic indication.<sup>3</sup> Compounds that were being tested in multiple trials in the same phase were counted as a single product. Of the drugs under development by the 10 firms, 72.6% were considered to be relevant to the therapeutic areas of interest to this project. The financial cost incurred in 2008 for the development of drugs for noncommunicable and communicable diseases was estimated by a correlational analysis.

The numbers of drugs in each phase of clinical trials were computed from the companies' web sites, as shown in Table 2, with each company's annual research and development budget for 2008, converted into 2008 international US dollars. While these companies disclose their research and development budget for the last financial year, they do not provide an indication of the share of research and development expenditure devoted to developing drugs for noncommunicable or communicable diseases. Therefore, the costs for 2008 were estimated.

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<sup>1</sup> Pfizer, Novartis, GlaxoSmithKline, Sanofi–Aventis, Johnson & Johnson, Roche, Merck, AstraZeneca, Amgen, Eli Lilly.

<sup>2</sup> European Federation of Pharmaceutical Industries and Associations. *The pharmaceutical industry in figures: key data. 2009 uptake*. Available from [www.efpia.eu/content/default.asp?pageid=559&doid=4883](http://www.efpia.eu/content/default.asp?pageid=559&doid=4883).

<sup>3</sup> Novartis discloses data on only 50 of 152 projects in development, and Johnson & Johnson discloses only a selected number of products in later stages of development.

**Table 1. Public sector spending on health research and development by category and by country (international US dollars, 2008)**

Disease	France	Germany	Japan	United Kingdom	United States	Total
Noncommunicable						
Cancer	211.4	21.5	50.8	324.1	4 573.8	5 181.6
Cardiovascular disease	110.1	6.2	18.7	159.1	1 538.4	1 832.5
Chronic respiratory diseases	110.1	N/A	2.2	23.6	587.8	723.7
Diabetes <sup>a</sup>		N/A	8.2	47.1	613.9	669.2
Mental health	103.6	30.2	23.1	259.3	3 864.1	4 280.3
All	535.1	57.9	103.0	813.1	11 178.0	12 687.1
Communicable						
HIV/AIDS			11.1		2 905.0	2 916.1
Others			40.7		2 809.4	2 850.1
All	110.6	23.1	51.8	147.3	5 714.4	7 042.2
Total	645.8	81.0	154.8	960.6	16 892.4	18 734.6

<sup>a</sup> Research on diabetes is included under research on cardiovascular disease.

<sup>b</sup> N/A: not available.

**Table 2. Numbers of drugs under active development by category and phase (international US dollars, 2008)**

Company	R&D budget (billion US\$)	Communicable diseases (phase)				Noncommunicable diseases (phase)				Other diseases (total)	Totals (phase)			
		I	II	III	Total	I	II	III	Total		I	II	III	Total
Johnson & Johnson <sup>a</sup>	8.4			8				11						23
Pfizer	7.9	3	5	3	11	31	21	8	60	29	40	33	27	100
Novartis <sup>b</sup>	6.1	5	1	11	17	0	9	20	29	4	5	16	25	50
GlaxoSmithKline	5.6	4	4	0	8	20	15	16	51	77	41	45	46	136
Astra Zeneca	5.2	7	2	1	10	23	22	8	53	13	38	25	9	76
Sanofi–Aventis	5.0	4	7	8	19	10	5	16	31	14	17	16	31	64
Merck	4.8	1	3	1	5	21	11	7	35	3	22	16	9	47
Eli Lilly	3.8	0	0	0	0	32	14	7	53	13	39	15	8	66
Amgen	2.9	0	0	0	0	7	10	7	24	16	13	13	14	40
Roche	2.6	2	1	1	4	32	20	17	69	13	42	23	21	86
<b>Total</b>	<b>43.9</b>	<b>26</b>	<b>23</b>	<b>25</b>	<b>74</b>	<b>176</b>	<b>127</b>	<b>117</b>	<b>409</b>	<b>182</b>	<b>257</b>	<b>214</b>	<b>213</b>	<b>665</b>

<sup>a</sup> Johnson & Johnson report only on selected drugs in later stages (phase III or registration) and not on the total number of drugs under development; the figures were therefore excluded from the analysis.

<sup>b</sup> Novartis reported details on only 50 of their 152 projects.

### 3.1.3 Funding by charities and private foundations

The Global Forum for Health Research estimated that US\$ 12.2 billion were invested in health-related research and development in 2005 by the private not-for-profit sector, which includes charities, foundations and institutes of higher education.<sup>1</sup> Funding from private universities was estimated to be US\$ 3.1 billion of that amount. The present study disregarded private funding from universities, as they do not systematically report on R&D funding by category of disease.

Foundations were identified from reviews of donor funding for health research and development, as did Shiffman,<sup>2</sup> and were ranked by the size of their endowments. Subsequently, the Working Group determined whether information on health research and development investments, on health research and development investments by disease and on investments in excess of US\$ 5 million was available for the largest 40 European and 50 United States foundations. Only five foundations met these criteria and were included in the study. This is a challenging sector to examine, as, unlike charities, few foundations disclose their investments in research and development.

<sup>1</sup> Global Forum for Health Research. *Monitoring financial flows for health research 2008. Prioritizing health research for health equity*. Geneva, 2008. Available from [www.globalforumhealth.org/layout/set/print/media-publications/publications/monitoring-financial-flows-for-health-research-2008-prioritizing-research-for-health-equity](http://www.globalforumhealth.org/layout/set/print/media-publications/publications/monitoring-financial-flows-for-health-research-2008-prioritizing-research-for-health-equity).

<sup>2</sup> Shiffman J. Donor funding priorities for communicable disease control in the developing world. *Health Policy and Planning*, 2006, 21:411–420.

Although charities usually report specific allotments for research and development, their large number makes reporting on this group also challenging. According to the National Center for Charitable Statistics, in 2008, there were 1 536 134 registered non-profit institutions in the United States, of which 974 337 were public charities and 115 340 private foundations.<sup>1</sup> A review of 372 United States-based charities, identified through “Charity Navigator”, excluded those for which research and development funding could not be attributed to specific diseases, resulting in the inclusion of 34 charities. The remaining charities either did not have a clear link to a disease group examined or focused on advocacy and support rather than research. All the identified charities reported research and development investments by programme activity in their financial statements.

The Working Group also sought to provide representation of the major charities based in France, Germany, Japan and the United Kingdom. French charities with annual research activities accounting for over €33 million were included. A search for charities in Germany and Japan, based on the same criteria, was inconclusive. In the United Kingdom, charities are regulated by the Charity Commission, a Government body that ensures that charities remain transparent and accountable to donors. There are 166 807 registered charities with a combined annual income of £51.1 billion. Although the Charity Commission does not maintain a register of charities by sector, some charities can be investigated by using keywords for objectives and activities. A search with the keywords “health”, “medical” and “research” was undertaken, and the sample was restricted to charities with a total income of over £10 million, resulting in 256 charities. The 14 charities that provided disease-disaggregated information on research and development funding were retained.

The results for charities and foundations in the United Kingdom and the United States (Table 3) are of greatest interest in the private not-for-profit sector, as they are clearly defined and are actively monitored by government agencies and interest groups. Of the total amount provided by the private foundations and charities included in this study (US\$ 2473.3 million), 66.7% (US\$ 1650.4 million) was allotted to noncommunicable diseases and 33.3% (US\$ 822.9 million) to communicable diseases. Cancers received the highest investment among noncommunicable diseases, accounting for 44.2% (US\$ 1092.7 million), followed by cardiovascular disease with 12.7% (US\$ 313.5 million) and diabetes with 9.3% (US\$ 230.8 million). Chronic respiratory diseases and mental health each accounted for less than 1% of investments.

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<sup>1</sup> National Center for Charitable Statistics. *Number of nonprofit organizations in the United States, 1998–2008*. Washington DC, 2009. Available from: [nccsdataweb.urban.org/PubApps/profile1.php?state=US](http://nccsdataweb.urban.org/PubApps/profile1.php?state=US). Accessed 5 October 2009.

**Table 3. Private not-for-profit sector investments in health research and development (R & D) by category (international US dollars, 2008)**

Disease category	R & D spending	
	US\$ million	Percentage of total
Noncommunicable diseases		
Cancer	1 092.7	44.2
Cardiovascular disease	313.5	12.7
Chronic respiratory diseases	12.9	0.5
Diabetes	230.8	9.3
Mental health	0.4	0.0
<b>Total</b>	<b>1 650.4</b>	<b>66.7</b>
Communicable diseases		
Infectious diseases	822.9	33.3
<b>Total</b>	<b>822.9</b>	<b>33.3</b>
<b>Total</b>	<b>2 473.3</b>	<b>100.0</b>

Charities and private foundations in the United States spent a total of US\$ 1537.6 million on relevant research in 2008 (Table 4), of which 61.1% (US\$ 939.3 million) was for noncommunicable diseases and 38.9% (US\$ 598.3 million) for communicable diseases. Most of the funding for communicable diseases came from private foundations such as the Bill & Melinda Gates Foundation, whereas funding for noncommunicable diseases came mostly from charities. The investments in noncommunicable diseases included US\$ 508.1 million for cancer, US\$ 223 million for diabetes and US\$ 199.78 million for cardiovascular disease; chronic respiratory disease (US\$ 8 million) and mental health (US\$ 0.4 million) received less funding. Charities alone invested 88.1% (US\$ 907.5 million) in noncommunicable diseases and 11.9% (US\$ 113.6 million) in communicable diseases.

**Table 4. Private not-for-profit sector investments in health research and development (R & D) by category in the United States (international US dollars, 2008)**

Disease category	R & D spending	
	Million US\$	Percentage of total
Noncommunicable diseases		
Cancer	508.1	33.0
Cardiovascular disease	199.8	13.0
Chronic respiratory diseases	8.0	0.5
Diabetes	223.0	14.5
Mental health	0.4	0.0
<b>Total</b>	<b>939.3</b>	<b>61.1</b>
Communicable diseases		
Infectious diseases	598.3	38.9
<b>Total</b>	<b>598.3</b>	<b>38.9</b>
<b>Total</b>	<b>1 537.6</b>	<b>100.0</b>

### 3.2 Conclusions

Estimates of global research and development spending in 2008, across the spectrum of noncommunicable and communicable diseases, were considered. Because of the limited time and resources for this work, only the largest sources, responsible for the majority of global funding, could be analysed. Moreover, the study was limited to data that were publicly available, so that it relied on what and how countries, organizations and industries choose to report. To avoid constraining or biasing the research, budgets and reports were accessed in the original languages on public portals. Nonetheless, public funding institutions report variably on disease-specific research and development budgets. Moreover, usually neither foundations nor private universities report disease-specific research funding. Industries disclose their project pipelines (in some cases only a subsample) and information on the therapeutic significance of active drugs in development, but not information on research and development into drugs for specific diseases. The Working Group managed to classify a share of disease-relevant research and development funding from less than half (in Germany) to as much as 95% (in the United States) of public funding. They also could classify over 70% of industry investments and the largest investments by foundations and charities, although these do not account for the majority of not-for-profit spending, given the sheer number of organizations with modest budgets.

Another challenge was the lack of standardization in reporting and classification systems between and within countries. Public bodies may report on budget appropriations, requests or commitments. Research expenditures may be aggregated across variably defined groups of diseases. Compounds under development may be classified across variably defined primary indications. Funding sources may not be discernible. While the results are therefore tentative and the relative share of research and development funding by disease cannot be generalized, they show a consistent 2:1 ratio in research and development funding allocated to noncommunicable diseases and communicable

diseases, across sectors (Table 5). Public spending for noncommunicable and communicable diseases varied widely in the countries analysed, noncommunicable diseases receiving from 65% to over 80% of national public budgets. In all countries, cancer research alone absorbed the equivalent of or more than that for research for all communicable diseases.

**Table 5. Total sector investments in health research and development by disease category (international US dollars, 2008)**

Disease category	Public sector		Private sector		Not-for-profit organizations		Total	
	US\$ million	% of total	US\$ million	% of total	US\$ million	% of total	US\$ million	% of total
Noncommunicable	12 168.7	67.8	29 390.0	68.4	1 650.4	66.7	43 209.1	68.2
Communicable	5 766.2	32.2	13 590.0	31.6	822.9	33.3	20 179.1	31.8
Total	17 934.9	100.0	42 980.0	100.0	2 473.3	100.0	63 388.2	100.0

While the Working Group estimated the cost for developing drugs for the aggregate classes of noncommunicable and communicable diseases, the sample was not large enough to allow estimates of the cost of drugs for specific diseases. The distribution of active projects for diseases can, however, provide an indication of the commitment of industry research and development to different diseases. Of all the projects in development in 2008 by the 10 pharmaceutical industries with the highest revenue (see Table 2), 84% were related to noncommunicable and 15.3% to communicable diseases. The distribution of drugs under development for various noncommunicable diseases is consistent with the distribution for research funded by the public sector: drugs for cancer constituted 31.5% of those under development (regardless of the stage); drugs for mental health and cardiovascular disease represented 22.4% and 11% of projects, respectively. While the analysis was limited to the 10 pharmaceutical companies with the largest revenue, the analysis is consistent with results provided by FierceBiotech:<sup>1</sup> of the 2900 medicines in development in the United States in 2008, 750 (25%) were for cancer, 312 (10%) for heart disease and stroke and 109 (3.7%) for HIV/AIDS.

In the private not-for-profit sector, communicable disease funding still comes primarily from private foundations (63.3%), while noncommunicable diseases are widely covered by charity funding (98.1%). Of the overall not-for-profit research and development commitment, 44% goes to cancer research. Interestingly, mental health, which is targeted by both public and private research and development, is neglected by the not-for-profit sector, even in countries where it constitutes an important item on the public research agenda, such as the United Kingdom and the United States.

It was beyond the scope of this study to link the mapping of research and development to the burden of disease. According to the United Kingdom Clinical Research Collaboration, however, the general distribution of public and not-for-profit funding by disease in the United Kingdom broadly follows the pattern of burden of disease, as measured by disability-adjusted life-year rates for the

<sup>1</sup> FierceBiotech. *R&D spending by US biopharmaceutical companies reaches record levels in 2008 despite economic challenges*. Posted 10 March 2009; retrieved 30 September 2009. [www.fiercebiotech.com/press-releases/r-d-spending-u-s-biopharmaceutical-companies-reaches-record-levels-2008-despite-econo](http://www.fiercebiotech.com/press-releases/r-d-spending-u-s-biopharmaceutical-companies-reaches-record-levels-2008-despite-econo).

country in 2006.<sup>1</sup> Similarly, Manton et al.<sup>2</sup> found a consistent longitudinal correlation between the level of investment in research by the United States National Institutes of Health and population changes in the risks for cardiovascular disease, stroke, cancer and diabetes over the past five decades.

The extent to which such research can change the risk or burden of these diseases in low- and middle-income countries remains unknown. This study showed that disbursement by the United States National Institutes of Health for research on HIV/AIDS amounted to almost US\$ 3 billion, and Ravishankar et al.<sup>3</sup> estimated that total funding by Development Assistance for Health for HIV/AIDS in the United States in 2007 was US\$ 5.1 billion. According to Moran et al.<sup>4</sup> however, National Institutes of Health funding for proposals specifically for neglected diseases in developing countries (including HIV/AIDS) was an estimated US\$ 1.06 billion in 2007. This gap shows the extent to which health research that is relevant to low- and middle-income countries is severely underfunded. A similar conclusion can be drawn by comparing research funding for communicable diseases across sectors. For example, the G-Finder estimated that US\$ 2.5 billion were spent on research and development for neglected diseases in low- and middle-income countries, whereas some US\$ 20.2 billion (Table 5) were allocated to all communicable disease research in an incomplete sampling of high-income countries. The gap between research and development relevant to low- and middle-income countries and all health research and development is considerable.

#### **4. COORDINATION OF RESEARCH AND DEVELOPMENT FOR COMMUNICABLE AND NONCOMMUNICABLE DISEASES<sup>5</sup>**

##### **4.1 Material**

Qualitative research methods were used for much of this assessment, comprising archival analysis, review of published and “grey” literature and interviews. As a first step, an inventory of research and development financing initiatives was drawn up on the basis of information from three sources: a list of initiatives in a draft report commissioned by the secretariat of the Expert Working Group on Research and Development Financing in the first quarter of 2009;<sup>6</sup> a catalogue of initiatives in a paper prepared for the WHO Commission on Intellectual Property Rights and Health;<sup>7</sup> and the

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<sup>1</sup> United Kingdom Clinical Research Collaboration. *UK health research analysis, United Kingdom*. London, 2006. Available from [www.ukcrc.org/PDF/UKCRC\\_Health\\_Research\\_Analysis\\_Report.pdf](http://www.ukcrc.org/PDF/UKCRC_Health_Research_Analysis_Report.pdf). Accessed 28 September 2009.

<sup>2</sup> Manton KG et al. NIH funding trajectories and their correlations with US health dynamics from 1950 to 2004. *Proceedings of the National Academy of Sciences of the USA*, 2009, 106:10981–10986. Available from [www.pnas.org/cgi/doi/10.1073/pnas.0905104106](http://www.pnas.org/cgi/doi/10.1073/pnas.0905104106).

<sup>3</sup> Ravishankar N et al. Financing of global health: tracking development assistance for health from 1990 to 2007. *Lancet*, 2009, 373:2113–2124.

<sup>4</sup> Moran M et al. Neglected disease research and development: How much are we really spending? *PLoS Medicine*, 2009, 6:e1000030.

<sup>5</sup> Material for this section was drawn from two papers prepared for the Expert Working Group on R&D Financing: S. Nishtar. *Coordinating arrangements for R&D*, and Matlin, S.A. *Existing or potential mechanisms for coordination of financial flows for R&D for both communicable and non-communicable diseases*.

<sup>6</sup> McCabe A. *Survey of R&D coordination and financing mechanisms for type II and type III diseases*. Geneva, World Health Organization, 2009.

<sup>7</sup> Ziemba E. *Public–private partnerships for product development: financial, scientific and managerial issues as challenges to ensure success*. Geneva, World Health Organization, 2005.

listing of industry partnerships in the databases of health partnerships prepared by the International Federation for Pharmaceutical Manufacturers & Associations.<sup>1</sup> The list was supplemented by additional searches of published sources and web sites; when the information was incomplete, initiatives were contacted for further details. A WHO internal document entitled “Geneva health research cluster: in search of alignment and synergies”, which was prepared for a discussion on 15–16 December 2009, provided invaluable budget and background information about United Nations health research coordinating mechanisms. Some initiatives contacted for further information suggested other relevant initiatives, and these were also included in the final inventory. The complete list of initiatives examined can be found in the background document.

## **4.2 Background**

Coordination, which implies a slightly more active approach than collaboration, can be defined as “synchronization and integration of activities, responsibilities, and command and control structures to ensure that the resources are used most efficiently in pursuit of the specified objectives”.<sup>2</sup> Collaboration and coordination for research and development have been sought almost as a matter of faith, like a holy grail, for decades. It is accepted that research produces knowledge, which is a public good and should therefore be shared. The means of generating that knowledge and possessing it confer power of one sort or another, and this exacerbates the intrinsic difficulty of collaboration. Only when there are clearly mutual interests will those who have the means to generate knowledge be willing to share it. Part of the remit of organizations like WHO, with its constitutional mandate to coordinate, is to demonstrate mutuality of interests and to provide a neutral forum for interchange or to act as an impartial broker or conduit for sharing necessary information. Another means of ensuring that knowledge is generated or shared is a dictate from the funding agency.

The primary objective of coordination in the present context is to ensure that new drugs, vaccines and diagnostics needed to treat diseases that are prevalent in low- and middle-income countries are developed and are safe, effective, affordable and suitable for the conditions in which they will be used, thereby contributing to better health and health equity globally. Secondary objectives could include avoiding unnecessary duplication of effort and wasted funding. It is also important to ensure that urgent or neglected areas become priorities, by assisting policy-makers and donors in setting and managing their priorities and in selecting the most productive areas in the innovation pipeline. In many cases, insufficient priority is given to certain areas of basic science; inadequate funding is provided for uptake and product development; funding or capacity for clinical trials at appropriate locations is lacking; and choices must be made within and between diseases among competing product development pipelines. Other objectives are to facilitate cooperation between the public and private sectors and to promote inclusion of a wider range of actors in research and development, such as by ensuring the involvement of researchers in low- and middle-income countries in finding solutions to relevant problems and ensuring research and development capacity-building in those countries.

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<sup>1</sup> [www.ifpma.org/healthpartnerships/](http://www.ifpma.org/healthpartnerships/). Accessed 1 June 2009.

<sup>2</sup> [www.businessdictionary.com/definition/coordination.html](http://www.businessdictionary.com/definition/coordination.html). Accessed 3 June 2009.

Difficulties in coordination are outlined in *Disease control priorities in developing countries*,<sup>1</sup> which stresses the relevance of research, especially population-based, and which states that health research is the product of individual or institutional effort rather than of States:

“No simple answer is available regarding the best ways to ensure effective collaboration in relation to global health. Global collaborations can be difficult, they are not inexpensive and their successes are limited in number. One set of lessons still to be learnt is what the best forms of collaboration are: individual scientist, institutional, transnational or multinational.”

Perhaps the answer lies in the nature of the problem to be solved. While the discovery phase can be addressed by all four forms of collaboration, the development phase is more likely to rely on one or other or all of the last three.

The “Bamako call to action: research for health”<sup>2</sup> was a milestone in stimulating global action in health research. With respect to collaboration, it states that “research activities of the private and the public sectors, including international product development partnerships, together with an increased involvement of civil society, can be mutually supportive and complementary in furthering health development and security globally.” Furthermore, it recognizes the need to “mobilize all partners and players (public, private, civil society) to work together in effective and equitable partnership to find needed solutions”.

### **4.3 Resource tracking and coordination**

While the coordination of health research and development may not involve only financing, it must be based on an understanding of the resources needed to tackle the targeted health problems and of the resources already available and how they are being used. Thus, coordination in general requires resource tracking for problem formulation, priority setting, programme planning and monitoring of progress.

The field of global resource tracking for health research and development is relatively new. The first estimate of worldwide spending on health research and development was made by the Commission on Health Research for Development,<sup>3</sup> which estimated that, in 1986, the world spent US\$ 30 billion on health research and development, of which only about 5% was applied to the health problems of low- and middle-income countries, where 93% of the world’s preventable deaths occurred. Since 2001, the Global Forum for Health Research has been tracking and reporting global financial flows for health research and development regularly and systematically, producing a biennial total, conducting studies of resource flows for specific diseases, conditions, actors and sites and, since

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<sup>1</sup> Bloom BR et al. Priorities for global research and development of interventions. In: Jamison DT et al., eds. *Disease control priorities in developing countries*. Oxford, Oxford University Press; Washington DC, The World Bank, 2006.

<sup>2</sup> *The Bamako call to action on research for health*. Geneva, World Health Organization. [www.who.int/rpc/news/BAMAKOCALLTOACTIONFinalNov24.pdf](http://www.who.int/rpc/news/BAMAKOCALLTOACTIONFinalNov24.pdf).

<sup>3</sup> Commission on Health Research for Development. *Health research: essential link to equity in development*. New York, Oxford University Press, 1990. [www.cohred.org/node/311?DocumentId=2834](http://www.cohred.org/node/311?DocumentId=2834). Accessed 18 October 2009.

2008, publishing an annual “report card” on the performance of funders in reaching targets and commitments.<sup>1</sup>

Interest in monitoring financial flows for particular aspects of health research and development has grown significantly in the past decade:

- groups that address specific diseases, like HIV/AIDS,<sup>2</sup> tuberculosis<sup>3</sup> and malaria,<sup>4</sup> have assessed funding flows and needs
- countries have assessed research funding as a single exercise in order to benchmark activity and compare funding with the burden of disease,<sup>5,6</sup> as a tool for advocacy to policy-makers<sup>7</sup> or as part of a systematic annual exercise to set priorities for national funding for health research<sup>8</sup>
- the Bill & Melinda Gates Foundation has funded the G-Finder project at the George Institute in Sydney, Australia, to track global resources for a set of neglected diseases over five years<sup>9</sup>
- the private sector has reported its own contributions to health in low- and middle-income countries and estimated the combined value of its donations to drug access programmes (excluding research and development on neglected diseases) to be in the region of US\$ 4.4 billion.<sup>10,1</sup>

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<sup>1</sup> Landriault E, Monot JJ, Matlin SA, eds. *Monitoring financial flows for health research 2009*. Geneva, Global Forum for Health Research, 2009, in press.

<sup>2</sup> HIV Vaccines and Microbicides Resource Tracking Working Group. Geneva, UNAIDS, 2009. [www.hivresourcetracking.org](http://www.hivresourcetracking.org). Accessed 18 October 2009.

<sup>3</sup> Agarwal N. *TB research & development: a critical analysis of funding trends 2005–7, an update*. New York, Treatment Action Group, 2009. [www.treatmentactiongroup.org/uploadedfiles/about/publications/tag\\_publications/2009/tag%20tb%202009%20web-version2.pdf](http://www.treatmentactiongroup.org/uploadedfiles/about/publications/tag_publications/2009/tag%20tb%202009%20web-version2.pdf). Accessed 18 October 2009.

<sup>4</sup> Malaria R&D Alliance. *Malaria research and development: an assessment of global investment*. Stockholm, 2005. [www.malariaalliance.org/PDFs/RD\\_Report\\_complete.pdf](http://www.malariaalliance.org/PDFs/RD_Report_complete.pdf). Accessed 18 October 2009.

<sup>5</sup> Jones CI, Williams JC. Too much of a good thing? The economics of investment in R&D. *Journal of Economic Growth*, 2000, 5:65–85.

<sup>6</sup> Families USA Foundation. *The world can't wait: more funding needed for research on neglected infectious diseases*. Washington DC, 2008. [www.familiesusa.org/assets/pdfs/global-health/the-world-cant-wait.pdf](http://www.familiesusa.org/assets/pdfs/global-health/the-world-cant-wait.pdf). Accessed 18 October 2009.

<sup>7</sup> Research! United States of America. Alexandria, Virginia, 2009. [www.researchamerica.org](http://www.researchamerica.org). Accessed 18 October 2009.

<sup>8</sup> de Azevedo Gesteira AS. *Flows of financial resources for health research and development in Brazil 2000–2002*. Geneva, Global Forum for Health Research, 2006. [www.globalforumhealth.org/Media-Publications/Publications/Flows-of-Financial-Resources-for-Health-Research-and-Development-in-Brazil-2000-2002](http://www.globalforumhealth.org/Media-Publications/Publications/Flows-of-Financial-Resources-for-Health-Research-and-Development-in-Brazil-2000-2002). Accessed 18 October 2009.

<sup>9</sup> Moran M et al. Neglected disease research and development: How much are we really spending? *PLoS Medicine*, 2009, 6:e1000030. [www.thegeorgeinstitute.org/shadomx/apps/fms/download.cfm?file\\_uuid=409D1EFD-BF15-8C94-E71C-288DE35DD0B2&siteName=iih](http://www.thegeorgeinstitute.org/shadomx/apps/fms/download.cfm?file_uuid=409D1EFD-BF15-8C94-E71C-288DE35DD0B2&siteName=iih). Accessed 18 October 2009.

<sup>10</sup> International Federation for Pharmaceutical Manufacturers and Associations. *Partnerships to build healthier societies in the developing world*. Geneva, 2006, [www.ifpma.org/pdf/IFPMA\\_Building\\_Partnerships\\_Eng\\_18Jul06.pdf](http://www.ifpma.org/pdf/IFPMA_Building_Partnerships_Eng_18Jul06.pdf). Accessed 18 October 2009.

## **4.4 Current arrangements**

At present, there is no global coordination of research and development for communicable and noncommunicable diseases, and it is unlikely that there will ever be a grand scheme for coordinating health research globally. The field is highly fragmented, most organizations working either in isolation or as part of small groups or networks of limited subsets of entities with shared goals. Thus, partial efforts are made to coordinate selected aspects of the overall system, often involving only a section of the innovation pipeline.

A new approach to collaboration among national agencies engaged in basic research emerged in mid-2009 with the formation of the Global Alliance for Chronic Diseases. This involves six of the world's leading health agencies: the Australian National Health and Medical Research Council, the Canadian Institutes of Health Research, the Chinese Academy of Medical Sciences, the United Kingdom Medical Research Council and the United States National Institutes of Health (specifically, its National Heart, Lung, and Blood Institute and the Fogarty International Center). These institutions collectively manage an estimated 80% of all public health research funding, collaborating in noncommunicable disease research to tackle cardiovascular diseases (mainly heart disease and stroke), several cancers, chronic respiratory conditions and type 2 diabetes. The Alliance will focus in particular on the needs of low- and middle-income countries and on those of low-income populations in more developed countries. The Indian Council of Medical Research will be invited to join the Alliance as a member. Research agencies in other countries and private funders may be invited to join in a second wave, and WHO is joining the Alliance as an observer. This new approach is to be welcomed. The proposed priorities were identified by Daar et al.<sup>2</sup>

Cooperation or coordination of research and development can be analysed in several ways, all of which may be classified as vertical: by disease, by health area or by product. Alternatively, cooperation or coordination can be divided into that which takes place at national and at international level. Coordination of research or research management is also necessary within organizations, such as WHO, as discussed further in section 4.8.

As it is beyond the scope of this analysis to list all possible initiatives, examples of research coordination in each category are given below.

## **4.5 Coordination by theme**

### **4.5.1 By disease: malaria**

The European Malaria Vaccine Initiative was established in 1998 by the European Commission and interested European Union Member States in order to address structural deficiencies in publically funded malaria vaccine development. The initiative provides a mechanism for accelerating the development of experimental malaria vaccines within Europe and in developing countries. It seeks “to bridge the conceptual and operational gaps between the bench product i.e candidate molecules and further validation, limited production and clinical testing, thus making further industrial development

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<sup>1</sup> Kanavos P. *The IFPMA health partnerships survey: a critical appraisal*. Geneva, International Federation of Pharmaceutical Manufacturers and Associations, 2006. [www.ifpma.org/documents/NR4467/IFPMArelease\\_partnerships\\_LSE\\_08Mar06.pdf](http://www.ifpma.org/documents/NR4467/IFPMArelease_partnerships_LSE_08Mar06.pdf). Accessed 18 October 2009.

<sup>2</sup> Daar AS et al. Grand challenges in chronic non-communicable diseases. *Nature*, 2007, 450:494–496. [www.nature.com/nature/journal/v450/n7169/pdf/450494a.pdf](http://www.nature.com/nature/journal/v450/n7169/pdf/450494a.pdf). Accessed 18 October 2009.

and production feasible.” It facilitates and contributes financially and technically to nationally and internationally funded malaria vaccine research and development and will see candidate molecules through to limited industrial production and clinical trials, in close collaboration with the African Malaria Network Trust. It will also provide a forum for scientists and policy-makers engaged in malaria vaccine research and development. It is not a research institute per se: the basic research on candidate molecules is performed nationally or internationally.

Coordination is a feature of its governance, and it is a major focal point of European malaria vaccine development. It coordinates research on malaria vaccines funded either nationally or by the European Commission. It has a board, an independent scientific advisory committee and a secretariat, with a specific mandate to ensure international collaboration with major players.<sup>1</sup>

#### **4.5.2 By health area: human reproduction**

Contraceptive research and development was established in 1986 under a cooperative agreement between the Eastern Virginia Medical School (United States of America) and the United States Agency for International Development but also receives funding through interagency agreements from the National Institute of Child Health and Human Development, the Centers for Disease Control and Prevention and the National Institute of Allergy and Infectious Diseases. Partnerships with a variety of for-profit entities have been established for specific projects, including Personal Products (J&J), Polydex, ReProtect, Biosyn, Schering AG (now Bayer Schering Pharma), Laboratorios Silesia (now part of Andromaco Group), Gedeon Richter, Aplicaciones Farmaceuticas and Integra LifeSciences.

The organization’s overall goal is to improve reproductive health, especially in developing countries. Its main objective is to help develop safe, acceptable, affordable products and methods that provide contraception or prevent the sexual transmission of HIV and other infections. Accordingly, the organization works by nurturing promising research in institutions worldwide, engaging in preclinical research, conducting clinical trials, partnering with private industry to get new products onto the market, collaborating with other agencies, foundations and nongovernmental organizations and training investigators throughout the world in preclinical and clinical research techniques.<sup>2</sup>

In 1995, Contraceptive research and development established the Consortium for Industrial Collaboration in Contraceptive Research to spur the pharmaceutical industry’s commitment to developing new contraceptives. The Consortium supports research and development on methods for addressing the needs and perspectives of women, with three priorities: male methods, monthly methods for women and vaginal methods that prevent pregnancy and sexually transmitted infections.

The coordinating mechanism is apparently internal, consisting of technical monitoring assessments and meetings of various thematic working groups. External monitoring is provided by a scientific advisory committee comprising independent experts in relevant disciplines, which provides guidance, monitors progress, assists in making critical decisions about product development and advises donors.

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<sup>1</sup> [www.emvi.org/](http://www.emvi.org/). Accessed 27 May 2009.

<sup>2</sup> [www.conrad.org/](http://www.conrad.org/). Accessed 30 May 2009.

### 4.5.3 By product

#### *Vaccines*

The aim of the WHO Initiative for Vaccine Research is to guide, provide vision, enable, support and facilitate the development of, clinical evaluation of and worldwide access to safe, effective, affordable vaccines against infectious diseases of public health importance, especially in developing countries. Its role includes providing guidance and vision for worldwide vaccine research and development; facilitating and coordinating clinical trials, ensuring proper scientific and ethical standards; providing normative guidance, standards and reagents; building capacity, providing training and facilitating technology transfer; addressing the issues of access and introduction of new vaccines; and encouraging partnerships.<sup>1</sup> The Initiative will focus on critical steps, encouraging existing research, developments and management opportunities and proactively identifying and promoting targets for each stage of development to shape the global portfolio.

One of the main activities of the Initiative is organization of the Global Vaccine Research Forum.<sup>2</sup> This conference began in Morges, Switzerland, in June 1996, when it was known as the Technical Review Meeting for Vaccine Research and Development. It has since grown in size and reputation, and, at the first meeting in the new millennium, it became known as the Global Vaccine Research Forum. The conference brings together every year a worldwide selection of top researchers and scientists and serves as a forum for the partners of the Global Alliance for Vaccines and Immunization to discuss vaccine research and development and to update research agendas. These conferences allow exchanges of information on existing initiatives and some view of future developments. In spite of rhetoric to the contrary and several initiatives, however, there is no evidence of a structured approach to genuine coordination of R&D in this area. Some measure of control is exerted because of the requirement to comply with global norms and standards, through the WHO Quality Assurance and Safety of Biologicals.

The comments made by UNICEF and WHO 14 years ago in *The state of the world's vaccines and immunization*<sup>3</sup> still echo:-

“The world has become inured to the topsy-turvy notion that, while antibiotics may be expensive, vaccines should come cheap, but today things are changing. Today vaccines belong not, as Salk resolutely maintained ‘to the people’ but to a complex web of biotechnology companies, universities, public and private sector research institutes and pharmaceutical companies.”

### 4.6 Policy coordination

As pointed out above, the nature of research and development makes coordination intrinsically difficult. Recently, however, there has been some limited movement in this sector, with initiatives to coordinate policies between funders and across various initiatives. For example, in 2008, the Swedish International Development Cooperation Agency hosted a meeting on capacity-building for research in

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<sup>1</sup> [www.who.int/vaccine\\_research/en/](http://www.who.int/vaccine_research/en/). Accessed 21 May 2009.

<sup>2</sup> [www.who.int/vaccine\\_research/about/gvrf/en/](http://www.who.int/vaccine_research/about/gvrf/en/). Accessed 2 October 2009.

<sup>3</sup> United Nations Children's Fund. *State of the world's vaccine and immunization*, Geneva, World Health Organization, 1996.

health,<sup>1</sup> to discuss improved policy alignment and harmonization. Various forums have also been established to allow international funding organizations and aid agencies to coordinate and harmonize their efforts and policies. Examples of current programmes for coordinating research in given areas are given below.

The *Alliance for Health Policy and Systems Research* is an international collaboration based in the Health Systems and Services cluster of WHO, which promotes the generation and use of health policy and systems research to improve the health systems of developing countries. Its governance structure consists of a board (maximum of eight members, meets once a year), a scientific and technical advisory committee (eight members) and the WHO Advisory Committee on Health Research, which oversees the board.<sup>2</sup>

*Enhancing Support for Strengthening the Effectiveness of National Capacity Efforts* (ESSENCE) is a collaborative framework of funding agencies to ensure synergy in addressing research capacity needs. Its aim is to improve the impact of investment in institutions and provide mechanisms to address needs and priorities within national strategies on research for health. The secretariat is hosted by TDR, and the initial executive group includes development cooperation agencies – the United Kingdom Department for International Development, the International Development Research Centre, the Ministry of Foreign Affairs of the Netherlands, the Norwegian Agency for Development Cooperation and the Swedish International Development Cooperation Agency – and the Bill & Melinda Gates Foundation, the Wellcome Trust and the Science, Technology & Innovation New Partnership for Africa's Development.<sup>3</sup>

The *UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction* (HRP) helps scientists throughout the world to undertake research guided and monitored by experts in many countries. Capacity-building enables the participation of developing country institutions in seeking solutions to local problems. HRP has strong connections in countries via its network of sexual and reproductive health and HIV/AIDS advisors, thus drawing upon policy-makers, programme managers, service providers, consumers and scientists in developing countries to define the research and technical activities that respond to the priorities of the poor and disadvantaged. It also ensures effective partnerships with a global network of scientists and health professionals in universities, professional and other nongovernmental organizations, the private sector and government bodies as well as foundations and multilateral development agencies. Within HRP, several complementary monitoring and advisory bodies ensure accountability: the Policy and Coordination Committee, the Scientific and Technical Advisory Group, the Gender and Rights Advisory Panel, the Regional Advisory Panels and the Scientific and Ethical Review Group Panel.<sup>4</sup>

TDR is an independent global programme of scientific collaboration that coordinates, supports and influences global efforts to combat major diseases of the poor and disadvantaged. Established in 1975, TDR is sponsored by UNICEF, UNDP, the World Bank and WHO. It is governed by a unique board made up of representatives from governments in funding and receiving countries, ensuring equal representation, regardless of economic level. In addition, TDR has a scientific and technical review

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<sup>1</sup> *Meeting on capacity-building for research for health*, Stockholm, 3–4 April 2008. 31 representatives of funding agencies and African partners met to discuss improving capacity-building for research in resource-constrained countries.

<sup>2</sup> [www.who.int/alliance-hpsr/en/](http://www.who.int/alliance-hpsr/en/). Accessed 25 May 2009.

<sup>3</sup> [apps.who.int/tdr/news-events/news/pdf/essence.pdf](http://apps.who.int/tdr/news-events/news/pdf/essence.pdf). Accessed 2 June 2009.

<sup>4</sup> [www.who.int/reproductive-health/hrp/publications/hrp\\_brochure.pdf](http://www.who.int/reproductive-health/hrp/publications/hrp_brochure.pdf). Accessed 20 May 2009.

committee that oversees the mix and range of scientific priorities; it has additional committees for specific research areas, made up of scientific experts from all over the world.<sup>1</sup>

The *International Forum for Research Donors* is a network of research donors who informally share information and build research partnerships for international development. Its mandate is to facilitate collaboration and information-sharing among policy-makers from organizations that support research in low- and middle-income countries.

The *Institutional Centre for South–South Cooperation in Science, Technology and Innovation* opened in March 2009. Its programme for 2009–2010 covers science and technology policy and human capacity-building for sexually transmitted infections within the framework of the UNESCO programme for natural sciences. Among its planned activities are a research and development management programme for high-level policy-makers.<sup>2</sup>

*Heads of International Research Organizations* is an informal policy organization that brings together government and philanthropic funding institutions for biomedical research for an annual meeting to exchange information and views and to discuss possible joint activities and relevant issues. In 2008, the meeting discussed pandemics, sharing worldwide databases (for example on genome testing), cross-border funding, peer review, clinical research training, open access publishing and biosecurity and biosafety.<sup>3</sup>

#### **4.7 ‘Mapping’ initiatives**

A number of organizations are attempting to map existing initiatives and facilitate coordination by sharing information.

The *Council on Health Research for Development* has set up a “health research web”, an interactive source of information on the structure and organization of research for health in and for low- and middle-income countries. Its aim is to maximize the impact of research on health, equity and development in those countries and to improve the lives of underserved populations everywhere. It is a response to the lack of a single source of information on research for health from the perspective of low- and middle-income countries and is organized to provide integrated information on research for health at country and regional level in order to strengthen national health research capability. Users can search by country for information on ongoing health research, health research priorities, key institutions, financing and partnerships, resources and country background, among others.<sup>4</sup>

The aim of the *Global Health Progress Initiative* is to bring research-based biopharmaceutical companies and global health leaders together to improve health in the developing world. Its programmes and initiatives database can be searched with keywords and dropdown menus, allowing

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<sup>1</sup> [apps.who.int/tdr/](http://apps.who.int/tdr/). Accessed 27 May 2009.

<sup>2</sup> [istic-unesco.org/](http://istic-unesco.org/). Accessed 20 May 2009.

<sup>3</sup> *Meeting of heads of international research organizations (HIRO)*, Ottawa, Canadian Institutes of Health Research, 2003. [www.cihr-irsc.gc.ca/e/18769.html](http://www.cihr-irsc.gc.ca/e/18769.html). Accessed 18 October 2009.

<sup>4</sup> [www.cohred.org/HRWeb/](http://www.cohred.org/HRWeb/). Accessed 29 May 2009.

users to search by disease, by background information (including by geography) and by global health community and partners.<sup>1</sup>

HRP publishes the *WHO Reproductive Health Library* on the Internet and on a CD-ROM, which includes systematic reviews of research.<sup>2</sup>

The *International Federation for Pharmaceutical Manufacturers and Associations* has a database of health partnerships, searchable by country, programme type, disease area and partners, which provides a synopsis of programmes and links to appropriate web sites. The same site offers access to a clinical trials portal, which is free of charge and easy to use, containing comprehensive information on ongoing clinical trials, clinical trial results and complementary information on related issues. Resources like this serve to increase industry transparency as well as to reduce duplication of efforts.<sup>3</sup>

TDR has established *TropIKA.net*, a global knowledge management electronic portal to share essential information and to facilitate identification of priorities and research gaps in the field of infectious diseases of poverty. Despite immense scientific advances, researchers and policy-makers face a haphazard flow of scientific information, which they lack time to screen, lack of awareness of what is relevant and essential for their domain and activities and skills for interpretation and application in health interventions. In 2004, TDR undertook surveys and consultations to develop this knowledge management platform. TropIKA.net is designed to enhance access to and share essential knowledge with health researchers and policy-makers.<sup>4</sup>

#### **4.8 Collaborative arrangements for global health research**

WHO and many other global health stakeholders have held a number of discussions and analytical exercises to improve collaboration among partnerships and global health initiatives in health research. Attempts are being made to identify opportunities, challenges and methods of successful collaboration. It appears logical that the first level of rationalization, cooperation and synergy should be achieved where there is one authority – WHO – and, as a next step, in the United Nations group of organizations. After several discussions about the need for more collaboration, WHO commissioned FSG Social Impact Advisors to analyse potential collaboration among eight health research organizations and initiatives that have some role in monitoring and reporting on research globally, although they are not themselves engaged in research and development. The eight selected were: Research Policy and Coordination, the Alliance for Health Policy and Systems Research, the Council on Health Research for Development, the Global Forum for Health Research, HRP, the Initiative for Vaccine Research, the WHO Secretariat on Public Health, Innovation and Intellectual Property (Intergovernmental Working Group) and TDR. The analysis is expected to outline those areas, such as capacity-strengthening and resource mobilization, in which collaboration and coordinated technical cooperation would be of greatest benefit.

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<sup>1</sup> [www.globalhealthprogress.org/programs/search.php?first=yes&parent=programs](http://www.globalhealthprogress.org/programs/search.php?first=yes&parent=programs). Accessed 1 June 2009.

<sup>2</sup> [www.who.int/reproductive-health/hrp/publications/hrp\\_brochure.pdf](http://www.who.int/reproductive-health/hrp/publications/hrp_brochure.pdf). Accessed 1 June 2009.

<sup>3</sup> [www.ifpma.org/Healthpartnerships/](http://www.ifpma.org/Healthpartnerships/). Accessed 29 May 2009.

<sup>4</sup> [www.tropika.net/](http://www.tropika.net/). Accessed 29 May 2009.

In a recent paper,<sup>1</sup> WHO mooted the idea of an effective global health governance structure – a multi-level, multi-party, multi-purpose partnership for global health governance, a platform coordinated by WHO and supported by high-level political commitment and policy coherence. It is envisaged that the platform could be operationalized through effective implementation of global action networks. Other ideas for the construction of a new arrangement have been proposed by independent and country experts.<sup>2</sup>

WHO has a constitutional mandate for coordination, which might include research and development at global regional and national levels. This is realized fully in the WHO research strategy. Some coordination might be exercised by WHO itself, but this role might be optimized if national and regional capacities were strengthened. An example of a regional network is given in the box below.

**Regional networks for innovation**

The African Network for Drug Discovery and Innovation is a new regional network to promote research on health priorities in African countries, supported by African ministries of health and ministries of science and technology (its secretariat is hosted by the African Development Bank). Similar regional networks are being initiated in Asia and Latin America, facilitated and supported by TDR in conjunction with the Global Forum for Health Research (which initially focused on neglected tropical disease research but is open to other research areas, such as health systems and operations). The regional research networks coordinate research policy but could also act in their own right, for (i) fund-raising (not only from donor agencies but also from industry, foundations, academia and philanthropic organizations), (ii) fund allocation (among the countries concerned and participating) and (iii) improving efficiency (e.g. regulatory harmonization and precompetitive research and development).

Several regional initiatives exist to facilitate global coordination of research and development. Regional approaches to funding research in developing countries offer particular benefits. In particular, regional centres of excellence facilitate the formation of a network of interdisciplinary research centres for the translation of research to address local and regional public health needs. This type of infrastructure results in high standards of scientific research, training in clinical and translational research, the application of population-based research findings to clinical practice, the conduct and application of health systems research, and the establishment of infrastructure to manage functions associated with research programmes, such as intellectual property. Regional centres also facilitate partnerships with other research institutions, private industry and product development partnerships, and in doing so reinforce synergy with existing multilateral and regional initiatives.

#### **4.9 General conclusions and comments**

These descriptions of the initiatives show that many “local” research and development coordinating arrangements are already in place. The aims of coordination within the respective initiatives vary, and it is structured either in formal governance and monitoring arrangements or

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<sup>1</sup> Sridhar D, Khangram S, Pang T. Are existing structures equipped to deal with today’s global health challenges—towards systemic coherence in scale up. *Global Health Governance*, 2. [www.ghgj.org](http://www.ghgj.org)

<sup>2</sup> Røttingen JA et al. Global-health research architecture—time for mergers? *Lancet*, 2009, 373:193–195.

through more flexible, quasi-prescribed initiatives. Some are internal to the organizational management hierarchy, whereas others are external. Broadly, they fall into three categories.

Firstly, many of the initiatives described above have governing arrangements – boards, councils, committees with broad-based representation, both geographically and by subject and institutional background. Most of these entities are internal to the organization or initiative and have governance and supervisory roles. Although they are not mandated to “coordinate” research and development at global level, they nevertheless constitute an important resource, and these multi-stakeholder governing arrangements should be used while exploring the need for establishing a global coordinating arrangement.

Second, many initiatives have mechanisms to draw on the strength and expertise of technical partners and have formed task forces, expert groups and scientific and technical advisory committees. These structures tend to have broad-based representation, in order to draw on the best possible advice and expert opinion from around the world. As in the previous case, these arrangements are not mandated to coordinate research and development globally; however, they share information informally.






The third category includes the plethora of informal networks of researchers and related stakeholders who have opportunities to share experiences, such as at meetings convened by agencies such as WHO or affiliated initiatives such as TDR.

In addition, many other structures map ongoing activities, draw up inventories and manage information. A number of structures coordinate arrangements at policy level, usually involving donor and development agencies that fund research and their research collaborators.

Nevertheless, there is no “global” coordination of research and development for major diseases, and the “global health research and innovation system” is highly fragmented. The system has four kinds of failure that lead to lack of effective treatment for health problems and the persistence of health disparities within and between populations: failures in science, in the market, in public health and in collecting, consolidating, interpreting and disseminating information. The extent of these failures in relation to disease types is shown in Table 6. To overcome these failures, a globally coordinated approach to research and development is proposed, which would involve:

- coordination in the identification of priorities for action;
- coordination in the distribution of research among various entities, in the public or private sector and in different geographical areas;
- coordination in the financing of research and development.

**Table 6. Failures in the global health research and innovation system in relation to disease type**

	Type I	Type II	Type III
Communicable diseases			
Science failures	+	++	+++
Market failures	+	++	+++
Public health failures	+	++	+++
Failure to collect, consolidate, interpret and disseminate information	+	+	
Noncommunicable diseases			
Science failures	-	+	+
Market failures	-	(+)	++
Public health failures	-	+	++
Failure to collect, consolidate, interpret and disseminate information	-	+	+

The size of the shaded area is an approximate indication of the relative burden of disease that can be attributed to the various categories.

These elements can be regarded as sequential. In particular, the coordination of financing of research and development for diseases prevalent in low- and middle-income countries would require both identification of the priorities in disease and determining who should receive the financing. Consequently, there is an argument for a comprehensive approach, involving all three elements and requiring an arrangement such as the following:

- establishment of working groups and a supervisory group to draw up research agendas and set priorities on the basis of information from a range of sources, including a new “global health research observatory”;
- decisions by working and supervisory groups about the distribution of the elements of the required research and development among researchers working in different settings, including basic research laboratories, development or scale-up plants, clinics, health services and communities, in public and private environments in high-income countries and low- and middle-income countries;
- creation of a global health research and innovation coordination and funding mechanism to provide funding for:

- targeted research and development for new drugs, vaccines, diagnostics and intervention strategies for health conditions of the poor, both communicable and noncommunicable diseases that are prevalent in low- and middle-income countries, and for which adequate interventions are not presently available;
- research primarily conducted in low- and middle-income countries that is essential to improve health, including: health policy and systems research, social science and behavioural research, implementation and operational research and research on the determinants of health. The funding would combine capacity-building with focused research to support national health programmes, such as health systems strengthening, improving reproductive health, eradicating target diseases and responding to health threats such as climate change;
- enhancing innovation capacity and environments in low- and middle-income countries, to enable them to strengthen their national innovation systems;
- operating a global health research observatory to ensure regular, accurate disease monitoring and research and development resource tracking, to provide both the input for priority setting and the means for monitoring progress;
- establishment of a structure responsible for collecting, collating, analysing, interpreting and disseminating information on funding for research and development.

In order to perform these functions, the mechanism would have to be financed at a level of US\$ 3–15 billion per year.<sup>1</sup>

It is likely, however, to be difficult to create a single, overarching governance structure to coordinate global research and development, owing to the nature of research and development and differences in the structure of the world's economies. Nevertheless, WHO should maintain its important role of collecting and widely disseminating information. The Expert Working Group on Research and Development Financing expressed strong interest in a global financing mechanism with regional expression and ownership, and WHO should be active in creating such a mechanism, the structures and processes of which will evolve as it is discussed in the relevant forums.

## **5. INNOVATIVE SOURCES OF FINANCING<sup>2</sup>**

### **5.1 Introduction**

Over 90 proposals for financing are circulating or have already been implemented. About half are pure financing proposals, to raise monies that could be allocated to any cause but are not yet used to fund health research and development. The other half are not financing proposals but rather allocation proposals, including structures to centralize, manage and allocate funds to health research and development (if funds were to be available), but without the mechanisms to raise the funds. A small number of proposals are for both raising and allocating funds.

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<sup>1</sup> The figure of US\$ 3 billion comes from the Commission on Macroeconomics and Health and is likely to be much higher now. US\$ 15 billion is an approximate calculation on the basis of the authors' experience in research coordination.

<sup>2</sup> Material for this section was drawn from a paper prepared for the Expert Working Group on R&D Financing by Mary Moran with the assistance of a team from the George Institute for International Health.

The vast majority of the proposals that are circulating, in operation or were submitted to the Expert Working Group concern public researchers and product developers in developed countries, and these were the basis for the Working Group's comparisons. To the extent possible, the Working Group examined these proposals from the point of view of research and development capacity in developing countries, particularly innovative developing countries, as it was considered that they will increasingly be the source of new products for their own needs.

## **5.2 Background**

The amount of funding needed for any health research and development depends on the answers to several questions.

*Does the solution for the health problem have a substantial, some or no market?*

Products for diseases with a substantial market in developed countries (Type I diseases) generally require less funding, as research and development for the developing world can be “piggy-backed” onto existing commercial programmes. Products for diseases with no commercial market (Type III diseases) require full funding, while those for Type II diseases, which have small markets in developed countries, sit somewhere in between.

*Does the solution for the health problem have a sound base in science and technology?*

Products for diseases with a sound base in science and technology (e.g. pneumonia vaccines) are less risky investments, while those for diseases with a weak base are highly risky. Thus, donors will have to fund the research and development themselves or provide incentives that are highly inflated for risk.

*What kind of research and development is needed?*

If basic research is needed, the per project costs are relatively small (in the hundreds of thousands to perhaps US\$ 2–3 million); however, scientific uncertainty tends to drive overall costs up, as many projects fail and are replaced before success is achieved. For all products, early development (preclinical testing and smaller clinical trials) is relatively cheap, costing in the hundreds of thousands of US dollars for diagnostics, to tens of millions US dollars for drugs and vaccines. In contrast, late development (large-scale clinical trials and manufacture) is far more expensive, costing a few million US dollars for diagnostics but up to US\$ 150–250 million<sup>1</sup> for drugs and US\$ 500–800 million for vaccines, if plant construction costs are included.<sup>2</sup>

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<sup>1</sup> Pekar N, ed. *The economics of TB drug development*. New York, Global Alliance for TB Drug Development, 2001. Available at [www.tballiance.org/downloads/publications/tba\\_economics\\_report.pdf](http://www.tballiance.org/downloads/publications/tba_economics_report.pdf).

<sup>2</sup> Serdobova I, Kieny MP. Assembling a global vaccine development pipeline for infectious diseases in the developing world. *American Journal of Public Health*, 2006, 22:1554–1559. Available at [www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1551949](http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1551949).

*How well does the proposal match the needs of the target group?*

Different types of research and development require different skills and are performed by different persons. Basic research is generally conducted by academics at public institutions; product discovery predominantly by small and large companies and product development partnerships, although public groups also play a role; and large-scale product development by large companies and product development partnerships. Firms in developing countries dominate manufacture and distribution for the developing world, and firms in innovative developing countries are increasingly moving into product discovery and development. These groups have very different cost structures, business models and needs. For instance, large multinational companies can invest more of their own resources and take higher risks before they receive a return on investment, or may even be able to conduct not-for-profit research. Most small companies, however, survive hand-to-mouth: they need ongoing capital during research and development and cannot afford to do not-for-profit work. Commercial groups also invariably require larger incentives than not-for-profit groups.

As a result of these differences, it is unlikely or impossible that a single allocation proposal could efficiently address all disease and product needs and the requirements of all relevant development groups.

### **5.2.1 Notes on methods**

An extensive list of proposals was assessed against agreed criteria to create a shortlist of proposals. As financing and allocation proposals are very different, they were reviewed separately. Fund-raising proposals were sorted into groups, and each proposal within each group was assessed for its capacity to raise funds, additionality (i.e. providing additional funding for health), the likelihood that the funds would be accepted as suitable for allocation to health research and development and ease of implementation. Allocation proposals were also sorted into groups, and each proposal within each group was assessed for its impact on health, operational efficiency and financial aspects for developing countries and for the likelihood that developers would find the incentive to start or increase research and development activities in both developing and developed countries. Performance rankings are identified by numbers (three being a high score, two a good score, one a moderate score and none a low score). Through such assessments, the Working Group determined which fund-raising and allocation approaches worked best overall and selected the highest-performing proposals. It was noted that the performance of proposals within groups varied significantly according to their design, most performing better against one criterion than another. These variations are themselves telling and helped us to identify which design features deliver the best outcomes. (See Annex 1 for details.)

While the shortlist of final proposals was largely based on their assessed performance, other factors were considered, in particular their ability to offer a broad solution for many diseases and products. We also sought overall balance in the shortlist, with proposals selected to collectively provide good coverage of the research and development field and those working within it and a reasonable balance of public and private risk.

The review could not have been completed without the efforts of those who came before the Working Group. Thus, the review of financing proposals drew heavily on the extensive work of working groups 1 and 2 of the Taskforce on Innovative International Financing for Health Systems, and we are indebted to the assistance of an analyst from that group whose input reduced duplication and inefficiencies in this review is much appreciated. The Working Group drew on many sources to

design the criteria for proposals, particularly the Brookings Institute for their *Innovative financing for global health* report,<sup>1</sup> and working group 2 for the financing effectiveness criteria that it drew up. The research and development criteria are also based on the extensive input of the public, private, philanthropic and civil society stakeholders who participated in the Expert Working Group consultations. (See section on methods.)

One important area of health research and development, operational research, is not covered by this report, because of a lack of proposals. Basic research proposals have been included only to the extent that they are additional to existing programmes run by most national governments.

As noted above, no one allocation proposal could effectively address the needs of all diseases, products and developers. The Working Group therefore chose a set of proposals that cover research and development from basic research through to distribution, that are best suited to maximizing research and development activity by all potential target groups and that deliver a maximum public health return for any given investment. The four financing mechanisms would nearly triple the available funds for research and development for neglected diseases in the developing world; the five funding allocation mechanisms would optimally allocate both existing funds and new funds raised by the four proposed financing mechanisms; and the two efficiency proposals would cut research and development costs across the board. All the shortlisted mechanisms are described in more detail below.

The financing and allocation mechanisms cannot be paired, because the allocation proposals, their scope (disease and products) and timeframe must be finalized in order to determine the amount needed per year for each mechanism. (In the absence of this information, a target figure of two to three times the existing amount spent on neglected disease programmes was used as a guide.) Donors are therefore urged to move quickly to decide which diseases and product areas they wish to target, in what order, so that appropriate funding can be mobilized and allocated quickly to achieve the goals.

### **5.3 Proposals for financing**

The following fund-raising options have been put forward on the basis of the likelihood that they can generate new funds for health research and development in a sustainable way. When these proposals were discussed by the Expert Working Group in the context of previous work in this area, it became apparent that some were more likely to garner support than others. Furthermore, international coordination of taxes is difficult, and there is wide national variation in the possibility of applying taxation, highlighting the need for locally suitable approaches. Those considered were: a new indirect tax (a consumer-based tax), voluntary business and consumer contributions, taxation of repatriated pharmaceutical profits and new donor funds for health research and development.

#### **5.3.1 A new indirect tax**

Indirect taxes are small taxes imposed on specified products or transactions. Typically, the tax is paid by the consumer or user of the product or transaction, collected by the retailer and forwarded to the taxation authority. Once in place, they are compulsory. The objective is to raise revenue or, in the

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<sup>1</sup> De Ferranti D et al. *Innovative financing for global health. Tools for analyzing the options*. Washington DC, Brookings Institute, 2008. Available at : [www.brookings.edu/~media/Files/rc/papers/2008/08\\_global\\_health\\_de\\_ferranti/08\\_global\\_health\\_de\\_ferranti.pdf](http://www.brookings.edu/~media/Files/rc/papers/2008/08_global_health_de_ferranti/08_global_health_de_ferranti.pdf). Accessed 17 July 2009.

cases of taxes on arms and excise duties on tobacco and alcohol, to discourage (excess) consumption of a particular product. In the latter cases, there are likely to be positive effects in terms of health. Taxes such as those for airline travel can contribute to addressing communicable diseases. All these, and others such as a digital tax, can be considered humanitarian contributions, which can together provide significant resources for the health needs of the world. The digital tax involves a charge on traffic over the Internet. It was first discussed in the 1990s, and various proponents have suggested different versions. Examples include a tax of 1 US cent on every 100 e-mails of 10 KB sent, a charge per number of e-mail messages (e.g. 10 cents per 1000 messages). The key element is a very low charge.

### **Performance**

*Fund-raising capacity and additionality:* An indirect tax could potentially raise significant amounts of revenue:

- A 10% tax on the arms trade might net about US\$ 5 billion per annum.
- Digital tax or “bit” tax: Internet traffic is huge and likely to increase rapidly; this tax could yield tens of billion US dollars from a broad base of users.
- Brazil’s *Contribuição Provisória Sobre Movimentação ou Transmissão de Valores e de Créditos e Direitos de Natureza Financeira*: a tax on bank account transactions, set at 0.38% levied on paying bills online and major withdrawals, it raised an estimated US\$ 20 billion per year, funding some 87% of the Government’s social protection programme (Bolsa Familia) before it was voted down. There is scope globally for expansion of bank transactions taxes.
- The airline tax has raised around US\$ 1 billion over two years (mostly in France), and this amount is expected to increase as more countries join (e.g. Portugal in 2009). The possible total revenue could be in the low billions of US dollars. At the end of 2008, 13 countries had implemented the airline tax, and several others were adopting it.

Tobacco taxes: Low-income countries raise around US\$ 13.8 billion in taxes on tobacco. In about one fourth of the 152 countries with tobacco taxes in place, the tax rate is less than 25%. A 5–10% increase in the rate could net US\$ 0.7–1.4 billion per annum. A similar increase in developed countries would net US\$ 5.5–11 billion. Alcohol taxes are already widespread.

While projections can be made, the revenue will ultimately depend on responses to price rises associated with the tax. A government decision to implement or expand one of these taxes for the purposes of directing the revenue to health in the developing world would result in additional funds. To estimate the funds that could potentially be raised, we took the example of introducing a very low indirect digital tax. This could be estimated conservatively to raise about US\$ 3 billion per annum.

*Likelihood:* There is a more obvious link between the source of the funds and the purpose (health research and development) of the taxes on tobacco, alcohol and arms. As the airline tax has shown, however, such links do not necessarily appeal to both politicians and consumers. An indirect tax like a digital tax might be appealing to politicians and consumers, who will accept a low tax across a broad base with an altruistic purpose.

*Operational efficiency:* Introducing a new tax or expanding an existing tax may require legal changes, nationally and internationally, depending on the tax, and ongoing regulation to ensure compliance. A new global tax would take longer to implement than expanding an existing tax within a

country. A tax that is global in scope allows developing countries to contribute to fund-raising, and there is a willingness to do so, as demonstrated by the airline tax. This framework could be applied to a type of digital tax.

As with the introduction of any tax, there are trade-offs:

- Revenue forecasts are only moderately certain, as the actual revenue depends on the response of providers and consumers to price rises associated with the tax and the scope of the tax. Furthermore, as seen with the withdrawal of Brazil's bank transaction tax, there are occasions, although rare, when a tax is removed.
- Some taxes could create perverse incentives. For example, a tax on arms trading is likely to result in an increase in illicit trading (and therefore a reduction in revenue); and an excessively high tax on alcohol could encourage people to consume illicit and often dangerous alcoholic products. An arms tax might have less political appeal than others, as governments would essentially be taxing themselves.
- Achieving wide geographical coverage with some of these taxes internationally might be difficult, as governments might resist introducing them. (For instance, the United States has not imposed an airline tax, citing problems with the tax dimension, and efforts are being made to obtain the revenue through voluntary contributions rather than a mandatory tax.)
- The digital tax has additional operational hurdles to overcome, in that monitoring Internet traffic cost-effectively in order to tax consumers might prove to be a challenge. The digital tax could place a high burden on companies that depend heavily on use of the Internet and send large amounts of data. This problem could be overcome by appropriate scoping of the tax.

### **5.3.2 Voluntary contributions from businesses and consumers**

This approach involves voluntary donations by individual consumers. It can operate in one of three ways: (i) voluntary linking of a donation to payment for a service (e.g. payment of mobile phone bills or income tax); (ii) automatic donations directly to a particular recipient (e.g. standing orders to Oxfam); or (iii) voluntary but non-automatic donations (e.g. private giving campaign or endowment). An income tax donation allows an individual to make a contribution from his or her income, which the government matches with the income tax that would have been paid.

Voluntary business contributions are donations from the business sector as a share of its revenue or of its profits for charitable causes, or pro bono in-kind support to charitable activities. In return, the business earns good will, which may lead to extra sales and profits, or it may act more altruistically in the context of corporate social responsibility. De-Tax, a mechanism that combines waiving tax and voluntary business contributions, and Product RED are examples of such mechanisms.

Voluntary contributions are less certain funding streams than taxes, but, once established, they are reasonably predictable.

## Performance

*Fund-raising capacity and additionality:* The amount of revenue raised varies.

- Airline ticket voluntary solidarity contributions are expected to raise about US\$ 980 million per annum, although this expectation has been revised downwards.<sup>1</sup>
- Mobile phone voluntary solidarity contributions would raise € 200–1300 million according to the Millennium Foundation.
- Private giving raises significant amounts for development: estimates suggest some US\$ 17 billion in OECD countries in 2001 and US\$ 34 billion in the United States in 2004 (including faith-based organizations and universities).<sup>2</sup> More of these funds could be diverted to health research and development.
- The World Bank estimated in 2009 that the lotteries in Belgium and the United Kingdom transferred US\$ 66 million to developing countries in 2007.<sup>3</sup>
- Product RED has raised more than US\$ 40 million per annum since 2006.<sup>4</sup>
- Internet advertising expenditure is growing rapidly in absolute terms and as a share of total advertising revenue.
- De-Tax could raise up to US\$ 2.2 billion on a base on 26 countries and 5% business uptake.<sup>5</sup>

The introduction of a voluntary fund-raising mechanism would provide additional revenue, although consumers might change their preference for voluntary contributions from an existing fund. For the purposes of this analysis, the example is given of use of two of the above proposals to raise funds for health research and development. Using Product RED as a guide, the introduction and use of voluntary business sector contributions could be estimated to raise in the order of US\$ 40 million annually; using the airline voluntary solidarity contribution as a guide to estimate voluntary consumer contributions, the revenue could be around US\$ 1 billion per annum.

*Likelihood:* Both the introduction and take up of Product RED and the airline ticket voluntary solidarity contribution demonstrate potential consumer and business willingness to make altruistic global health-based contributions. A mechanism is needed to direct this revenue to health research and development. (See allocation proposals.)

*Operational efficiency:* The introduction of voluntary contribution schemes, like the airline ticket scheme, is not expected to meet any legal obstacles or require amendments to international law. Other mechanisms, like De-tax would, however, require changes to law. De-tax is formally supported by the Taskforce for Innovative Financing for Health Research and Development and is being tested in

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<sup>1</sup> [www.internationalhealthpartnership.net/cms\\_files/documents/working\\_group\\_2\\_-\\_report\\_en.pdf](http://www.internationalhealthpartnership.net/cms_files/documents/working_group_2_-_report_en.pdf).

<sup>2</sup> [news.bbc.co.uk/1/hi/uk/7946518.stm](http://news.bbc.co.uk/1/hi/uk/7946518.stm).

<sup>3</sup> [www.internationalhealthpartnership.net/cms\\_files/userfiles/fs\\_detax\\_raffaella%20final%20final.pdf](http://www.internationalhealthpartnership.net/cms_files/userfiles/fs_detax_raffaella%20final%20final.pdf).

<sup>4</sup> [www.joinred.com/home.aspx](http://www.joinred.com/home.aspx).

<sup>5</sup> [www.internationalhealthpartnership.net/cms\\_files/userfiles/fs\\_detax\\_raffaella%20final%20final.pdf](http://www.internationalhealthpartnership.net/cms_files/userfiles/fs_detax_raffaella%20final%20final.pdf).

Italy,<sup>1</sup> with the funds to be allocated to the health systems of developing countries. Voluntary contributions face few political hurdles and are likely to be sustainable in the long term, as they are applicable in both developed and developing countries.

### **5.3.3 Taxation of repatriated pharmaceutical industry profits**

In this approach, funds are raised by direct taxation of pharmaceutical company profits in the countries that join. The Brazilian proposal is that the governments of “associated countries” (i.e. any developing or developed country that agrees to sign) tax non-domestic pharmaceutical companies that undertake activities on their territories. The tax would be on all profits remitted to the overseas parent company.

#### ***Performance***

*Fund-raising capacity and additionality:* Initial estimates suggest that if profits from the pharmaceutical industry in low- and middle-income countries are in the order of US\$ 16 billion per annum and if a tax rate of 1% was applied in these countries, the revenue generated could be in the order of US\$ 160 million per annum. This figure would increase significantly if the profits from one or more high-income countries were included. These funds would be additional for health research and development. Like other taxes, payment is compulsory once in place. Given the embryonic nature of this proposal, the certainty of revenue is untested and would depend on uptake of the mechanism by countries.

*Likelihood:* The clear link between the source of the funds and the purpose makes this option particularly attractive for funding health research and development.

*Operational efficiency:* By setting a low tax rate over a broad base, the proposal would minimize any distortionary tax effects and therefore increase sustainability. Existing entities could be used to implement the mechanism at country level.

The potential disadvantages are that, like all taxes, it would be subject to some political uncertainty and systemic impediments. This uncertainty would be reduced as more countries join the scheme. Once the proposal has gained political commitment, implementing the tax system at national level would require administrative and legislative changes. The World Trade Organization would have to confirm that it is not seen as an unfair subsidy, whereby revenue is collected in one jurisdiction and given to some countries but not others.

### **5.3.4 New donor funds for health research and development**

This approach is based on three main sources of additional funding, from:

- new, non-traditional donors, which are not currently on OECD’s Development Assistance Committee, such as China, India and Venezuela;
- existing (Development Assistance Committee of OECD) donors, for example earmarking a percentage of gross domestic product for health research and development; and

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<sup>1</sup> [www.internationalhealthpartnership.net/cms\\_files/userfiles/fs\\_detax\\_raffaella%20final%20final.pdf](http://www.internationalhealthpartnership.net/cms_files/userfiles/fs_detax_raffaella%20final%20final.pdf).

- philanthropic organizations.

### **Performance**

*Fund-raising capacity and additionality:* The Taskforce on Innovative International Financing for Health Systems estimated that additional funding for health might amount to some US\$ 7.4 billion by 2015 from traditional donors<sup>1</sup> (under optimistic assumptions and if donors meet their commitments to aid). There would be a gap in additional funds until then, as they rise from US\$ 2.8 billion in 2009 to US\$ 7.4 billion in 2015. On the basis of these estimates, removing the potential for double-counting from the indirect tax (about US\$ 3 billion) and assuming that 10% could be earmarked for health R&D, new donor funds could amount to US\$ 440 million per annum by 2015. These funds do not include additional contributions from philanthropic organizations or innovative developing countries, so the estimate is conservative. This approach is appropriate in the current economic climate; however, the Working Group expects to see future growth in funding from innovative developing countries.

*Likelihood:* New funding from traditional donors could be allocated to health research and development, because it is generally easier to fund new activities with additional resources than at the expense of existing activities. An argument can be made for directing some of this new stream of funding to health research and development, as some countries already direct part of their health aid budget towards research and development for developing countries. Channelling these resources in this way can only be achieved, however, if there is political will to do so and a convincing case is made. These funds would by design be additional for health research and development. Support from non-traditional donors currently tends to be not as grants but to support infrastructure; therefore, this preference would have to be changed to allow the resources to be used for health research and development. As philanthropic organizations are already significant contributors, a case would have to be made for them to increase their donations.

*Operational efficiency:* Directing new funds from traditional or non-traditional donors to the health needs of the developing world is a policy allocation decision, and its operationalization will take different forms in each country. Many countries on the OECD Development Assistance Committee will be giving 0.7% of their gross national income to health by 2015. As donors are not legally required to commit and disburse certain amounts of funding, the sustainability of future funding is uncertain, especially in difficult economic times.

### **Acceptability to funders**

Overall, funding organizations showed a strong preference for solutions that are broad-based and which include new sources of funding. Government funding agencies were attracted to mechanisms that are simple, automatic, can be operationalized fairly easily and are sustainable. An international tax or levy was viewed as more appropriate than a national tax, which could put countries implementing it at a disadvantage with respect to those not implementing it. This would probably not be the case for the tax on pharmaceutical profits, as companies would continue to sell the products where there was a market for them.

The nature of the allocation component was considered important by funding initiatives. They had to know what the money would be used for (what will it deliver? when?) and to assess the

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<sup>1</sup>Taskforce on Innovative International Financing for Health Systems. *Constraints to scaling up and costs, Working Group 1 Report*. Geneva, World Health Organization, 2009.

associated risk (i.e. the likelihood of a health return on their investment). The choice of allocation mechanisms is therefore crucially important.

### **Conclusions**

The proposed set of fund-raising mechanisms provides a balance between:

- the consumer, government and the pharmaceutical industry;
- voluntary and non-voluntary (i.e. taxes) contributions;
- developing and developed country contributions;
- those that would require managed, sustained political commitment (new donor funds and taxes) and those that would not (voluntary consumer and business contributions);
- those that are difficult to operationalize (new taxes) and those with fewer operational requirements (voluntary contributions);
- taxes that provide greater certainty once in place and voluntary contributions.

The estimated revenue from this combination is in the order of US\$ 4.6 billion per annum (by 2015), which would nearly triple current research and development funding for neglected diseases in developing countries.<sup>1</sup> Further analysis is needed, however, to determine the potential revenue streams accurately and their alignment with the amount needed. Further funds could be raised by redirecting current expenditure on research and development funding allocation mechanisms that were assessed as ineffective in this review to mechanisms that were assessed as more effective (see next section).

Funding alternatives and decisions ultimately rest with national governments and philanthropic organizations. They cannot be applied uniformly. For example, the United Kingdom is unlikely to support new hypothecated taxes, and in the United States the regionally based sales tax system would complicate national implementation. Different governments will choose the approach that best suits their political perspectives, objectives, budgetary cycles and taxation systems. As noted above, the advancement of these fund-raising proposals is linked to the existence of a mechanism for allocating the funds in an efficient, effective way. Approaches to do so are examined in the following section.

The Group considered that voluntary consumer contributions were the most innovative funding proposal and the most likely to be sustainable. Additional revenue streams must be allocated transparently and earmarked for research and development, and attention was drawn to issues in the targeting and use of such funding.

## **5.4 Approaches to funding allocation**

The following five approaches provide optimal funding allocation at all stages of research and development, in a manner best designed to maximize public health returns in the developing world:

- product development partnerships;

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<sup>1</sup> Moran M et al. Neglected disease research and development: How much are we really spending? *PLoS Medicine*, 2009, 6:e1000030.

- direct grants to small companies and for trials in developing countries;
- “milestone” prizes;
- “end” prizes (cash), and
- purchase or procurement agreements.

#### **5.4.1 Product development partnerships**

Product development partnerships operate as ‘quasi venture capital funds’ in the domain of health in the developing world. They raise funds from a wide range of public and philanthropic sources, select the projects that offer the probable highest health return for investment and closely monitor and manage the progress of the portfolio they have invested in. All product development partnerships operate on a not-for-profit basis.

Such partnerships have product portfolios for many types II and III diseases but only marginal activity for Type I diseases. They managed nearly 30% of all grant funding for research and development on neglected diseases in 2007 and about half of all grant funding, if the United States National Institutes of Health are excluded.<sup>1</sup> As a result, they consolidate public funding, investment risk and global coordination of research and development in their field. Product development partnerships invest predominantly in product discovery and development (although a few also fund basic research or research and development on platform technologies); they invest in projects conducted in academic research institutions and large and small pharmaceutical companies in both developed and developing countries.

Product development partnerships have no reliable revenue stream, as they are entirely reliant on annual donor funding. It can be difficult for donors to choose the “right” partnership, as most donors do not have the resources to conduct annual due diligence or to compare widely differing product portfolios, nor do all product development partnerships have the right governance structure, oriented to public good, to allow monitoring of their ultimate objectives and *raison d’être*. Housing such partnerships to meet the needs of developing countries is also difficult, given the lack of relevant policy frameworks in those countries for public–private engagement, which must be created in order to allow their institutionalization. As there are no product development partnerships in the area of noncommunicable diseases, this area offers significant potential for investment.

The current approach is direct grant funding to product development partnerships. Three alternative proposals are circulating, which would provide reliable, long-term funding to these partnerships and automate, centralize or instigate funding decisions from recipients to a lesser or greater degree.

The *Fund for Research and Development in Neglected Diseases* is a central fund supported by donors, industry, foundations, academia and others to finance the discovery and development of drugs for neglected diseases and other important diseases of low- and middle-income countries by product development partnerships, industry and public research institutes. Within the wider governance structure oriented towards public good, a portfolio management committee allocates funds on the basis

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<sup>1</sup> Moran M et al. Neglected disease research and development: How much are we really spending? *PLoS Medicine*, 2009, 6:e1000030.

of unmet needs and a scientifically determined likelihood of success, replacing partnerships for the development of individual products or industry portfolio management. Commercial revenues, including income from intellectual property rights, are fed back into the Fund through licensing agreements with development partners. This applies to product development partnerships but also to other areas, described by Moran et al.<sup>1</sup>

The *Industry Research and Development Facilitation Fund* is a long-term fund, supported by donors, that automatically reimburses a fixed percentage (e.g. 80%) of the funds that product development partnerships disburse to companies in developed or developing countries. It is designed to encourage industry to join the development partnerships for public health and thus provide low- or cost-price products. It allocates funds for all drug portfolios of product development partnerships globally, most funding going to those that advance their portfolios most efficiently. The partnerships retain management of their portfolios.

The *Product Development Partnership Financing Facility* raises funds by selling bonds in private capital markets to support research and development conducted by three partnerships for the development of vaccines: against HIV, tuberculosis and malaria. Bond holders are repaid from royalties on sales in high- and middle-income countries and from donor-funded premiums on sales in low-income countries. To reduce the risk to bond holders and allow the financing facility to borrow at low interest rates, it would back its borrowing with guarantees from donor governments and, possibly, foundations.

### **Performance**

Overall, product development partnerships had high scores for their impact on health in developing countries (Table 7), as they focus on affordable, suitable products for use in those countries, they work routinely with researchers and developers in those countries and, to varying degrees, they build capacity in those countries (high scores for the International AIDS Vaccine Initiative, the Drugs for Neglected Diseases initiative and the Meningitis Vaccine Project; a lower score for the Medicines for Malaria Venture). Most of their funding proposals also have a high impact on health in developing countries (except the Product Development Partnership Financing Facility); nevertheless, the proposals varied substantially in operational efficiency and feasibility. The Industry Research and Development Facilitation Fund scored well with regard to its impact on health and very well for operational efficiency and feasibility, because of its automated fund allocation, linkage of funding with efficiency and use of existing product development partnership structures and practices.

**Table 7. Scores of product development partnerships and other mechanisms with regard to impact on health in developing countries and operational efficiency and feasibility**

Mechanism	Impact on health in developing countries	Operational efficiency and feasibility	Data gaps
Product development partnerships	3	3	
Industry R&D facilitation fund	2.5	3	
Fund for R&D in neglected diseases	2	1	2
Product development partnership financing facility	1	1	1

Product development partnerships are highly transparent with respect to the composition of their boards, scientific advisory panels, stakeholders and staff. They are less transparent regarding funding sources, budgets and spending, and much less transparent about decision-making procedures, agreements with industry and the costs of research and development<sup>1</sup>

As data were missing on the Product Development Partnership Financing Facility and the Fund for Research and Development in Neglected Diseases, they could be assessed only partially. The impact of the Fund for Research and Development in Neglected Diseases on health in developing countries was good, but the low operational score reflected lack of data and also design issues. A central group manages the global drug research and development portfolio for product development partnerships, industry and academics, which is an advantage for global coordination but not for major funders (or the partnerships), who expect to have strong control over their multimillion dollar investments, as expressed in interviews. Nevertheless, the high score for the Fund for Research and Development in Neglected Diseases, despite data gaps, suggests that it has great promise.

The Product Development Partnership Financing Facility has more fundamental problems, reflected in its lower scores for both impact on health and operational efficiency and feasibility. The main problem is its focus on HIV, tuberculosis and malaria vaccines, as it is unlikely that a sufficiently effective HIV or malaria vaccine will be available in the next 10 years to provide the planned 7–10% royalty-derived revenue from developed country markets, and the revenues from a tuberculosis vaccine might have to be used to subsidize other areas. Alternatively, developing country markets will be squeezed for margins on less commercially successful vaccines (e.g. malaria and HIV vaccines of initial lower efficacy). As poor countries may not be able to pay higher prices (or only at the cost of reduced patient access), donors will probably have to pay the price premium on their behalf, and their willingness to do so is questionable. Bond purchasers looking at these figures and delivery timelines might also be disinclined to risk funds. If the Product Development Partnership Financing Facility is restricted to more commercially attractive vaccines for Type II diseases that are already being developed (for e.g. tuberculosis, pneumonia and meningitis), it would probably perform much better.

The financial aspects of these proposals could not readily be compared because of differences in their scope. The projected funding needs and outcomes are shown in Table 8. One can, however, assess the overall viability of product development partnerships as a funding route. As noted above, donors are increasingly favouring such partnerships to disburse funding for neglected diseases, and smaller donors disburse virtually all their funding in this way (probably because this mechanism minimizes the need for donor management). For example, in 2007, Ireland channeled 100% of its funding for research and development on neglected diseases through product development partnerships, suggesting willingness to support these partnerships financially.

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<sup>1</sup> Moon S, Ruffolo G. *Designing strategies for neglected disease research*. San Francisco, California, University of California at Berkeley, School of Law; Center for International Development, Harvard Kennedy School of Government. Available at [gspp.berkeley.edu/iths/RDStrategies/lecture16.ppt](http://gspp.berkeley.edu/iths/RDStrategies/lecture16.ppt).

**Table 8. Projected funding needs and outcomes of product development partnerships and other mechanisms**

Mechanism	Revenue stream (and whether secure)	Annual investment (US\$)	Annual projects	Scope
Product development partnerships	No revenue stream; based on milestones reached by recipients	About 584 million	More than 22 existing projects for neglected diseases	Malaria, tuberculosis, HIV/AIDS, helminthiasis diseases caused by kinetoplastids, dengue, meningitis, diarrhoeal diseases; drugs, vaccines, diagnostics, insecticide devices
Industry R&D facilitation fund	No revenue stream; based on milestones reached by recipients	130–190 million	To fund 80% of developing and developed country industry inputs to all product development partnership projects	Tuberculosis, malaria, diseases caused by kinetoplastids, helminthiasis, diarrhoeal diseases; drugs only
Fund for R&D in neglected diseases	No revenue stream; based on milestones reached by recipients	600 million–1 billion	All neglected disease drug projects by product development partnerships, industry and academic institutions	Likely to cover malaria, tuberculosis, diseases caused by kinetoplastids, helminthiasis, (including lymphatic filiriasis, onchocerciasis and schistosomiasis), leprosy, sexually transmitted infections, tuberculosis–HIV co-infection; drugs only
Product development partnership financing facility	Commercial bonds underwritten by government guarantees. Estimated US\$ 73–230 million per years (US\$ 2.2–6.9 billion over 30 years)	About 150 million	Only for HIV, tuberculosis and malaria vaccine R&D projects in the International AIDS Vaccine Initiative, the Malaria Vaccine Initiative and the Aeras Global TB Vaccine Foundation	Tuberculosis, HIV and malaria vaccines only

### ***Acceptability***

Multinational pharmaceutical companies rated provision of funding through product development partnerships as one of their two preferred approaches for product discovery and development. Diagnostics firms and innovative developing countries were moderately enthusiastic about product development partnership funding as an incentive for conducting research and development, and small-to-medium enterprises said they would not respond to additional funding routed through these partnerships.

### ***Conclusions***

Product development partnerships already coordinate and fund a great deal of research and development on neglected diseases undertaken globally. Funding through these partnerships has a strong impact on health in developing countries, is operationally efficient and is the only mechanism that stimulates early and sustained involvement of multinational pharmaceutical companies. A mechanism is needed, however, to help donors provide funds in a far simpler manner. Product development partnerships do not cover all needs for types II and III diseases, and all partnerships are not equally efficient. In-depth analysis is needed to determine which of the mechanisms or combination of mechanisms described above is most suitable for providing reliable, long-term, centralized funding and to link the funding to the efficiency of the partnerships.

#### **5.4.2 Direct grants to small companies and for trials in developing countries**

Many countries and some philanthropic organizations provide direct grants or contracts to small companies working in areas of public health importance, for which venture capital is either suboptimal or lacking entirely, e.g. for orphan diseases or, less often, neglected diseases in the developing world. When an innovation reaches the end of the scope of a grant (e.g. discovery of a promising molecule or conclusion of a Phase II trial), small-to-medium enterprises are expected to raise third-party funding from private investors and capital markets or to seek additional public or philanthropic funding to bring the product to registration.

Direct grants are vital for cash-constrained small firms, which need “push” funding to conduct research and development. Such grants do not dilute company equity (a bonus for small companies) and fit well within traditional national business grant funding schemes. Grants are usually used for basic research, discovery and early development, up to Phase II trials. Public grants are rare for expensive, large-scale clinical trials and manufacture, although they can be crucial in persuading a developer to undertake such trials. Support for large-scale trials is almost invariably provided by philanthropic organizations, often via product development partnerships (e.g. for HIV, malaria and tuberculosis drug and vaccine trials). One multinational pharmaceutical company noted that, without grant support, they would not have undertaken the additional clinical trials needed to make their product available for use in developing countries.

Funding schemes for small companies fall into two categories: grants or contracts to companies in developed countries to conduct research and development relevant to developing countries; and grants to small-to-medium enterprises in developing countries (especially innovative developing countries) to conduct locally relevant research and development. The impact on health in developing countries and the funding needed for these two types of scheme are different, and the two are therefore

reviewed separately. Typical schemes in circulation or submitted to the Expert Working Group (although many others exist<sup>1</sup>) include:

*Domestic grant or contract schemes for small-to-medium enterprises in developed countries*

- The United States Small Business Innovation Research Program is a Government scheme, in which the National Institutes of Health provide early-stage financing for small innovative businesses to bring technologies to the market. The scheme addresses mainly niche markets and needs, e.g. West Nile virus, hepatitis C, malaria.
- The United Kingdom Small Business Research Initiative involves a wide range of companies in competitions for ideas that result in short-term development contracts, such as for projects to design pathogen tests for hospital-acquired infections.
- DARPA Contracts, an arm of the United States Department of Defense, funds unique, innovative research by the private sector, academic and other non-profit organizations and Government laboratories. The programmes funded include research into both chronic and infectious diseases.
- Wellcome Trust Seeding Drug Discovery funds small and large pharmaceutical companies and not-for-profit research organizations for identifying promising molecules in areas of unmet medical need, such as cancer and neglected diseases.
- The International AIDS Vaccine Initiative Innovation Fund provides funds to small-to-medium enterprises to conduct experiments on pioneering ideas and technologies for an AIDS vaccine. It includes technical and scientific support from the International AIDS Vaccine Initiative and funding and product development support for successful projects.
- The European Medicines Agency's support scheme provides financial and administrative assistance to small-to-medium enterprises, including reduction or deferral of regulatory fees, scientific advice and regulatory support. It is designed to contribute to costs and not to cover the full costs of any development stage.

*Grant schemes for small-to-medium enterprises in developing countries*

- The State of São Paulo Research Foundation funds Research and Development projects through its Technological Innovation in Small Businesses programme. The research grants awarded have addressed diseases such as HIV, tuberculosis, Chagas disease, helminthiases, hepatitis C and cancer.
- The Indian Small Business Innovation Research Initiative, launched by the Indian Government's Department of Biotechnology in 2005, promotes high-risk pre-proof-of-concept research and end-stage development by small-to-medium enterprises. Applications

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<sup>1</sup> Rezaie R et al. Brazilian health biotechnology—fostering crosstalk between public and private sectors. *Nature Biotechnology*, 2008, 26:627–644. [www.nature.com/nbt/journal/v26/n6/pdf/nbt0608-627.pdf](http://www.nature.com/nbt/journal/v26/n6/pdf/nbt0608-627.pdf).

from the health sector addressed diseases such as cancer, typhoid and malaria and genetics research.<sup>1</sup>

- The Regional Health Research and Development Coordination Office in southern Africa funds regional research and development projects on predefined disease priorities, such as diarrhoeal diseases and tuberculosis.
- A proposal has been made for an international grant scheme similar to the Small Business Innovation Research Program, in which pooled funds from developed country donors and innovative developing country host countries will be provided to local small-to-medium enterprises in participating innovative developing countries to address global health challenges. The scheme, which is still in its early stages, will fund a variety of projects based on global health needs as determined by the funding agencies.

**Table 9. Scores of direct grants to small companies and for trials in developing countries with regard to impact on health in developing countries and operational efficiency and feasibility**

Mechanism	Impact on health in developing countries	Operational efficiency and feasibility	Data gaps
International AIDS Vaccine Initiative Innovation Fund	1	2	2
International grants for small-to-medium enterprises in innovative developing countries	2	2	2
Domestic grants for small-to-medium enterprises in developing countries	1	1	3
Domestic grants to small-to-medium enterprises in developed countries		3	
The European Medicines Agency initiative for small-to-medium enterprises (regulatory, financial and scientific support)		3	

### *Performance*

The performance of these various schemes is illustrated in Table 9. In terms of impact on health in developing countries, schemes based in developed countries performed less well, as they do not clearly and specifically target the needs of developing countries or define outputs relevant to those countries. Firms are likely to focus their research and development on commercially relevant needs (e.g. malaria products for travellers, disease strains prevalent in developed countries). These schemes are unlikely to include or encourage technology transfer to or capacity-building in developing countries or to encourage recipients to take into consideration suitability for their countries and price issues. The example of the International AIDS Vaccine Initiative Innovation Fund, which has a

<sup>1</sup> biospectrumindia.ciol.com/content/CoverStory/10806041.asp.

relatively high score despite significant data gaps, indicates that these issues can be improved by better targeting, although technology transfer and capacity-building remain unaddressed. Domestic grant schemes performed well for operational efficiency and feasibility, even allowing for data gaps. Some legislatures (e.g. in the United States) might, however, have difficulty in extending existing schemes to diseases that are not domestic priorities.

The international small-to-medium enterprise grant scheme also performed well for impact on health in developing countries and on some operational aspects (e.g. coordination of grant allocation). It would be more difficult to implement than national schemes, as it would require that local grant schemes be set up in many countries, as well as a central group to manage funds and make allocation decisions to projects in developing countries. The Working Group could not assess grant schemes for small-to-medium enterprises in developing countries because there are so many and they are so diverse. Conclusions can nevertheless be reached from the few schemes examined. Schemes in developing countries could have a much greater impact if they were well designed, in particular if they included requirements that the final product be affordable and meet high regulatory standards (which may be higher than those of some host developing countries). All these schemes, however, are less likely to perform well on technology transfer, as most are national rather than designed for international partnerships.

The financial aspects of developed country grant schemes could be readily assessed (Table 10). Large-scale schemes cost several hundred million US dollars per year, while more targeted schemes cost tens of million US dollars per year. Top-line outputs, for the United States scheme in particular, appeared to offer a good return on investment. As there were only limited data on schemes in developing countries (the Indian scheme is listed in Table 10), it was not possible to draw reliable conclusions about their costs and outputs; however, in principle, these schemes should not cost more than similar schemes in developed countries and might be substantially cheaper because of lower local costs.

**Table 10. Financial aspects of direct grants to small companies and for trials in developing countries**

Mechanism <sup>a</sup>	Revenue stream (and whether secure)	Annual investment	Annual projects	Scope
Domestic grants to small-to-medium enterprises in developed countries				
IAVI	Not mandated	About US\$ 3 million	5 projects (15 projects over 3 years)	Solely for HIV vaccines
WT	Not mandated	£20 million	No data	
SBIR	Legislated. All Government agencies with R&D budgets > US\$ 100 million give 2.5% of their extramural research funds	US\$ 570 million	2069 grants awarded; 50% of grantees had ≤ 1 peer-reviewed publication; 40 led to patented invention	Any disease (but guided by donor preference)
SBRI	Not legislated	Phase 1: £50 000–100 000 for 6 months. Phase 2: £250 000–1 million for 2 years (each award). Total value of grants unknown.	No data	Any disease (but guided by donor preference)
Domestic grants to small-to-medium enterprises in developing countries				
SBIRI	Not legislated	US\$ 17 million	18 projects (37 projects over 2 years); includes some projects in non-health sectors	Any disease

<sup>a</sup> IAVI, International AIDS Vaccine Initiative Innovation Fund; WT, Wellcome Trust Seeding Drug Discovery; SBIR, Small Business Innovation Research Program (United States); SBRI, Small Business Research Initiative (United Kingdom); SBIRI, Small Business Innovation Research Initiative (India).

### Acceptability

Small developers (small-to-medium enterprises, innovative developing countries and diagnostics firms) gave unanimous support to direct grant programmes, rating them as one of the two incentives most likely to stimulate them to commence or expand research and development programmes in developing countries. Large companies were less likely to respond, although they noted that grant programmes would be a welcome support to subsidize the cost of large-scale clinical trials in developing countries. These grant schemes were rated highly by all donors, public and philanthropic, in developed and developing countries.

### Conclusion

Developed and developing countries grant schemes clearly encourage broad participation of small-to-medium enterprises in research and development relevant to developing countries, schemes based in those countries being particularly promising. Grant schemes should also be extended to fund large-scale clinical trials by other groups (e.g. multinational pharmaceutical companies). These recommendations come with provisos: schemes based in developing countries should include opportunities to increase technology transfer, while those based in developed countries must be

carefully designed to maximize their impact on health in developing countries. Failure to do so can lead to wastage of substantial funds on products that will be neither suitable nor used in developing countries.

### **5.4.3 ‘Milestone’ prizes**

Milestone prizes are cash rewards given for reaching interim steps in development; for example, solving a basic research problem, developing a new animal model or discovering a production technique that can reduce costs. A problem can be defined more or less loosely by the group seeking a solution, and the intellectual property may or may not be handed over at the time the prize is paid.

Prizes encourage innovative thinking and mobilize far more activity than the value of the prize itself, as each group invests up to the value of the prize. They often help move a field forward by more clearly defining the problem.

While milestone prizes can theoretically be awarded at any point of development, they are best suited for the solving of basic research and technical questions and are unlikely to be awarded for clinical development. Prizes can be given for any disease or problem, from those given for many diseases to those specific to one disease or even one product, as outlined below.

Only one pure prize proposal was presented to the Expert Working Group; however, several more complex proposals include elements of a milestone prize:

- InnoCentive is a pure prize. It is an online marketplace where “seekers” (public, private and philanthropic) can post challenges. The award is paid to the “solver” who best meets the requirements, and a commercial agreement is then negotiated.
- A prize fund for development of low-cost rapid diagnostic tests for tuberculosis gives interim prizes for technical and best contributions; the amount is unclear but appears to be less than 10% of the total prize fund.
- The Chagas disease prize fund provides interim prizes for technical and best contributions; the amount is not reported.
- The priority medicines and vaccines prize fund gives interim prizes for technical and best contributions to the value of 20% of the total prize fund.

### ***Performance***

With the exception of InnoCentive, the above proposals could not be properly assessed as the elements of their milestone prize were sketchy. The Working Group therefore assessed InnoCentive in detail, on the assumption that any other prize model with a similar approach would perform similarly. All the proposals other than InnoCentive are part of mechanisms for pooling intellectual property, so that their management of intellectual property may not be the same as InnoCentive’s straight commercial approach. InnoCentive scored moderately well for its impact on health in developing countries (Table 11); however, an InnoCentive-type prize would have even greater benefits if two aspects were improved. Firstly, the prize question should be designed carefully to ensure that factors relevant to developing countries, such as suitability and cost of goods, are addressed even at early stages of research. Second, the commercial nature of the deal between the seeker and the solver leaves the seeker largely in control of the use of any future product. This could be addressed by posting

problems by public-health groups, including product development partnerships, which include negotiations on lower prices for developing countries in their contracts. InnoCentive performed particularly well on capacity-building in developing countries, over one third of the solvers being located in the developing world (20% in China, 15% in India) and in the Russian Federation (15%), each solver subsequently signing a deal with the seeker company to take their research forward.

**Table 11. Scores of ‘milestone’ prizes with regard to impact on health in developing countries and operational efficiency and feasibility**

Mechanism	Impact on health in developing countries	Operational efficiency and feasibility	Data gaps
InnoCentive	2	2	2

‘Milestone’ prizes are easy to put in place, can be scaled and present no administrative or legal hurdles. Their operational efficiency and feasibility scores were therefore high and would probably be higher if data gaps had not existed.

The InnoCentive milestone prize system is also strikingly cost-effective, with an average of 300 problems posted per year and around 130 solved, for an annual operating cost of US\$ 6–9 million. It has, however, been difficult to find prize funding or funds to support the running costs for noncommercial disease areas, unlike InnoCentive’s commercial arm, which is self-sustaining through user fees.

***Acceptability***

Large companies supported the idea of InnoCentive-style prizes but said that they would not respond themselves. All the small groups responded warmly, including innovative developing country firms, diagnostics firms and small-to-medium enterprises, one group noting that “A series of pulls along the development path are our No. 1 preference.”

Many cautioned that milestone prizes should operate within the intellectual property system, rather than substituting for it. This was a key factor in their attraction for both seekers and solvers. It is therefore important to have more detail on the other prizes, all of which are part of solutions that include pooling intellectual property to a greater or lesser degree.

***Conclusion***

InnoCentive-style milestone prizes are a highly cost-effective means for encouraging small firms to generate innovative solutions to basic research questions and technical problems up to the point of clinical development; however, maximum involvement of the private sector is likely to be obtained by managing prizes within the intellectual property system. Prize design is crucial for a strong impact on health in developing countries.

#### **5.4.4 ‘End’ prizes (cash)**

Cash end prizes are given as a large lump sum at the end of product development, as a reward. They can in theory be given in connection with any disease, although in practice they are usually considered for products with an insufficient market. The prize can be awarded as a pure reward for innovation, allowing intellectual property holders to retain their rights to the product, or as a “fee” to purchase the intellectual property from the developer to allow free exploitation by the prize-giver. In theory, the end prize is meant to reward the entire development process, from discovery through to registration; however, as shown below, an end-stage “pull” is likely to be insufficient for most products.

Although the notion of cash end prizes has been discussed, only one such proposal was submitted to the Expert Working Group: the prize fund for development of a low-cost rapid diagnostic test for tuberculosis. The proposal is rather complex, involving a US\$ 100 million prize fund, which is used to fund a US\$ 90 million end prize for development of a test, an open information reward and a range of interim prizes. The developer must give over the intellectual property to an open licensing pool administered by a tuberculosis licensing agency in order to receive the prize; the licensing agency can then issue non-exclusive licences to many developers to make the test available at low price to developing countries. Other aspects include a price ceiling or a market penetration test and a prize for the “best contributions” to the science and know-how needed to develop new tuberculosis diagnostic tests. At least half of the prize money for ‘best contributions’ would be set aside for research teams in developing countries.

#### ***Performance***

The proposed end prize for a rapid diagnostic test for tuberculosis performs well for impact on health in developing countries, as the product is designed to suit their needs and the licensing approach encourages low-cost manufacture and distribution. Researchers in developing countries are given priority, and the proposal requires that both intellectual property rights and technical know-how be handed over to manufacturers of generic products, many of whom are in developing countries. The complexity of the proposal and the requirement for groups to administer the fund, administer licences, assess market penetration and administer the various prizes and grants mean that it scores poorly for operational efficiency and feasibility.

The Working Group therefore also assessed a prototype simpler version, i.e. a prize to purchase or reward an innovation, without the associated interim prizes and market penetration test. This also performed well for impact on health in developing countries, on the assumption that the product was designed to meet their needs and that the prize was for purchase of the intellectual property to allow free exploitation, rather than simply a reward for innovation. These simpler end prizes would be expected to perform far better for operational efficiency and feasibility, like InnoCentive-style milestone prizes. The scores for the two versions are shown in Table 12.

**Table 12. Scores of end prizes with regard to impact on health in developing countries and operational efficiency and feasibility**

Mechanism	Impact on health in developing countries	Operational efficiency and feasibility	Data gaps
Prize fund for development of low-cost rapid diagnostic test for tuberculosis	3		1
Simplified version of end prize (cash)	3	*	3

\* More information about the actual operational model would be needed to assess operational efficiency and feasibility

### *Financial aspects and acceptability*

The financial aspects and acceptability of end prizes are discussed together, as prizes work only if they are of the correct size for their targets. Developers considered that prizes would be effective in only two cases: if the prize was equal to the commercial value of either the market or selling the intellectual property, or if the prize was supplemented with “push” funding to reduce research and development costs and thus give a smaller return. Most considered that prizes are unsuitable for drug and vaccine research and development, as the developer would have to assume all the risk and cost over a period of 7–15 years. “Prizes as the main pull at the end don’t de-risk the development process.” In these cases, the final prize would have to be very large and probably too large for donors to contemplate. Diagnostics were nevertheless seen as a suitable target, given their short development time (3–5 years) and relatively low cost (US\$ 5–10 million). In this context, the tuberculosis rapid diagnostic test appears to be overpriced at US\$ 90 million.

Small firms and companies in innovative developing countries stated clearly that end prizes simply do not work for them, because they need early, continuous cash; large companies were unlikely to respond, although they could see that a market-sized prize might work for others. The only group that responded positively was diagnostics firms, in particular large firms; smaller firms would possibly still need additional interim prizes or “push” funding to reach the end prize. Some public funders have already expressed interest in funding “smaller prizes directed to specific uses”.

### *Conclusion*

End prizes are probably suitable only for the development of diagnostics, for which prizes that are sufficiently large to reward the developers are within the reach of public funders. The impact of the prize on health in developing countries would be optimized by giving the prize for buying intellectual property rights rather than purely as a reward for innovation.

#### **5.4.5 Purchase or procurement agreements**

Purchase or procurement agreements are contracts between a purchaser (often a government, regional or multilateral group) and product developers, which set out the price at which a product will be purchased or the volume of product that will be supplied. The majority of agreements apply to generic products and are designed to secure bulk price discounts and security of supply, but they do not stimulate research and development.

A more recent innovation is purchase agreements for novel products or products still in development. These proposals are more relevant to this report as they not only secure patient access but can also provide incentive or reward research and development. Purchase funds for novel products appear to be more suitable for stimulating late development and manufacture of products that are already in the pipeline, including conducting the necessary trials in developing countries and plant construction for large-scale production. They provide less incentive for basic research, discovery or early development; the “pull” effect has limited application to earlier stages of research and development (see comments from developers below).

Both approaches are considered, as both include elements of potential interest. Examples, from the simplest to the most complex, are:

- a minimum volume guarantee, which aggregates demand for generic products for reproductive health in the form of prior purchase commitments, resulting in lower prices, which are passed on to clients;
- a minimum volume guarantee for a novel product; e.g. GlaxoSmithKline has signed a long-term price and volume agreement with the Government of Brazil for its novel pneumonia vaccine, stipulating a higher initial price and lower subsequent price over an 8-year period, including provisions for technology transfer so that Brazil can make the vaccine cheaply itself once the contract expires, as well as applying the technology to other domestically produced vaccines;
- the affordable medicines facility for malaria, in which pooled demand is used to negotiate lower prices for antimalarial medicines (artemisinin-based combination therapies), including novel drugs, and in which the cost to patients in least-developed countries is underwritten;<sup>1</sup> and
- a pilot project for advance market commitment, whereby donors commit to price and volume purchase contracts with companies for pneumonia vaccines that meet public health requirements; developers are assured higher initial prices (with the patient price subsidized by donors) in return for a lower, unsubsidized subsequent price. Negotiations can be complex, as they require advance definition of the desired product profile, and contracts are signed before the vaccine is made.

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<sup>1</sup> The Affordable Medicines Facility for malaria also has a fund to subsidize prices for patients; this is not discussed further here, as it is not pertinent to R&D.

**Table 13. Scores of purchase or procurement agreements for novel products with regard to impact on health in developing countries and operational efficiency and feasibility**

Mechanism	Impact on health in developing countries	Operational efficiency and feasibility	Data gaps
Affordable medicines facility for malaria	2	3	
Advance market commitment	1	2	1
Minimum volume guarantee for access to reproductive health products	1	2	2
Minimum volume guarantee (agreement between GlaxoSmithKline and Brazil)	*	3	1

\* The full impact on health in developing countries cannot be scored, as this is a one-off agreement for a middle-income country.

### *Performance*

The performance of purchase agreements for novel products varied significantly with the design of the agreement (Table 13). The advance market commitment performed least well, because of its failure to provide preferential incentive for low-cost products and thus low prices and a weak stimulus for technology transfer. It is also operationally complex and scored low on political feasibility, as it would be difficult to scale up for broad use. As regards the agreement between GlaxoSmithKline and Brazil, reliable conclusions can be drawn about only some of its aspects. Like the advance market commitment, this agreement does not provide incentive for or reward low-cost products; however, it has a strong technology transfer component, is operationally simple and could easily be scaled up for use in other countries and for other diseases, as it is based on standard commercial agreements. The probable impact on health in developing countries is difficult to estimate, as the agreement was tailored to Brazil's high purchasing power as an upper-middle-income country, but it would presumably be structured at levels closer to advance market commitment prices for low-income developing countries. The affordable medicines facility for malaria had the highest rating, as it involves bulk procurement to secure the lowest prices and requires that participating countries ensure access by even the poorest populations as part of their national plans; this is a condition for receiving the subsidized product.

The minimum volume guarantee model for access to reproductive health products is included to show the limited impact on health in developing countries of agreements that cover only generic products and the good operational efficiency and feasibility of this model, which is almost the same as that of the advance market commitment, despite the substantial data gaps.

All purchase commitments for novel products for developing countries have difficulty in finding financing, as donors and recipients are used to accepting long waits for cheaper, generic versions. From a purely financial perspective, the easiest option is straight purchase contracts between developers and developing countries that can afford their products (probably middle-income countries such as Brazil), as purchase costs can be offset against savings on treatment and hospitalizations. Where this is not possible (in most low-income developing countries), donors have to provide the

necessary purchase funds, as the GAVI Alliance and the Global Fund currently do for a range of products. As the sums required are very large, this option is probably viable for only a few vital products, such as vaccines for diseases that cause high mortality in developing countries. A globally pooled model, with tiered pricing between middle- and low-income developing countries might be another option. The financial aspects of these options are shown in Table 14.

**Table 14. Financial aspects of purchase or procurement agreements**

Mechanism	Revenue stream (and whether secure)	Funding for manufacture and distribution	Scope
Minimum volume guarantee	Not applicable. As it efficiently pools demand, no revenue is needed, and there are no purchases. Applicable for purchaser (purchase contract)	No funding needed, as purchases are pooled. Saving of US\$ 11 million in first 3 years, giving a return on investment of 0.6–2.4. Estimated start-up costs of US\$ 5 million for first 3 years, then sustained from user fees.	Reproductive health products (oral contraceptives and devices)
Advance market commitment	No for funder. Yes for developer (purchase agreement)	US\$ 1.5 billion over 10 years for about 200 million doses annually, distributed among contracted vaccine manufacturers (probably < 1 million subsidized for low- and middle-income countries. Larger sums will be required for future advance market commitments for novel products. Start-up cost relatively high.	Vaccines for pneumococcal diseases
Affordable medicines facility for malaria	No for funder. Yes for developer	Estimated cost of artemisinin-based combination therapy for pilot phase, US\$ 212 million for 11 developing countries. Operational costs, US\$ 6.6 million per year	Artemisinin-based combination therapy
Minimum volume guarantee	Yes, funding is essential. Not applicable for diversity of funders	€1.5 billion for 104 million doses over 8 years for Brazil (middle-income country)	Vaccines for pneumococcal disease

**Acceptability**

Developers gave purchase commitments the highest ranking of all the proposals reviewed, with a unanimous top rating by large and small companies, innovative developing country firms, diagnostics companies and product development partnerships. All the developers considered that purchase commitments – or, rather, demonstrated government willingness to purchase products – was the best advance signal of demand and would provide incentive to conduct research and development. They noted that purchase funds for novel products would not stimulate the whole research and development process, which would probably require additional early “push” funding, but would have the effect of “steering existing research and development towards the needs of developing countries”, providing the final added incentive needed. Of the various types of purchase funds, advance market commitments were least well received, being viewed unfavourably by small firms and with mixed views from large companies: “We’re trying to persuade governments to do a purchase fund, not an advance market commitment.”

Funders showed a marked preference for the advance market commitment approach for vaccines, although they also supported drug purchase funds, such as the affordable medicines facility for malaria.

### **Conclusion**

Purchase funds for novel products are a vital factor in stimulating increased research and development and providing large-scale access to new products; they are also well suited to steering existing programmes towards the needs of developing countries, such as research and development programmes for Type I diseases that would otherwise focus on developed country product profiles and on production capacity to meet developed country needs. Purchase agreements provide limited room, however, to negotiate decreased prices of new products, particularly if there is no competition from similar products. Although standard purchase contracts were preferred to advance market commitments, standard contracts would achieve better outcomes if demand was pooled to leverage and tier price negotiations and if developers were sent early signals about the desired profile (suitable for developing countries and low price) that would encourage donors to put up purchase funds for the final product. In other words, donors would use the purchase fund “pull” to direct R&D rather than simply purchasing what developers have already made.

## **5.5 Proposals to improve efficiency**

The two proposals described below, regulatory harmonization (focused on developing countries) and precompetitive research and development platforms, reduce the costs of research and development, thus reducing overall funding requirements and expediting the access of patients in the developing world to new products.

### **5.5.1 Regulatory harmonization (with focus on developing countries)**

A large proportion of the cost of developing and marketing new products is for regulatory requirements to establish that the product is safe, effective and of high quality before it is given to large numbers of patients. Costs can be increased further when different countries have different regulatory requirements, each regulatory agency requiring its own set of information as the basis for national approval and use.<sup>1</sup> The aim of regulatory harmonization is to improve this situation, by aligning the requirements of a number of developing countries.

A “quasi-regulatory” process was established by WHO to assess registered products for their suitability for use in developing countries. The programmes include drug and vaccine prequalification, the WHO Pesticides Evaluation Scheme, testing of diagnostics for field use and the WHO Essential Drugs List, which is a guide to the pharmaceuticals most suitable and necessary for local use in developing countries. These programmes are vital, as regulatory approval is based on national needs and not on suitability for e.g. resource-poor settings with limited pharmacovigilance and poorly controlled use. These programmes are not, however, always aligned with the work of other regulatory bodies, with the result that WHO often repeats assessments made elsewhere; furthermore, WHO reviews are sometimes slow because of limited resources and because of parallel capacity-building work. There may therefore be long delays before new products are given the WHO seal of approval for use in developing country markets. The access of patients in developing countries to new products

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<sup>1</sup> In developed countries, such differences have been partly addressed in a “common technical document”, agreed by Europe, Japan, the United States and the research-based pharmaceutical industry.

would be expedited if WHO integrated or recognized approvals by rigorous regulatory authorities elsewhere, to the extent possible. Such improvements in efficiency, by harmonization of regulation in developing countries and better integration of WHO processes with those of rigorous regulators elsewhere, would save money, and the benefit would apply to products for all diseases that affect the developing world.

Harmonization of regulation in developing countries has begun in some regions, although progress is slow. For instance, in Africa, early steps were taken by the African Union and by various regional economic communities, such as acknowledging the value of a harmonized regulatory dossier (Economic Community of West African States), harmonizing standards and practices for quality assurance (East African Community) and a pharmaceutical business plan for full regulatory harmonization over the period 2007–2013 (Southern African Development Community). An African drug registration harmonization consortium has been formed, led by the New Partnership for Africa's Development, the Pan African Parliament, the Bill & Melinda Gates Foundation, the Department for International Development (United Kingdom), the Clinton Foundation and WHO, which assists African regional economic communities and organizations in formulating high-level plans to attract donor support for harmonization. Regulatory harmonization in developing countries can be furthered by studying examples elsewhere.

Other regional regulatory harmonization initiatives include those of the Association of South-east Asian Nations and Pan America Network for Drug Regulatory Harmonization. The Committee for Product Development in the WHO South-East Asia Region and the Asian AIDS vaccine enterprise in China are calling for regulatory harmonization in Asia.

In the system set up by the Patent Co-operation Treaty of the World Intellectual Property Organization, a company can file for intellectual property protection with a centralized agency or with national agencies, for registration in all countries that have joined the system. A final decision is made by the national authorities.

WHO reviews are integrated to some degree with those of other regulatory agencies. For example, the WHO Drug Prequalification programme and the United States Food and Drug Administration have a confidentiality arrangement that allows the exchange of review and inspections reports, so that products can be added rapidly to the WHO Drug Prequalification approved list. This agreement does not, however, extend to other major agencies, such as the European Medicines Agency.

### ***Performance***

Harmonization of regulation in developing countries is likely to have a strong impact on health in those countries (Table 15), as it will mean more rapid registration of many products (both generic and brand) in some countries and may lead to product registration in countries that would otherwise not have had access to the product. It is likely to increase patient access, as developers are more likely to register products that are to be offered for sale in many developing countries if the cost and difficulty of doing so are decreased; and it may have a broader impact if lower development costs mean lower prices (although this is far from being a certainty).

Harmonization is feasible, as witnessed by the agreement cited in the footnote above, and is essentially cost-free, apart from the cost of negotiating agreements; however, it ranked only moderately in terms of operational efficiency. Disparate national legislative frameworks are a substantial obstacle, and countries may not have sufficient trust to move to a regionally harmonized

system (it took the European Medicines Agency nearly 40 years). National sovereignty is an issue, and loss of income from regulatory fees can pose difficulties for resource-poor nations. Finally, countries have to strike a balance between regional rationalization and national regulatory capacity-building, as national regulatory skills will continue to be needed. Integration of WHO processes with those of other regulatory agencies is also likely to be slow.

**Table 15. Scores of regulatory harmonization with regard to impact on health in developing countries and operational efficiency and feasibility**

Mechanism	Impact on health in developing countries	Operational efficiency and feasibility	Data gaps
Regulatory alignment in developing countries	3	2	

**Acceptability**

Product developers consistently rated regulatory efficiency as of high priority. Large and small companies and product development partnerships described them as “very, very significant in terms of de-risking” and “an enormous help as currently the entire burden is on developers”; while diagnostics companies made even stronger statements, noting that the slowness and difficulty of the WHO system were deterring companies from conducting research and development of diagnostics systems for poor countries.

Public and philanthropic funding agencies also expressed strong interest; many already support regulatory harmonization, in which WHO and its regional offices have played key roles. In contrast, some developing countries were less enthusiastic about regulatory harmonization, for the reasons set out above. WHO and the major regulatory agencies have been slow to reach agreements. The role of WHO in supporting research and development from a regulatory perspective has not, however, been clearly defined; prequalification was largely designed to support procurement by United Nations agencies.

**Conclusion**

Political will to move forward on regulatory harmonization and integration in developing countries would result in major cost savings and greatly increase the access of people in those countries to high-quality products.

**5.5.2 Precompetitive for research and development platforms**

Precompetitive research and development platforms also increase efficiency, but, unlike regulatory harmonization, require prior investment. These platforms increase the efficiency of research and development for many products, such as for an animal model that more accurately predicts the value of a tuberculosis vaccine in humans or surrogate markers that accurately predict the effect of an HIV drug, without requiring months or years of follow-up. Such findings are described as precompetitive as they are available to many developers rather than being proprietary to one company. Advances like these can save tens of millions to even hundreds of millions of US dollars on research and development for a single product, both by decreasing the development time and by early detection

and elimination of leads with low performance before more million dollars have been invested in their development.

Examples of precompetitive platform research include:

- The European Commission's Innovative Medicines Initiative, cofunded by the European Union and the European Federation of Pharmaceutical Industry Associations, awards research grants to European public-private collaborations working on platform breakthroughs. The focus is on diseases of relevance to Europe, although the second call for proposals includes diagnostics for tuberculosis and pneumonia.
- The Program for Appropriate Technology in Health is a United States-based product development partnership, which develops enabling and platform technologies and makes them available to all companies with products relevant for its programmes. For example, new assays and cell cultures are available to all manufacturers of a rotavirus vaccine for developing countries; and a consensus animal model is used for all candidate pneumococcal vaccines.
- The United States National Institutes of Health have developed many platforms to support R&D for neglected diseases, such as distributing parasites and biological materials, including infected animals, vectors and snails and transgenic parasites that express fluorescent labels, through three resources centres, one for schistosomiasis, one for filariasis and one for malaria and reference reagents.

Precompetitive platform advances are useful for many products in a given area but not necessarily for other diseases.

### ***Performance***

The impact of precompetitive research and development platforms on health in developing countries (Table 16) depends on their design and targeting. Thus, the European Commission Innovative Medicines Initiative platform may have a high impact, but researchers might choose to focus on commercially interesting subjects that are less relevant to developing countries, such as “high-tech” rather than “low-tech” solutions for diagnosing tuberculosis. The Initiative is operational but complex and takes years to put in place: grant partnerships must include at least two small-to-medium enterprises or universities and two members of the European Federation of Pharmaceutical Industry Associations; public funds go exclusively to the public sector and small-to-medium enterprises; and the grant process is intensive, only 10% of applicants being successful (whereas, for instance, one third are successful under the grant scheme of the United States Small Business Innovation Research Program). While this approach is cumbersome, it has the merit of pairing “blue-skies” academic innovators and small-to-medium enterprises with industry groups focused on application, an approach that has been shown to improve outcomes.<sup>1</sup>

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<sup>1</sup> Moran M et al. *The new landscape of neglected disease drug development*. London, London School of Economics and The Wellcome Trust, 2005.

**Table 16. Scores of precompetitive platforms for research and development with regard to impact on health in developing countries and operational efficiency and feasibility**

Mechanism	Impact on health in developing countries	Operational efficiency and feasibility	Data gaps
European Commission's Innovative Medicines Initiative		2	1
Program for Appropriate Technology for Health model	3	*	3

\* More information about the actual operational model would be needed to assess this aspect.

Precompetitive platforms that focus specifically on the needs of developing countries and place priority on projects that best address those needs are likely to have a greater impact on health in developing countries, as demonstrated by the Program for Appropriate Technology in Health. There was, however, information on the platforms provided by various organizations (including product development partnerships and academic institutions) for evaluation of the operational performance of this smaller in-house approach. Furthermore, the Working Group did not have access to the budget of the Program for Appropriate Technology in Health; however, investment in the European Commission's Innovative Medicines Initiative is significant, with a five-year budget of €2 billion (50:50 European Union: European Federation of Pharmaceutical Industry Associations) and 15 projects receiving an average of €16.5 million each in the first round of calls in 2008. Of the total for 2008, €110 million came from the European Union to support public partners in the consortium (universities and research organizations) as well as small-to-medium enterprises, patient groups and organizations, and regulatory bodies; and a further €136 million was provided in kind by European Federation of Pharmaceutical Industry Associations partners for their role in the projects.

### **Acceptability**

Both companies and product development partnerships ranked investment in precompetitive platforms as a high priority, noting for instance that “ways to reduce the cost of, and simplify, research and development is a real gap” and that “surrogate marker work is incredibly important to accelerate research and development.” Industry interest is underlined by their willingness to co-fund the European Commission Innovative Medicines Initiative platform.

Philanthropic organizations were also strongly supportive: “We really like these as they mitigate risk all the way along”, this being borne out by their willingness to fund the platform work of the Program for Appropriate Technology in Health and others such as the work of the TB Alliance on mouse models. Public funders outside the European Commission were less enthusiastic, one noting that precompetitive platform research and development is “interesting and valuable but not something we would support ourselves.” This position is echoed in G-Finder data for 2008, which shows that only 0.2% of global public funding for research and development on neglected diseases went into platform development.

## **Conclusion**

Investment into precompetitive research and development platforms targeted at products relevant to developing countries can result in substantial cost savings for all programmes in the same disease area. Platform research and development for developing countries targets nevertheless tends to be poorly supported because of issues related to public good and economic free riding. Greater political will in this area would expedite research and development and reduce costs.

## **5.6 Promising proposals**

Five further proposals are not described above, either because it is not clear how effectively they could be expanded into broad solutions or because their design is weak in some areas. All nevertheless contained innovative elements, which were so promising that we considered that the proposals should be examined further with a view to either amendment (if possible) and review for implementation or integration of the high-performing elements into other proposals.

### **5.6.1 Open source**

The basis of open source is that collaborations in biology allow interested parties to contribute knowledge or possible solutions (e.g. posting raw scientific data) to a biomedical problem. Collaborators forgo patents, as the outputs are placed in the public domain, although arrangements can differ. For instance, the key idea behind Sage Bionetworks<sup>1</sup> is to make Merck's previously proprietary data accessible to all interested parties without protection of intellectual property. Versions have already been implemented, including by the Indian Government and by organizations such as Synaptic Leap and the Tropical Disease Initiative's "open access" research site<sup>2</sup>.

While it is not clear whether many developers would use this approach, the concept scored sufficiently highly to warrant further exploration. It is also a low-cost solution.

### **5.6.2 Patent pools (UNITAID model)**

The UNITAID approach is based on creation of "upstream" and "downstream" patent pools, initially focusing on fixed-dose combination antiretroviral drugs for the treatment of HIV/AIDS. The aim of the "upstream" patent pool is to facilitate creation of adult and paediatric fixed-dose combinations suitable for developing countries (e.g. once daily, heat stable). The "downstream" pool is designed to lower the cost of existing HIV drugs by facilitating production of generic copies. Patents in these areas are submitted voluntarily to the patent pool by companies, researchers or academics. Manufacturers can obtain a licence to any patent in the pool and use it to create new or cheaper products. A small royalty is payable to the patentee for use of the patent.

The UNITAID patent pool model scored well for operational efficiency and feasibility, despite substantial data gaps, and very well on its impact on health in developing countries. As it is based on voluntary donation of intellectual property, however, questions remain about the quantity and quality of intellectual property that patent holders would choose to donate, particularly outside the area of HIV/AIDS. For the pool to work well, a minimum critical mass is needed, and it is not clear whether

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<sup>1</sup> (<http://sagebase.org/index.html>).

<sup>2</sup> (<http://www.tropicaldisease.org>).

this would be achieved voluntarily for many diseases. The patent pool model is low-cost, and it is highly recommended for further exploration of its adaptability to other disease areas.

### **5.6.3 Health impact fund**

The health impact fund is a voluntary system that provides financial payments to developers of new drugs, which are then sold globally within an administered low price bracket. Instead of the patent returns offered by the regular market, the fund offers payments based on the incremental therapeutic impact of the drug or vaccine, calculated annually from the quality-adjusted life-years gained. In return, the company forgoes the opportunity to earn profits on sales of the product during the reward period and must agree to offer a royalty-free open licence to allow generic manufacture of the product simultaneously with its own sales. At an approximate cost of US\$ 6 billion annually, the health impact fund would have to be financed by international donors.

The difficulties associated with this proposal are that developers have to fund research and development up front, which is difficult or impossible for most, especially if the final profits are limited; the method of assessing health impact is not agreed and is open to dispute; it is uncertain what the exact pay-out will be to individual developers; and control of the “market” by a central committee is cumbersome and expensive, costing around US\$ 600 million per year. The statistics on health impact are likely to be most reliable for high-profit commercial diseases, for which developers would probably choose the intellectual property system over the health impact fund, and least reliable for low-profit neglected diseases, for which the health impact fund would theoretically be more attractive.

The fund nevertheless deserves further consideration for some of its innovative aspects, which could perhaps be captured in other ways. In particular, it creates markets where none previously existed and it ties financial rewards to health impact.

### **5.6.4 Priority review voucher**

This proposal offers “priority regulatory review” of a commercial product in return for registration of a drug for a neglected disease in the United States. Priority review allows a company to bring a product to the market faster, resulting in many hundreds of millions of dollars of additional sales if the product is successful. It has been estimated that a reduction in the review time from 19.4 to 6.4 months for a drug receiving priority review could be worth US\$ 322 million to developers.<sup>1</sup> The vouchers can be traded.

The design of the priority review voucher has, however, major flaws and it could be of substantially greater value if these were addressed. A neglected disease product need not be suitable for use in developing countries, and developers need only to register the product in the United States. Thus, firms can register products in the United States that have already been used in other countries for many years (as was the case with the first product to receive a priority review voucher); and there is no link between award of the voucher and actual uptake of the product in developing countries, i.e. the firm does not have to register or sell the product in developing countries in order to receive the voucher.

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<sup>1</sup> Ridley DB, Grabowski HG, Moe JL. Developing drugs for developing countries. *Health Affairs*, 2006, 25:313–324.

The priority review voucher may be worth further consideration because of its attraction for small-to-medium enterprises; it may be one of the more potent “pulls” to bring these firms into the field, including firms in innovative developing countries. This would only be the case, however, if the priority review voucher was redesigned to address the flaws described above in order to deliver far better value for money for both the funders and the recipients (patients in developing countries).

### **5.6.5 Orphan drug legislation**

Several countries and regions have implemented orphan drug legislation to stimulate development of products for rare diseases,<sup>1</sup> including Australia, the European Union, Japan and the United States of America. Such legislation encourages developers to make products for low-profit markets by offering both “push” incentives (tax credits, regulatory fee waivers and priority review) and “pull” incentives (domestic market exclusivity ranging from seven years in the United States to 10 years in Europe). The “pull” element is by far the strongest incentive for developers and is the key to the success of this proposal.

Although orphan drug legislation is designed primarily to encourage research and development on rare diseases in developed countries, it is also used for products for neglected diseases in developing countries. It performs far less well in the latter context, however, as the domestic market “pull” is generally tiny. A further issue is that orphan drug legislation does not require regulators to review the product for suitability for developing countries but only for domestic suitability.

This proposal is nevertheless included as it might be a more attractive incentive if the disparate market pulls could be aggregated. This has happened to a certain extent; for instance, Australia and the United States have linked recognition of orphan drugs, so that a product that receives orphan drug legislation status in the United States automatically receives the same status in Australia. If approval in one jurisdiction automatically triggers approval in most other jurisdictions – and possibly also WHO Prequalification or Essential Drugs List listing – the aggregate “pull” of orphan drug legislation for the neglected disease market would be substantially increased. Specific requirements for regulatory review sensitive to developing countries would have to be incorporated for reciprocally approved orphan products for neglected diseases.

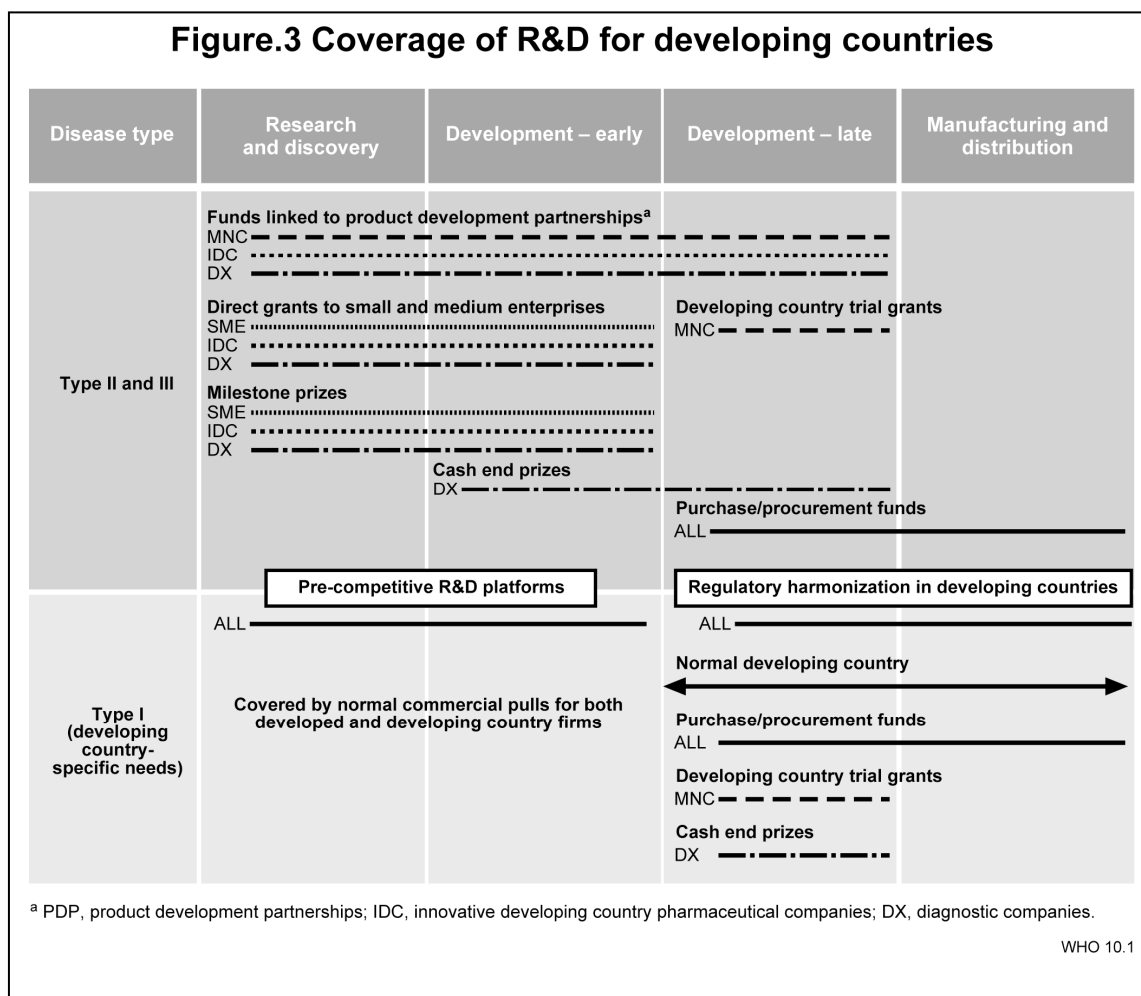
## **5.7 Gaps**

The allocation proposals presented above (except for promising proposals, which have yet to be tested) cover research and development on all disease areas relevant to developing countries and all development groups (see Figure 3). One area, however, in which all groups may not be mobilized is the discovery and early development of drugs for types II and III diseases, which are conducted independently by large companies outside product development partnerships. Large companies may self-fund early discovery (many already do), but development up to Phase II represents significant costs, which a company would be unlikely to want to bear alone. In areas in which no product development partnerships are active, large companies have no suitable incentives, as they are unlikely to respond to milestone prizes or to be sufficiently motivated by the promise of support for trial costs and a low-price purchase fund.

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<sup>1</sup> Rare diseases are those with a prevalence of fewer than 5 cases per 10 000 inhabitants in Europe and fewer than 200 000 cases in the United States.

This gap may be partially covered by the proposal for a fund for research and development in neglected diseases, which covers drug development by both product development partnerships and industry for a range of diseases. Alternatively, development could rely on the response of small-to-medium enterprises to incentives, or even new product development partnerships in key areas in order to take advantage of larger-scale funding solutions. Such decisions must be weighed as part of the in-depth review described below.



A wider issue is that, in order to perform optimally, additional measures are needed that fall outside research and development. The first is coordination of funding outside product development partnerships (e.g. small-to-medium enterprise grants, grants for clinical trials in developing countries). Funding through the mechanisms of the proposed product development partnership automatically provides a level of coordination and project prioritization. This does not exist for other funding routes, leaving donors facing, for example, a series of choices about grants awardees and types of prizes. In order for these proposals to work for donors, a mechanism will be required to coordinate funding to areas other than product development partnerships, although, as noted above, this might be resolved by further work on solutions such as a fund for research and development in neglected diseases to give them broader coverage.

Another issue is the priority given to prizes and purchase funds. Coordination of milestone prizes is probably less important, as they are small. End prizes, however, and particularly purchase funds imply a far greater financial commitment. Funders and developing countries must therefore decide carefully which diseases matter most and which products are most feasible in terms of development, in order to determine where to award the first prizes and purchase funds.

The driving force behind the Commission on Intellectual Property Rights, Innovation and Public Health, the Intergovernmental Working Group and now the Expert Working Group on Research and Development Financing was securing earlier access to medical breakthroughs for patients in the developing world. It was considered untenable that these patients should have to wait for patents to expire before they had access to affordable treatments. At the same time, it was clear that patents were the key to funding research and development for these new products. Our set of proposals addresses this issue fairly well for products for types II and III diseases, as linkage of product development partnership funding mechanisms, cash end prizes and purchase funds collectively ensures broad access to suitable low-cost products. Proposals for funding independent industry activity outside these routes are also expected to perform well if they are carefully designed to ensure that substantial injections of public funds are adequately reflected in lower-priced products. The members of the Working Group were disappointed and troubled to find, however, that none of the proposals for securing early, low-cost patient access to products for Type I diseases performed well; indeed, most performed exceptionally poorly. The Group sought to fill this void as best it could with the materials at hand, including the use of public subsidies for clinical trials (which would have to be tied to lower prices in low-income developing countries), end prizes that allow the handing over of intellectual property and purchase funds, ideally for products suitable for developing countries. The rapid growth of the capacity of innovative developing countries to design and supply medicines for Type I (and Type II) diseases will also, it is believed, go some way towards addressing these needs. The larger problem of access to Type I products registered and used in developed countries remains unresolved. Its resolution is increasingly pressing, as the waiver on TRIPS implementation, which allows low-income developing countries to delay protection of patent monopolies, will expire in seven years.

## **5.8 Comments**

The fund-raising mechanisms described above could raise an additional US\$ 4.6 billion per year by 2015 for health research and development for the developing world, depending on the choice of proposals within them. The proposed allocation and efficiency mechanisms would ensure efficient allocation of these funds in a manner that provided coverage of types II and III diseases and would maximize developer activity. If the provisos noted are taken into account, these allocation mechanisms can also be expected to provide good results with regard to public health and capacity-building in the developing world. The funds could be increased substantially if donors diverted current financial support from proposals that do not meet the agreed criteria (see Annex 2) to those that do.

Some of the recommended approaches are either already in place, or the general approach is in place to act as a framework, host or model for a version of the mechanism specific for developing countries (e.g. product development partnerships, grant schemes, milestone prize vehicles, purchase or procurement funds hosted by the GAVI Alliance, the Global Fund and others; regulatory harmonization and integration initiatives; and isolated precompetitive platform initiatives in individual organizations). Other proposals would require implementation, including mechanisms to fund product development partnerships and cash end prizes.

Unlike many of the proposals reviewed that had poorer performance, none of the recommended mechanisms has a revenue stream, and all currently rely on donor contributions and philanthropy. The

financing mechanisms proposed in this report are, however, well suited to address these funding deficits. The proposed financing and allocation mechanisms will, if implemented, provide a sustainable solution to the needs of patients in developing countries with new types II and III diseases. Type I disease products do not fare so well.



## ANNEX 1

### METHOD FOR EVALUATING PROPOSALS TO FINANCE HEALTH RESEARCH AND DEVELOPMENT

#### Evaluation framework and inventory

An inventory of more than 90 health research and development financing proposals was initially compiled from the following sources:

- submissions to the public hearing of the Expert Working Group on Research and Development Financing in March–April 2009;
- submissions from members of the Expert Working Group;
- literature searches of large databases and of the “grey” literature;
- proposals from related working groups, commissions and projects:
  - the Commission on Intellectual Property Rights, Innovation and Public Health;
  - the Taskforce on International Innovative Financing for Health Systems, co-chaired by the Prime Minister of the United Kingdom and the President of the World Bank;<sup>1</sup> and
  - the Brookings Institute analysis of evaluation tools, *Innovative financing for global health: tools for analyzing the options*.<sup>2</sup>

The initial inventory was reviewed for completeness and supplemented with proposals submitted at the second Internet-based public hearing organized by WHO, in August–September 2009.

These proposals defined the scope of our evaluation. They were inserted into an evaluation framework and grouped into two main categories: those intended solely to raise funds and those that also had provisions to allocate the funds to research and development. Fund-raising proposals were subgrouped according to the source of funding (e.g. government, consumers) and type of funding (e.g. front-loading, taxes), while allocation proposals were subgrouped according to their stated research and development target, including disease type (I, II, III, all), product type (drug, vaccine, diagnostic, all), research type (building health research and development in developing countries, basic research, product development, manufacture and distribution) and principal actors (public, private, academic,

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<sup>1</sup> Taskforce on Innovative International Financing for Health Systems. *Raising and channelling funds, Working Group 2 Report*. Geneva, World Health Organization, 2009. Available at: [www.internationalhealthpartnership.net/pdf/IHP%20Update%2013/Taskforce/Johansbourg/Taskforce%20Working%0Group%202%20Report.pdf](http://www.internationalhealthpartnership.net/pdf/IHP%20Update%2013/Taskforce/Johansbourg/Taskforce%20Working%0Group%202%20Report.pdf). Accessed 17 July 2009.

<sup>2</sup> De Ferranti D et al. *Innovative financing for global health. Tools for analyzing the options*. Washington DC, Brookings Institute, 2008. Available at: [www.brookings.edu/~media/Files/rc/papers/2008/08\\_global\\_health\\_de\\_ferranti/08\\_global\\_health\\_de\\_ferranti.pdf](http://www.brookings.edu/~media/Files/rc/papers/2008/08_global_health_de_ferranti/08_global_health_de_ferranti.pdf). Accessed 17 July 2009.

product development partnership, multinational company, generics manufacturer, small company). The evaluation framework was based mainly on the type of research, which also provided the basis for the structure of the report.

### Evaluation tool

An evaluation tool was developed, with high-level criteria against which to assess proposals. The initial tool was refined on the basis of feedback from more than 20 groups, including WHO Member States, funding agencies, civil society groups, private industry, product development partnerships and regulatory authorities, during the second public hearing organized by the WHO Secretariat. The final tool contained three high-level criteria divided into 12 subcriteria (and close to 100 detailed criteria), as shown below. The detailed criteria were subsequently used to make a comparative analysis and screen the mechanisms.

<p>Impact on health in developing countries</p>	<p>Health impact, including incentives for R&amp;D on health priorities for and use by developing countries, with measures to ensure safety, quality and efficacy and encourage innovation</p> <p>Access: price, registration, distribution, intellectual property approach, including whether the cost of goods is suitable for the requirements of developing countries, it maximizes both affordability and access, it encourages generics manufacturers or increases competition and increases distribution</p> <p>Capacity-building, including whether capacity in developing countries is encouraged and whether regulators or manufacturers in developing countries are involved.</p> <p>Technology transfer</p>
<p>Operational efficiency and feasibility</p>	<p>Risk management, including whether funding arrangements are mandatory, there is a diversity of funders, the funding stream for recipients is certain, the risk for investors is spread and (for manufacture and distribution proposals only) it mitigates against stock-outs</p> <p>Technical feasibility, including whether the mechanism requires changes to legal, regulatory or administrative systems and whether it can be operationalized quickly by using existing entities or structures</p> <p>Long-term functioning, including whether the mechanism provides clear rules on funding allocations to allow long-term planning by principal groups, whether it can be adapted in the light of actual experience and whether it would be politically sustainable</p> <p>Accountability, governance and transparency, including whether the mechanism has a sound governance structure, covers all appropriate groups (including developing countries), whether there is a means for dispute resolution, whether it operates transparently, including having an accountability system and documented roles and responsibilities, and whether participating groups are treated equitably and fairly</p> <p>Interactions with other proposals</p>

Financial aspects	<p>Revenue stream and size</p> <p>Costs</p> <p>Quality of funding for the allocation proposals, including additionality, certainty of revenue, reliability and applicability of mechanisms, absence of inefficient conditions and additional benefits such as reduced research and development time and cost</p> <p>For fund-raising proposals, the degree of certainty of revenue forecasts, a potentially wide geographical scope, whether the mechanism is free of inefficient conditions and distortionary tax effects and has spillover benefits for the global good and the development agenda</p>
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## Screening

Each proposal was independently screened against the evaluation tool by two to six people to determine how well it met each of the up-to-100 criteria. The evaluators had skills in the following areas:

- international public health, including clinical management, epidemiology and profiles of infectious diseases (HIV/AIDS, malaria, Chagas disease, tuberculosis, pneumonia and meningitis) and health policy in Africa, Latin America and South-East Asia;
- health finance and financing mechanisms, including public expenditure, sector strategy development, financing issues around global health partnerships and aid instruments, and advisory work for global initiatives such as the Taskforce for Innovative International Financing for Health Systems, the Affordable Medicines Facility for malaria, UNITAID and the Global Fund;
- pharmaceutical R&D (cost, pipelines, portfolio management, regulatory processes), including health economic modelling, health technology assessments, pharmaceutical market analysis, tracking resources for R&D on neglected diseases and analysis of drug and vaccine portfolio development for neglected diseases;
- regulation (in developed and developing countries), including regulatory affairs for multinational pharmaceutical companies and for non-members of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and emerging markets;
- intellectual property management in both private pharmaceutical companies and government agencies; product developers' characteristics, including strengths, weaknesses, needs and preferences, in industry, product development partnerships and academic innovators (in developed and emerging countries); and
- international development of health systems and policies in developing countries, including work for the Department for International Development (United Kingdom), the Overseas Development Institute, the United States Agency for International Development, AusAID, UNAIDS and UNDP.

The objective and scope of the proposal determined the set of people who screened it. Marked discrepancies in screening results were resolved through further research and discussion among the evaluators. When a criterion was not applicable to a proposal, it was not screened or scored against that criterion.

**Allocation proposals** were sorted into like groups, each proposal in a group being assessed for its impact on health in developing countries, operational efficiency, financial aspects and the likelihood of whether it provided incentive for developers in both developing and developed countries to start or increase research and development. Performance is represented in the tables by a score, three being high, middle ranking by a score of two and low-scoring proposals by a one or zero. Financial aspects were analysed and tabulated separately. While the shortlist of final proposals was essentially based on their assessed performance, other factors were considered, in particular whether they offered a broad solution for many diseases and products.

**Fund-raising proposals** were also sorted into like groups and assessed for their capacity to raise funds, additionality, the likelihood that the funds would be accepted as suitable for allocation to health R&D and ease of implementation. Evaluation of fund-raising proposals was based primarily on recent analyses conducted by Working Group 2 of the Taskforce on Innovative International Financing for Health Systems, which shortlisted and reviewed 24 financing mechanisms. Several of the criteria used by the Taskforce were relevant to our analysis, including general criteria covering the value added, past experience, technical feasibility, political sponsors and time needed for implementation; financial criteria, including revenue potential, additionality and costs; and aid effectiveness criteria based on the Paris agenda.<sup>1</sup> Screening was based not only on use of these reviews but also our own, additional criteria and analysis.

The Working Group also sought overall balance in the shortlist, by selecting proposals to ensure good coverage of the research and development field and those working in it and a reasonable balance of public and private risk. Overall balance was also sought among the fund-raising proposals, by considering a mix of consumers, governments and the pharmaceutical industry; voluntary and non-voluntary (i.e. taxes) contributions; developing and developed country contributions; and proposals that would be easy to implement versus those that would be sustainable.

By this assessment technique, the Working Group was able to determine those approaches worked best overall. For the allocation mechanism, the best-performing proposals were selected from the approaches. For the fund-raising mechanisms, details of the tax or form of voluntary contribution are the responsibility of each country.

While every effort was made to answer each question for each proposal, sometimes no data were available for a criterion. These proposals therefore require more work, and data gaps are indicated in the tables. The results should be read in conjunction with the scores for impact on health in developing countries and operational efficiency and feasibility. Thus, when many data were lacking, the score could potentially be improved if more data were made available. This led to the group of “promising proposals requiring further work”.

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<sup>1</sup> *Paris Declaration on Aid Effectiveness*. Paris, Organisation for Economic Co-operation and Development, 2005.

## **Key criteria for determining acceptability**

In order for proposals to work in the real world, they have to be acceptable to both funders and those with the skills and tools to develop the desired products. Therefore, in parallel, a range of public, philanthropic, industry and civil society groups were asked to nominate the criteria for an R&D financing proposal that were most important to them, feedback being submitted through the WHO web site and with follow-up interviews when necessary. These groups were asked in particular to list those criteria that were essential or highly important. Funders and product developers were also asked which proposals were most and which were least likely to encourage them to fund or conduct R&D to generate new products for the developing world. The responses were sorted into groups: public funding organizations, philanthropic institutions, large companies, small companies, product development partnerships, developing country industry and civil society.

The responses of each group were analysed to determine the most important factors, which determined how high the “bar” should be set for each criterion. For example, impact on health in developing countries was considered important by almost all funders, while operational efficiency and feasibility were almost unanimously nominated as the most important features by developers. None of the groups considered that value for money was the most important driving principle.

## **Shortlisting of proposals**

In order to shortlist the proposals, cut-off points were set, below which a proposal was not included for further consideration. In response to feedback on the criteria, high cut-off points were set for impact on health in developing countries and operational efficiency and feasibility but only a moderately high cut-off point on value for money. The responses from funders and product developers were used to further shortlist proposals, i.e. to select those that scored high and were acceptable (the most effective proposals) and those that scored low and were not acceptable (the least effective proposals).

Although the issues of impact on health in developing countries and operational efficiency and feasibility were given equal importance, some components of a mechanism are easier to address than others. For instance, it is relatively easy to re-target a proposal so that it has a better impact on health, e.g. by revising the list of diseases or by adapting the product profile to suit the needs of developing countries. It is, however, difficult to change how a proposal operates. Readers should therefore concentrate on proposals that perform well operationally and that can be re-targeted for better health outcomes in developing countries.

Generally, the fund-raising proposals do not have an allocation component, i.e. they raise money, but the money could be spent on virtually anything. Thus, fund-raising proposals were not assessed for their impact on health in developing countries but only for operational and financial aspects.

## ANNEX 2

### **PROPOSALS THAT DID NOT MEET THE AGREED CRITERIA**

The following proposals did not meet the criteria set out for the analysis:

- transferable intellectual property rights
- green intellectual property
- removal of data exclusivity
- biomedical research and development treaty
- large end-stage prizes (impact-based rewards)
- neglected disease tax breaks for companies.

The remaining proposals in the inventory of the Expert Working Group on Research and Development Financing were either too specific to be used more widely or performed insufficiently well to merit further consideration.

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