

## Research and Development Priorities to Achieve the “Grand Convergence”

### Working Paper 1

#### Priority Research Areas for Basic Science and Product Development for Neglected Diseases

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### Working Paper 2

#### An Initial Scan of Priority Research Areas for Public Health, Implementation Science and Innovative Financing for Neglected Diseases

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#### About the *Lancet* Commission on Investing in Health:

The *Lancet* Commission on Investing in Health is an international, multi-disciplinary group chaired by Lawrence H. Summers and co-chaired by Dean Jamison to examine how the context for health investment has changed since the World Bank's landmark *World Development Report 1993: Investing in Health*. The Commission has explored national policy opportunities for low- and middle-income countries to achieve dramatic health gains over the next 20 years and to reduce illness-related poverty and the future role of international collective action for health, particularly in supporting research and development (R&D).

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**Working Paper 1**

**Priority Research Areas for Basic Science and Product Development for Neglected Diseases**

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## INTRODUCTION

Research and development (R&D) is a critical contributor to improving health and therefore an essential component of investments in health<sup>1</sup>. The R&D landscape spans initial discovery, proof of principle, risks and benefits, delivery, and evaluation of impact. With such a wide range of possible contributions from so many ongoing R&D initiatives globally, it is exceedingly difficult to predict which innovations and discoveries in fundamental science will lead to a translational breakthrough. At a time when the pace of discovery across the R&D spectrum is being threatened by economic austerity, it becomes opportune to note that for every decade without continuing investments in R&D, the development of new and better technology for diagnostics, drugs, vaccines, and strategies to implement them, with improved or wider potential impacts on health, is also set back by a decade<sup>2</sup>. The question is no longer whether to invest in R&D, but instead, invest in what, by whom, and how much?

In this working paper, we reflect on historical R&D prioritization efforts and examine disease-specific R&D priorities for basic science and product development in malaria, HIV/AIDS, tuberculosis (TB), neglected tropical diseases (NTDs), and childhood pneumonia and diarrhea (CPD). Among the insights gained from this exercise, we draw attention to the need for not only systematic methods to establish and make progress on R&D priorities in increasingly collaborative ways, but also public goods that will facilitate the sharing of this knowledge across stakeholders throughout the R&D spectrum.

## LOOKING BACK – R&D in 1993

- What were the main R&D messages of *WDR 1993*?
- What has happened in the two decades since *WDR 1993*?
  - Investments in R&D for health
  - Investments in R&D for neglected diseases
    - Disease-specific investments
    - Funder-specific investments
  - Initiatives relevant to R&D at the global level
    - Working Groups, Commissions, WHA Resolutions
  - Initiatives relevant to R&D at the national level

### MAIN R&D MESSAGES OF THE WORLD DEVELOPMENT REPORT 1993

*The World Development Report 1993: Investing in Health*, hereafter *WDR 1993*, emphasized that “investments in research have been the source of the enormous improvements in health in this century” (p.148)<sup>3</sup>. It discussed the role of governments and the international community in promoting research, from basic science, to translation to products, to operational research; it highlighted the critical need for building capacity for research in all countries, and the importance of local contextualization.

<sup>1</sup> Commission on Health Research for Development. *Health Research: Essential Link to Equity in Development*. 1990. p. xvii.; World Health Organization (WHO). Coordinating and priority-setting in R&D to meet health needs in developing countries. Draft Working Paper 2. Department of Public Health Innovation and Intellectual Property. May 2013.; WHO. A global health R&D observatory—developing a case for its development. Draft Working Paper 1. Department of Public Health Innovation and Intellectual Property. May 2013.; CEWG Report 2012.

<sup>2</sup> Fineberg HV. Toward a new social compact for health research. *Jama*. 2013; **310**(18): 1923-4. <http://www.ncbi.nlm.nih.gov/pubmed/24219939>.

<sup>3</sup> World Bank. *World Development Report 1993: Investing in Health*. New York: Oxford University Press; 1993.

The *WDR 1993* recommended greater investment in research and product development when cost-effective interventions did not yet exist but experts felt they were feasible to develop (e.g. inexpensive, simple, and reliable diagnostics for respiratory infections). At the same time, they argued for greater efforts in program development and operational research for problems contributing to a large burden of disease and for which cost-effective interventions already existed.

**Table 1** depicts selected recommendations of *WDR 1993* and qualitative descriptions of the magnitude of investment and progress made in the last 20 years. See **Appendix 1** for an extended summary of recommendations from the *WDR 1993*.

<b>Table 1. Selected Recommendations for R&amp;D from WDR 1993 – Estimated Investment and Progress</b>		<i>Low to Modest Investment</i> Insufficient progress in most aspects	<i>Modest to Moderate Investment</i> Some progress in at least 1 aspect	<i>Moderate to High Investment</i> Some progress in most aspects
<b>PRIORITIES FOR RESEARCH ACCORDING TO BURDEN OF DISEASE IN POOR</b>				
Tuberculosis	Methods of ensuring compliance; monitoring tools for drug resistance; simpler diagnostics; new and cheaper drugs		X	
Child routine vaccines	New and improved diphtheria, polio, pertussis, measles, tetanus vaccines to reduce visits, permit immunization at younger ages, and improve heat stability of some vaccines		X	X
Diarrheal diseases	Rotavirus and enterotoxigenic <i>E. coli</i> vaccines; improved cholera vaccine; ways of improving hygiene; case management of persistent diarrhea; promote breastfeeding		X	X
Respiratory infections	Reduce impact of indoor air pollution on pneumonia (e.g. improved stoves); inexpensive or simplified antibiotic regimens; simple, reliable diagnostics; pneumococcal vaccine		X	X
Perinatal and maternal	Methods of lowering costs of maternal and perinatal interventions and improving delivery in rural areas	X		
Cerebrovascular disease	Low-cost prevention, diagnosis, and management methods for ischemic heart and cerebrovascular disease	X		
<b>BUILDING CAPACITY FOR RESEARCH &amp; DEVELOPMENT IN POOR COUNTRIES</b>				
<b>Role of governments to support essential national health research in LIC and MIC</b>				
	standardize and finance the collection, analysis, dissemination of health information (to guide program design, policies and public spending) including monitoring and evaluation at district and facility levels	X		
	collect and synthesize epidemiological and other information necessary to monitor health status, detect disease outbreaks (i.e., surveillance) and guide public policy	X		
	conduct research on variations in clinical practice, consumer satisfaction, and women's health; providing consumers, health researchers, and communities with information about quality of care	X		
<b>Role of global community to support research capacity and attention to diseases afflicting LIC and MIC</b>				
	support collection of data for international comparisons and to target national action (e.g. standardized household survey programs)		X	
	assist local institutions to build capacity in epidemiology, health economics, health policy, and management including supporting international partnerships or networks	X		
	catalyze technological development through basic research and product development, incentivize products and technology development related to diseases of the poor	X		

## WHAT HAS HAPPENED IN THE 20 YEARS SINCE *WDR 1993*?

### *Investments in R&D for health*

Investments in R&D for health are estimated to have increased approximately five-fold since *WDR 1993*, from U.S. \$50 billion to U.S. \$240 billion in 2009<sup>4</sup>. Consistently, around 90% has been invested in high-income countries (HICs), although now predominantly by the private sector. This has remained largely focused on diseases affecting HIC populations. Only a small percentage of the total is invested in R&D for neglected diseases primarily affecting the global poor. Clinical trials, now increasingly conducted in low- and middle-income countries (LMICs), are 7 to 8 times more likely to address diseases of HICs. Even where disease burdens are converging (for example, non-communicable diseases such as heart disease, stroke, diabetes, and cancer), the products under development as well as their costs and delivery mechanisms will remain challenges for LMICs.

### *Investments in R&D for neglected diseases*

In 2011, total reported funding for neglected disease R&D was \$3,045m (\$3,318m in unadjusted 2011 US\$). Even with the global financial crisis, public funding decreased very little in absolute terms; reduced funding by the philanthropic sector was offset by increased industry funding largely in the form of multinational pharmaceutical company investments<sup>5</sup>. Approximately 70% of total funding has been invested into product development for the semi-commercial diseases, 60% for diseases with a significant philanthropic stake, and less than 50% for diseases that rely heavily on the public sector.

### *Disease-specific investments*

In 2011, HIV/AIDS, malaria and TB received 33.8% (\$45.7m), 18.4% and 17.3% respectively. The proportion of funds allocated to these three declined from 76.6% to 69.4% in the last 5 years, in large part due to an overall 10% decline in funding for HIV/AIDS. In 2011, funding increased for only malaria, and only by about 3%<sup>6</sup>. In 2011, almost 1 out of 4 dollars went to bacterial pneumonia and meningitis, diarrheal diseases, helminth infections, kinetoplastids (chagas disease, leishmaniasis, sleeping sickness), and dengue. Funding increased for dengue, bacterial pneumonia and meningitis, and helminth infections by ~31.8%, 13.1%, and 3.3%, respectively. Funding decreased for kinetoplastids (chagas disease, leishmaniasis, sleeping sickness) and diarrheal diseases by 14.1% and 7.8%, respectively. In the last 5 years, less than 0.5% of global R&D funding has gone to the group of neglected diseases that include trachoma, leprosy, Buruli ulcer and rheumatic fever<sup>7</sup>.

**Figure 1** depicts the distribution of R&D investments by disease and research type category in 2011. In **Figure 2**, R&D investments for 2011 are segmented by initiative associated with a particular disease area and research type, then ordered from most to least amount invested.

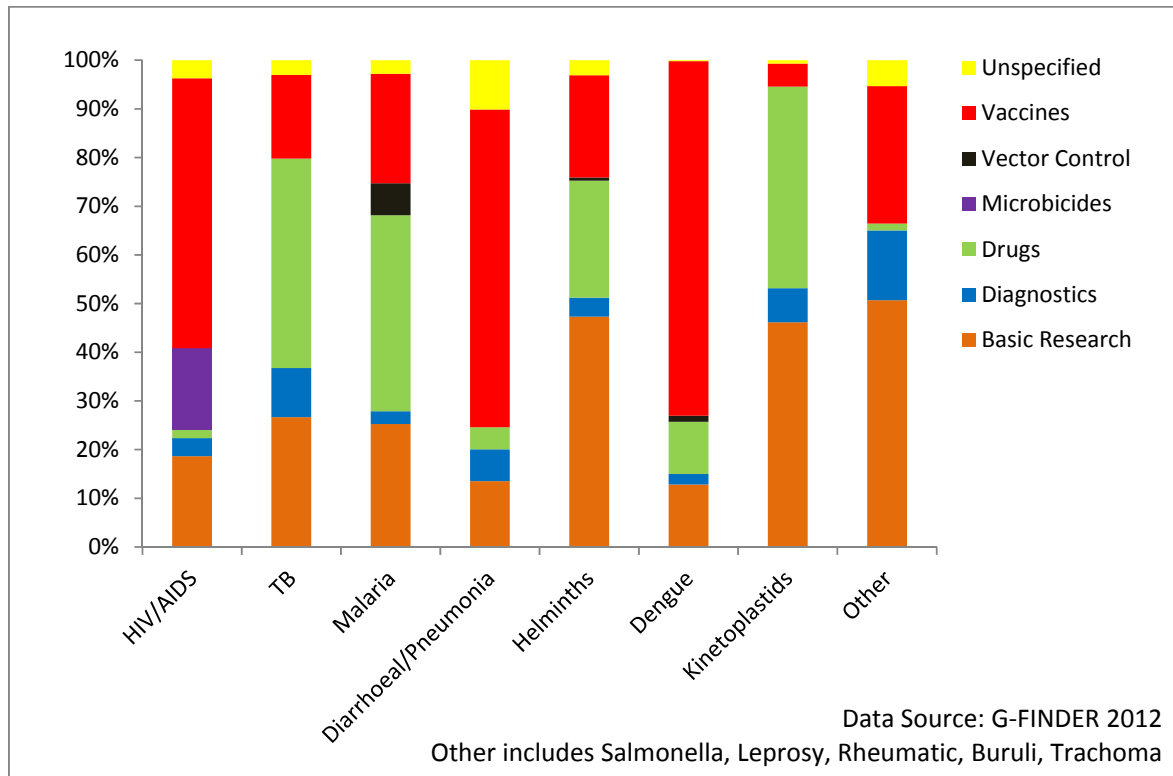
<sup>4</sup> Røttingen JA, Regmi S, Eide M, Young AJ, Viergever RF, Ardal C, Guzman J, Edwards D, Matlin SA, Terry RF. Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory? *Lancet*. 2013 Oct 12;382(9900):1286-307.

<sup>5</sup> Moran M, Guzman J, Henderson K, Liyanage R, Wu L, Chin E, et al. G-FINDER 2012. Neglected disease research and development: a five year review. Sydney: Policy Cures; 2012. [http://www.policycures.org/downloads/GF2012\\_Report.pdf](http://www.policycures.org/downloads/GF2012_Report.pdf).

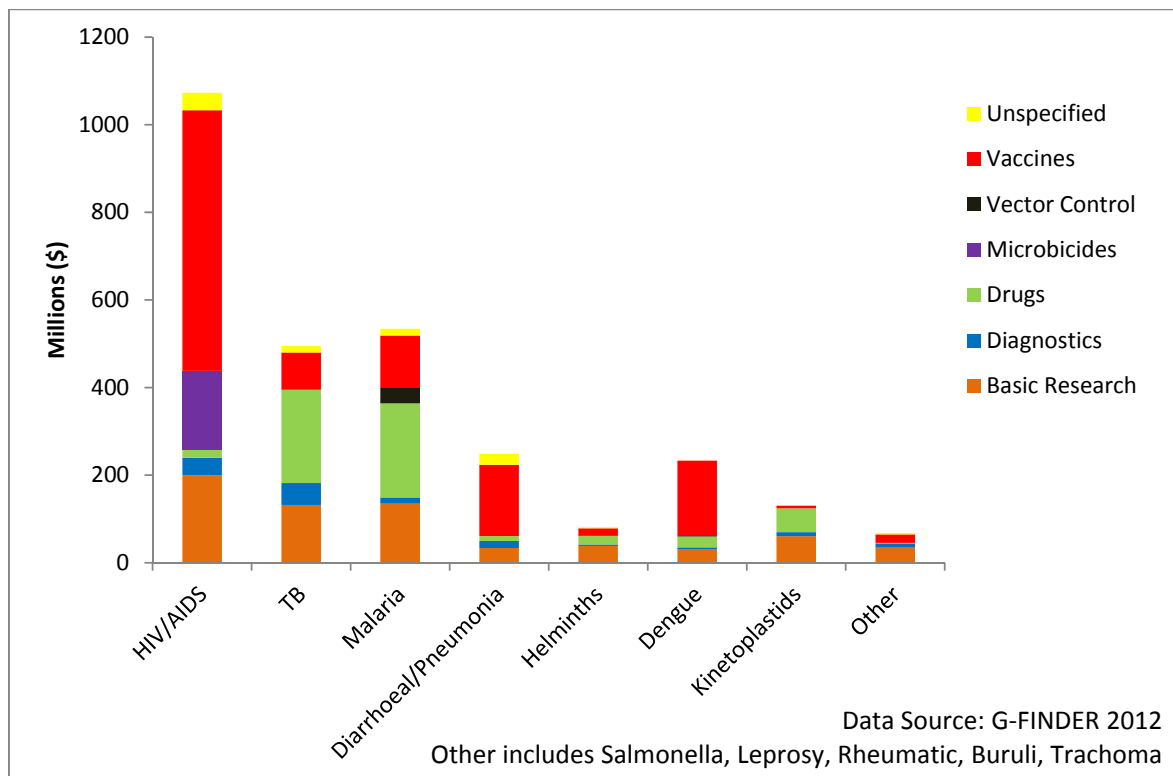
<sup>6</sup> Policy Cures 2012. G-FINDER 2012.

<sup>7</sup> Policy Cures 2012. G-FINDER 2012.

**Figure 1: Distribution of investments in R&D by disease area and research type (2011)**



**Figure 2: Allocation of investments in R&D by disease area and research type (2011)**



We refer readers to another working paper produced for the *Lancet* Commission on Global Health<sup>8</sup> for a review and analysis of the shifting distribution of funders and actors in the global health space. In the section below (“Funder-specific investments”), we briefly highlight the insights provided in the comprehensive report of results from G-FINDER<sup>9</sup>.

### *Funder-specific investments*<sup>10</sup>

Between 2007 and 2011, close to 2 out of 3 dollars for global R&D funding were provided by the public sector, the vast majority (>95%) if which from governments in high-income countries. Basic research accounted for 31.2% of total public funding in 2011 compared to 26.0% in 2007.

The United States (US) provided just under 70% of all public funding (~\$1.4bn); while the decline in their 2011 contribution was only 2%, the implications were substantial because of the high absolute amount (~\$31m). Public funding from the United Kingdom (UK) declined by a similar absolute amount (~\$29m)—representing a much greater 20% decline in funding—mainly due to cuts by the Department for International Development (DFID). Some countries, such as Australia and the Netherlands, increased funding in 2011 (from roughly 27% to 35%) although these were low absolute amounts (\$6.7m and \$6.1m, respectively), while others decreased funding (e.g. European Commission, Belgium, Netherlands, Brazil, Canada). In terms of middle income countries, India is the leading funder for R&D.

Philanthropic funding accounts for 12.4% of HIV/AIDS funding, 23.5% of TB funding, and 30% of malaria funding. While these contributions are lower in absolute terms, philanthropic funding accounts for about a third of global R&D funding for bacterial pneumonia and meningitis (35.0%), diarrheal diseases (30.1%), helminths (30.7%), and kinetoplastids (31.7%). Declines in philanthropic funding are largely due to a 27.4% (~\$170m) reduction in contributions from the Bill & Melinda Gates Foundation since 2008. Approximately 79% of philanthropic funding is allocated toward product development. Product development partnership (PDP) funding declined in 2011 (down \$31.8m, or 6.6%) with the largest drop from the Bill & Melinda Gates Foundation (down \$31.4m, or 12.4%), which provides 1 of every 2 dollars that goes to PDPs. Eight out of twelve aid agencies also cut their funding to PDPs, with a collective reduction of \$30.6m in 2011.

R&D funding for diseases with strong industry support has been robust, contributing nearly 50% of funding for dengue, bacterial pneumonia and meningitis. When TB is included along with dengue, bacterial pneumonia and meningitis, these “semi-commercial diseases” accounted for 28.4% of total R&D funding in 2011. Increases for dengue, mainly in the arena of clinical development for vaccines, is up \$115.8m and almost entirely due to industry multinational pharmaceutical company funding.

### *Actors and stakeholders funding R&D*

In the past 20 years, a host of new actors and stakeholders have joined the traditional funders in global health R&D, such as the US’s National Institutes of Health and the UK’s Wellcome Trust (<http://www.nih.gov/>; <http://www.wellcome.ac.uk/>). These also include the academic sector and its growing interests in global health education and research, foundations such as the Bill & Melinda Gates Foundation, an increasing number of public-private-partnerships (PPPs) including many that focus on product development needs for specific diseases, such as the Global Fund for AIDS, Tuberculosis and Malaria and the Global Alliance for Vaccines and Immunization, but also policy-focused initiatives such as the Alliance for Health Policy and

<sup>8</sup> Global collective action in health: The WDR+20 landscape of core and supportive functions, authored by Nathan Blanchet, Milan Thomas, Rifat Atun, Dean Jamison, Felicia Knaul, and Robert Hecht. Available at <http://globalhealth2035.org/sites/default/files/working-papers/global-collective-action-in-health.pdf>.

<sup>9</sup> Policy Cures 2012. G-FINDER 2012.

<sup>10</sup> Policy Cures 2012. G-FINDER 2012.

Systems Research to improve health policy and systems research as a way to improve the performance of the health system<sup>11</sup>.

### *Initiatives relevant to R&D at the global level*

The problem of how to ensure that global research and development (R&D) efforts meets the health needs of all, especially the specific health needs of the world's poorest or most neglected populations, has been on the international health agenda for decades (**Appendix 2: International Commissions, Intellectual Property, WHA Resolutions**).

In 1990, as the work to draft *WDR 1993* began, the Commission on Health Research for Development (CHRD) estimated that in 1986 out of US\$ 30 billion of health research worldwide, US\$ 1.6 billion was oriented to the needs of developing countries. Of this, US\$ 685 million was spent in and by developing country institutions, overwhelmingly funded by governments, and only eight countries accounted for 75% of this spending. The commission estimated that only 5%, or US\$ 1.6 billion, of total spending was devoted to the health problems of developing countries. They recommended that governments should spend 2% of their health budgets on what it called essential national health research and that donor nations should spend 5% of their aid for health in developing countries on research and the strengthening of research capacity.

#### **Commission on Health Research for Development (1990)**

The Commission on Health Research for Development (CHRD) concluded that “93% of the world’s burden of preventable mortality (measured as years of potential life lost) occurs in the developing world... [yet] only 5% [of research] was devoted specifically to health problems of developing countries...For each year of potential life lost in the industrialized world, more than 200 times as much is spent on health research as is spent for each year lost in the developing world.”

In 1996, the Ad Hoc Committee on Health Research Relating to Future Intervention Options published another careful study of spending on health R&D in 1992 estimating a figure of US\$ 2.4 billion (or 4.3% of global spending on health research). The committee proposed a global forum to bring donors and funders for health research together, resulting in the establishment of the Global Forum for Health Research in 1998<sup>12</sup>.

Motivated by, and simultaneous with these efforts, several commissions and working groups were established to examine ways to improve priority setting in global health R&D. Following the *WDR 1993*, the Commission on Macroeconomics and Health in 2001 emphasized the need for global knowledge to fight disease and explored various mechanisms for mobilizing resources and monitoring their use<sup>13</sup>. The Commission called for the establishment of a new Global Health Research Fund of US\$ 1.5 billion annually and for an equivalent increase in the amount of money going through existing channels to bodies such as WHO or public–private partnerships, making a total of US\$ 3 billion.

In response to the increasing awareness of the globalization and the relations between intellectual property rights, innovation and public health, WHO established the Commission on Public Health, Innovation and Intellectual Property Rights in 2003 (**Appendix 2. International Commissions, Intellectual Property, WHA Resolutions**). The WHO then established the Intergovernmental Working Group (IGWG) in 2006 which proposed a strategy and plan of action aimed at securing a sustainable basis for needs-driven, essential

<sup>11</sup> <http://www.gatesfoundation.org/>; <http://www.theglobalfund.org/en/>; <http://www.gavialliance.org/>; <http://www.who.int/alliance-hpsr/en/>.

<sup>12</sup> Ad Hoc Committee on Health Research Relating to Future Intervention Options. Geneva: WHO; 1996.

<sup>13</sup> Commission on Macroeconomics and Health. *Macroeconomics and health: investing in health for economic development*. Geneva: WHO; 2001.

health R&D relevant to diseases that disproportionately affect developing countries<sup>14</sup>. Building on the IGWG report, the WHO later established the Expert Working Group in 2008 to examine current financing and coordination of R&D and proposals for new and innovative sources of financing and stimulating global R&D<sup>15</sup>. The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPOA) was adopted by the sixty-first World Health Assembly (WHA) in 2008 and soon thereafter, Resolution WHA60.15 requested the Director General of the WHO to "submit to the sixty-second World Health Assembly (2009) a strategy on the management and organization of research activities within WHO." While the draft was postponed for discussion to the sixty-third WHA in 2010, the need for a more harmonized approach to R&D funding is finally gaining momentum with the publication of the WHO Consultative Expert Working Group (CEWG) report in 2012. The 2012 WHO Consultative Expert Working Group (CEWG) report concluded with a package of recommendations constituting a global framework for health needs-driven R&D to be implemented through a convention<sup>16</sup>. Recommendations included establishing working groups to synthesize information that can inform priorities, creating a mechanism for the funding and coordination of global health research and innovation and developing mechanisms to support and track research capacity building. At the 65th World Health Assembly (WHA) in 2012, WHO Member States called for an intergovernmental meeting to consider how to move forward in the three interlinked areas of coordination, financing, and monitoring<sup>17</sup>. Following deliberation at the WHO Executive Board in January 2013<sup>18</sup>, the CEWG resolution [A66/23] was approved at the 66<sup>th</sup> World Health Assembly<sup>19</sup>. The approved resolution contains three areas of action: establishing a global health R&D observatory, setting up demonstration projects, and developing norms and standards to better collect data on health R&D.

It is notable that in every major commission, working group report, and advisory committee described above, the critical need to focus on national capacity for R&D—along with the responsibility of the global community to support this effort—was emphasized. As early as 1990, CHRD recommended that “all countries should undertake essential national health research.” CHRD recommended that LMICs apply 2% of their total health budget (excluding the portion from external sources) to R&D<sup>20</sup>. Most recently, the CEWG recommended developing and developed countries invest 0.05–0.1% and 0.15–0.2% of GDP on total health R&D, respectively, and at least 0.01% on research on products to meet the specific health needs of developing countries<sup>21</sup>. While not a focus of this working paper, the authors emphasize that investment in research capacity for health is a critical priority—it is not addressed here purely for pragmatic reasons related to bounding the scope of what was possible to do in a finite time period.

<sup>14</sup> Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG). (2008). The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property. WHO, Geneva.

<sup>15</sup> Expert Working Group (EWG). (2008). R&D: Coordination and Financing. WHO, Geneva.

<sup>16</sup> Consultative Expert Working Group (CEWG). (2012). Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination. WHO, Geneva.

<sup>17</sup> WHO. (2012). Follow up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, WHA Resolution 65.22. WHO, Geneva.

<sup>18</sup> WHO. (2012). Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination. Report by the Director-General to the 132<sup>nd</sup> Session of the Executive Board. Paper EB132/21. WHO, Geneva.

<sup>19</sup> New W. Debate Erupts At WHO Over “Consensus” On Financing R&D For The Poor. Intellectual Property Watch. 2013. <http://www.ip-watch.org/2013/01/28/debate-erupts-at-who-over-consensus-on-financing-rd-for-the-poor/>.

<sup>20</sup> Commission on Health Research for Development. Health Research: Essential Link to Equity in Development. New York: Oxford University Press; 1990. p. 88.

<sup>21</sup> Røttingen JA, Regmi S, Eide M, Young AJ, Viergever RF, Ardal C, Guzman J, Edwards D, Matlin SA, Terry RF. Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory? *Lancet*. 2013 Oct 12;382(9900):1286-307.

## ACHIEVING CONVERGENCE

### *What R&D investments are needed to achieve ‘convergence’?*

For infectious diseases in the poor, how feasible is it to ‘close the gap’ (i.e. levels attained by the quartile of countries with the best health profiles) by 2035? Will currently available tools be adequate for disease-specific 2035 aspirations? Are there specific investments that would be most likely to be “game-changers”? Given the challenges associated with the lack of organized institutional structures, lack of governance of funding, and there being no formal process in the “global community” to prioritize investments for R&D across diseases, addressing the above questions is not straightforward.

Several major efforts have been completed in the last five years to identify research priorities for TB, malaria, HIV/AIDS, neglected tropical diseases, and childhood pneumonia and diarrheal diseases; Many of these represent major synthesis efforts, have engaged a broad range of experts and stakeholders, and have identified research gaps in basic science, product development, and implementation. However, there are two general limitations to these efforts. First, they are conducted by disease for the most part, and no mechanism exists to inform R&D investment decisions requiring tradeoffs between disease areas. Second, there is no overarching process that coordinates the collective results of these efforts across the plethora of global health funders. On the one hand, focusing on the unique challenges of each infectious disease has catalyzed scientific progress and has served to bridge and connect basic science and translational communities; on the other hand, priority setting within each of these domains occurs “by definition” within a single “disease silo” rather than across “silos.” The reality, however, is that resources need to be allocated both within, and across, disease areas. Furthermore, beyond the need to make choices and tradeoffs with regard to R&D investments, does the current format of available information and the processes by which the information is generated allow for identification of synergies, interdependence, and economies of scale between and across disease-specific efforts?

Leveraging major synthesis efforts referred to above, we sought to assess the ease with which priorities could be examined using currently available information. We conducted a series of searches on Google Scholar, Web of Science and PubMed to identify relatively recent (2005-present) reports (or peer-reviewed journal articles) that either focused on R&D or included a dedicated section to R&D. We complemented this search with specific documents relevant to priority setting for global health R&D (e.g. World Health Assembly meeting minutes and technical briefing notes) found on institutional websites of the WHO, UNICEF, UNAIDS, World Bank, the Global Fund to Fight AIDS, Tuberculosis and Malaria and the Bill & Melinda Gates Foundation. We selected 67 reports and peer-reviewed journal articles for inclusion in the exercise. We mapped information on disease-specific priorities to slightly modified categories used by the G-FINDER reports, since they are consistent with the five research activities described by the WHO (2008) as well as several major disease-specific priority reports, and allow us to relate information on funding to the results (**Appendix 3: Research Categories for R&D**). Final categories included basic science, diagnostics, drugs, vaccines, vector control, epidemiology, public health, implementation science, and innovative financing.

### *A Stylized Exercise*

We conducted a stylized exercise using a selected sample of reports to explore the feasibility of organizing and compiling *disease-specific* information for priority setting *across diseases* (**Appendix 4: Sources Reviewed for Identification of Existing R&D Priorities**). This working paper [**Working Paper 1**] focuses on basic science and targeted product development, including diagnostics, drugs, vaccines, microbicides and vector control products.

A companion working paper [**Working Paper 2**] looks at research areas identified as priorities in the domains of implementation and innovative financing [**Working Paper 2: “An Initial Scan of Priority Research Areas for Public Health, Implementation Science and Innovative Financing for Neglected Diseases”** by Jennifer S.

**Edge, Steven J. Hoffman, Cherie L. Ramirez, Sue J. Goldie].** The approach described below is applicable to the methods used in both working papers.





For each identified resource, we:

- Developed a summary document for each individual report or paper.
- Extracted R&D priorities from each report or paper.
- Subdivided between broad R&D goals and the specific activities needed to achieve them within each R&D topic area and compared findings across reports.
- Combined priorities extracted from each report into a disease-specific master document.

Below, we provide an example of each of the above mentioned steps using *PLoS Medicine's* collection entitled "malERA: a research agenda for malaria eradication" (2011).

For each identified resource, we:

- *Developed a summary document for each individual report or paper.*
  - We condensed the executive summary, methodology, key figures and all R&D related material from the *malERA* collection into a 31-page report overview (see **Working Paper 1 & 2 Supplementary Material: Part 1<sup>22</sup>**).
- *Extracted R&D priorities from each report or paper.*
  - We identified the core R&D focus areas and main research priorities discussed in each *malERA* chapter (see **Working Paper 1 & 2 Supplementary Material: Part 2**). Examples include:
    - Fundamental science research:
      - Key focus area of R&D: Better understand the stage-specific biology of the parasite
      - Main research priorities: Examine the entire parasitic life cycle-based approach to better understand transitions from one host to another; Distinguish essential metabolic pathways through systematic mutagenesis on a genome-wide scale
    - Diagnostic development:
      - Key focus area of R&D: Identify tools that can rapidly detect and monitor unexpectedly high transmission that lead to outbreaks and that can identify reintroduction of infections that may be asymptomatic
      - Main research priorities: Design antigen-detecting rapid diagnostic tests with greater consistency in *P. Falciparum* detection and stable tests to detect non-*P. Falciparum* parasites; Discover a robust, sensitive, and specific standardized method for assessment of transmission intensity in the intervening period when transmission continues at low levels.
- *Subdivided between broad R&D goals and the specific activities needed to achieve them within each R&D topic area and compared findings across reports.*
  - We listed the R&D goals and specific research activities in the *malERA* collection alongside the R&D-related priorities identified in other sources (see **Working Paper 1 & 2 Supplementary Material Part 3**. For additional samples, see **Secondary Supporting Background Material**).

<sup>22</sup> Working Paper 1 & 2 Supplementary Material and     are available at: <http://investinginhealth2035.org/working-papers>.

- Combined priorities extracted from each report into a disease-specific master document.
  - We identified where overlapping priorities existed between reports (e.g. goals and priorities that were identically stated or highly similar in their intent) and collated our findings into a malaria-specific summary document (see **Working Paper 1 & 2 Supplementary Material: Part 4**). Combined priorities for the rest of the disease areas examined are available in **Working Paper 1 & 2 Supplementary Material: Parts 5-8**.

**Table 2. Representative Sample of Disease-Specific Priority Efforts**

	Selected Resources Reviewed <sup>23</sup>	R&D Goals Identified as Priorities						
		Basic Science	Diagnostics	Drugs	Vaccines	Microbicides	Vectors	Total
Malaria*	14	26	24	22	15	N/A	14	<b>101</b>
Tuberculosis	10	31	47	18	51	N/A	N/A	<b>147</b>
HIV	15	31	11	25	31	9	N/A	<b>98</b>
Neglected Tropical Diseases**	11	18	22	21	24	N/A	21	<b>106</b>
Childhood Pneumonia and Diarrhea***	17	9	4	1	24	N/A	N/A	<b>38</b>
<i>Total</i>	<b>67</b>	<b>115</b>	<b>108</b>	<b>87</b>	<b>145</b>	<b>9</b>	<b>35</b>	<b>499</b>

\*Malaria includes: *plasmodium falciparum*, *plasmodium vivax*, others.  
 \*\*For NTDs, helminths include: roundworm (ascariasis), hookworm (ancylostomiasis & necatoriasis), whipworm (trichuriasis), lymphatic filariasis (elephantiasis), strongyloidiasis & other intestinal roundworms, onchocerciasis (river blindness), schistosomiasis (bilharziasis), tapeworm (cysticercosis/taeniasis); Kinetoplastids include: chagas disease, leishmaniasis, sleeping sickness; Other includes: dengue, leprosy, rheumatic fever, trachoma, & buruli ulcer.  
 \*\*\*For childhood pneumonia and diarrhea, diarrheal infections include: rotavirus, Enterotoxigenic *E. coli* (ETEC), cholera, *Shigella*, *Cryptosporidium*, Enteroaggregative *E. coli* (EAggEC), *Giardia*; Bacterial pneumonia & meningitis infections include: *Streptococcus pneumoniae* & *Neisseria meningitidis*.

**Table 2** shows results from a representative sample of disease-specific priority efforts. For example, for TB we reviewed 10 reports or papers, and after combining R&D priorities from each report, identified 31 for basic science, 47 for diagnostics, 18 for drugs and 51 for vaccines. If an identically worded R&D priority was included in multiple reports, it was only entered once.

Note that for this exercise we purposefully did not use disease-specific experts—rather we wanted to evaluate the results published by experts from the perspective of a non-scientific expert “hypothetically charged by a decision maker or policy maker” with organizing a priority setting exercise across disease areas.

Therefore, for the initial stage of analysis we elected not to collapse extracted priorities that were similar in context but differed in terms of how they were expressed or in the level of detail. Considering malaria, TB and HIV, neglected tropical diseases, and childhood pneumonia and diarrhea, there were approximately 500 individual R&D priorities stated.

<sup>23</sup> See **Appendix 4: Sources Reviewed for Identification of Existing R&D Priorities**.

**Comparison of disease-specific R&D priorities**

We did not identify any priority setting reports that attempted to assess the relative merits across R&D priorities for different diseases. A minority of reports did attempt to categorize R&D priorities within a single disease-specific area by selected attributes. For example, in 2011 a report was published describing the development of a comprehensive roadmap for global TB research<sup>24</sup>. The objective was to “identify the key research questions to achieve TB elimination by 2050, and thus the key areas in which to encourage investment, with a view to enhancing and harmonizing funding across the research spectrum and providing basis for better coordination of research.” Methods were based on a previously used tool in child nutrition and included “a several-stage Delphi technique, involving multidisciplinary stakeholders; a series of systematic reviews; an open web-based survey; and a clear, transparent, objectively measurable priority ranking exercise, conducted by a group of 50 multidisciplinary research experts.”

The report presented R&D priorities for the next 5–15 years, based on the criteria above, and proposed key questions related to the development of tools for improved TB control. After choosing those priorities that scored the highest on several attributes (efficacy and effectiveness, necessity, deliverability, equitability, and answerability), they estimated the timeframe (<5 years, 6-10 years, >10 years) and feasibility (moderate, good, excellent) for the remaining 53 priorities.

**Figure 3** shows the distribution of priorities according to timeframe and feasibility. Each priority is represented by a single shape (blue circles – basic science, gold squares – drugs, turquoise diamonds – diagnostics, green triangles – vaccines). Note that only 1 in 53 priorities for TB R&D was deemed to take longer than 10 years, and only 9 of the 53 priorities were deemed to have only moderate feasibility.

**Figure 3. Distribution of selected TB R&D priorities according to feasibility and timeframe**



<sup>24</sup> World Health Organization/Stop TB Partnership. An international roadmap for tuberculosis research: towards a world free of tuberculosis. Geneva: World Health Organization; 2011.

### *Assessment of information availability for priority setting analysis*

In general, based on our stylized exercise, we concluded the following:

1. An enormous amount of information has been generated from the substantial efforts to identify research priorities for TB, malaria, HIV/AIDS, neglected tropical diseases, and childhood pneumonia and diarrheal diseases, and reflects contributions across the entirety of the R&D space. That being said, the synthesized findings provided in reports were disease-specific the vast majority of the time.
2. There was virtually no synthesized information looking at both the entirety of the research spectrum *and* the entirety of the major neglected disease spectrum.
3. Since within the disease-specific efforts, the methods and the criteria used to differentiate the relative importance of different research questions varied extensively, compiling findings was enormously labor and time intensive and the ability to make meaningful comparisons was limited.

We assessed that it was currently not possible to conduct an analytically rigorous comparative exercise across different investment choices, within the context of the entire research spectrum *and* inclusive of all major neglected infectious diseases.

Given we would not be able to conduct a quantitative comparative analysis, we explored whether it might be possible to synthesize information across diseases in such a way as to provide insight into the information and format that would allow one to identify “synergies, interdependence, economies of scale” across disease-specific efforts.

### *Summarizing information to identify potential “synergies, interdependence, economies of scale”*

We used as our starting point for this exercise the master documents of disease-specific R&D priorities generated for the stylized exercise described earlier (**Working Paper 1 & 2 Supplementary Material: Parts 4-8**<sup>25</sup>). Within the domains of basic science, diagnostics, drugs, vaccines, microbicides, and vectors, a total of 499 specific research priorities were identified across malaria, HIV/AIDS, TB, NTDs, and CPD. For each disease-specific R&D priority, we determined how likely an advance in that priority would be likely to impact each of the other disease areas under consideration, whether because the R&D effort could hypothetically be carried out concurrently or because the discovery could be applied directly to efforts in another disease area.

Of the 499 priorities, we determined that 263 priorities had high potential for synergies beyond the original disease-specific priority area and that 185 priorities could yield findings of high potential relevance to all disease areas. From the list of 263 priorities, we grouped similar priorities into sets to allow us to more easily spot trends. To illustrate this process, we have provided the priorities that fall under the theme of “Develop and optimize technologies for point-of-care testing.” We identified 14 themes of opportunities for synergistic collaboration across multiple disease areas, which are summarized in **Box 2**.

While we hope our exercise to identify these common themes across disease-specific efforts may be a helpful starting point for discussions, we wish to emphasize here that due to various constraints in availability, consistency, and completeness of data as well as assumptions taken into account for this exercise, this should not be considered an exhaustive analysis. Even if using the same initial master documents of disease-specific R&D priorities and standardized methods were used for internal consistency on what constitutes “synergy,” there is still much room for experts to diverge or disagree. For instance, with the most ‘lenient’ of constraints, any priority could result in a high likelihood of synergy as conceivably any

<sup>25</sup> **Working Paper 1 & 2 Supplementary Material** is available for download at: <http://investinginhealth2035.org/working-papers>.

research finding could apply to any other. On the other hand, if each R&D priority is examined at face value only (for instance, with regard to a particular protein under study), then the opportunity to identify synergies among downstream applications of the knowledge or technique may be lost.

**Box 1. Example of R&D priority set related to “Develop and optimize technologies for point-of-care testing.”** The key for references is divided by disease area and can be found in **Appendix 4**.

R&D Area	Disease	R&D Priorities for Achieving Goals
Diagnostics	HIV	Research tools that will simplify and accelerate HIV testing (rapid point-of-care tests){E}
Diagnostics	HIV	Develop high-quality, cost-effective point of care (POC) CD4 testing options to reduce loss to follow-up for rural patients{J}
Diagnostics	HIV	Develop viral load testing methods that could be conducted at the point of patient care with assays meeting WHO’s ASSURED criteria and reduce the need for infrastructure and training for use{J}
Diagnostics	Malaria	Develop rapid and robust point-of-care glucose-6-phosphate dehydrogenase (G6PD) test to improve safety of 8-aminoquinoline use{E}
Diagnostics	Malaria	Design a multiplex point-of-care (POC) test that detects several common causes of fever at one time (e.g. malaria, dengue, and influenza) {L}
Diagnostics	TB	Design an improved sputum preparation process for Antigen detection, point-of-care tests and 16S rRNA testing{A}
Diagnostics	TB	Develop a simple and inexpensive test with at least as good a detection limit as direct microscopy 1x 10 <sup>4</sup> bacteria/ml for Antigen detection, point-of-care tests and 16S rRNA testing to reduce the workload of laboratory personnel{A}
Diagnostics	TB	Develop an indirect assay antibody detection point-of-care test that uses a simple ELISA or lateral flow format as an ideal test{A}
Diagnostics	TB	Determine whether NAATs can be successfully implemented at the point-of-care to enable same-day TB diagnosis and treatment (i.e. a “test and treat” approach){E}
Diagnostics	TB	Investigate the clinical effect and accuracy of the new point-of-care immune-chromatographic (dip-stick) assay that detects mycobacterial lipoarabinomannan in urine in different settings{G}
Diagnostics	CPD	Find ways to improve point-of-care diagnostic techniques{A}

**Box 2: Opportunities for synergistic progress to achieve R&D priorities across disease areas including malaria, HIV/AIDS, tuberculosis, neglected tropical diseases, and childhood pneumonia and diarrhea.**

**Basic Research and Fundamental Science**

- Improve understanding of innate, adaptive, and protective immunity and develop strategies for targeted stimulation
- Study expression and metabolic profiles of pathogens and/or hosts for identification of novel biomarkers for development of advanced diagnostics and treatments
- Develop improved animal models
- Analyze mechanisms that lead to drug resistance
- Investigate mechanisms of resistance to insecticides used for vector control

**Product Discovery and Development**

- Develop mucosally-targeted vaccines or treatments with novel delivery methods
- Optimize existing molecular diagnostics (e.g. test sensitivity/specificity, cost, ease of use) and develop tests for additional diseases and disease states
- Develop and optimize technologies for point-of-care testing
- Develop & optimize non-invasive testing methods (e.g. using urine, saliva, breath samples, etc.)
- Develop pediatric drug formulations & optimize drug treatment regimens in children
- Develop efficacious microbicides
- Investigate drug combinations to avoid development of drug resistance
- Develop and carry out clinical trial protocols on populations that have traditionally been more challenging to test (e.g. children)
- Improve means of collecting and sharing genetic sequence and clinical trial data across investigators and research efforts

## INSIGHTS

Identifying critical research gaps in basic science, product development, and implementation is necessary for making informed decisions about the most valuable investments to achieve convergence. We offer three insights from the work described in this paper, while simultaneously emphasizing the intended limited scope of these efforts.

**1. To facilitate the identification of critical research gaps and how to optimally address them, we need to—at a minimum—use consistent methods to extract data, solicit expert opinion, and synthesize results.**

The diverse knowledge needs of the heterogeneous players in R&D, from bench scientists to investors, present both challenges (e.g., diverse perspectives, lack common disciplinary language) and opportunities (e.g., discourse and deliberation - that might not otherwise happen - revealing unexpected connections or new ideas). In parallel with efforts to streamline R&D prioritization efforts by dedicated decision-making bodies, there is an urgent need to ensure results from such exercises are translated and disseminated 'equally' as knowledge-related public goods.

**2. Equally important is to reflect in our prioritization efforts those attributes that might differ between efforts located at different points on the research spectrum.** For example, in the case of basic science, it is not always possible to predict a priori what innovation and discovery will lead to a translational breakthrough. In fact, more often than not, “discoveries” catalyze progress as opposed to providing a specific completed product, and more often than not, “progress in fundamental science” does not result in a major paradigm shift but allows for incremental “smart” steps to build on existing knowledge and extend it, increasing the probability of new products and technologies. While “breakthroughs” and “game-changers” do indeed occur, they do so in the context of ongoing long-term research efforts and investments, many of which inevitably

fail. While it is hard to predict what would happen precisely, without ongoing major commitments to research at the fundamental basic level—linked to well-funded translational efforts that allow for iteration in addition to evaluation—it is fairly certain that scientific progress to improve health will slow or halt. Simply put, for every decade without continuing investments in R&D, the development of new and better technology for diagnostics, drugs, vaccines, and strategies to implement them, with improved or wider potential impacts on health, is also set back by a decade.

**3. The dynamic nature of science in the 21<sup>st</sup> century makes it ever more likely that there may be synergies across disease-specific efforts.** The availability of new methodological approaches such as genomics, proteomics, synthetic chemistry, materials science, molecular and genetic epidemiology, make it difficult to believe we would not find synergies across disease-specific efforts. In **Appendix 5**, we provide a very brief description of selected recent progress in vaccine research, genomics, and nanotechnology. For example, advances in nanotechnology may lead to the development of new drug and vaccine formulations with increased shelf-lives and resistance to temperature sensitivity, breakthroughs that could have an impact on prevention and treatment within numerous disease areas<sup>26</sup>. We will lose opportunities unless we continue to expand the breadth of investigative approaches, irrespective of disease focus. The “convergence of disciplines” we are witnessing in so many fields mandates that we find new ways to work across boundaries so we can maximize the gains from R&D investments.

We need an investment in “public goods” that could provide decision makers and investors (national and global) with an understanding of the relative value, probability and magnitude of significant “return” on alternative investment choices. While an evidence-based investment portfolio based on rigorous analytics would be ideal, it may or may not be possible to directly compare R&D across both the research stage spectrum *and* the individual disease spectrum for all the reasons mentioned above. That being said, a more anticipatory approach—and systematic process—to set priorities for research and development, undoubtedly would provide guideposts for deliberation, and allow for a much more nuanced and informed decision making process. Further, while not a guarantee, it would at least make transparency *possible*, setting the stage for a broader range of contributors to a discussion of priorities.

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<sup>26</sup> Chadwick S, Krieger C, Amiji M. Nanotechnology solutions for mucosal immunization. *Advanced drug delivery reviews*. 2010 Mar 18;62(4-5):394-407.

**Working Paper 2**

**An Initial Scan of Priority Research Areas for Public Health, Implementation Science and Innovative Financing for Neglected Diseases**

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## INTRODUCTION

The purpose of this working paper is to explore the feasibility of compiling and synthesizing *disease-specific* information to inform the deliberation and discourse on identifying priorities for research to improve health – with a specific focus on the dimensions of public health, implementation science and financing. This working paper is a companion to **Working Paper 1**, which focused on basic science and targeted product development, including diagnostics, drugs, vaccines, microbicides and vector control products [**Working Paper 1: “Priority Research Areas for Basic Science and Product Development for Neglected Diseases”** by Sue J. Goldie, Jennifer S. Edge, Christen Reardon, Cherie L. Ramirez].

## METHODS

Methods for identifying disease-specific extracted priorities are described in **Working Paper 1** (See “A Stylized Exercise”). Within the domains of public health, implementation science and innovative financing, a total of 543 specific research priorities were identified across the five disease areas. Of these priorities, 136 priorities were identified as opportunities for synergistic collaboration in R&D (96 in public health and implementation science, and 40 in innovative financing).

These 136 priorities were coded and collapsed into 17 priority areas for collaboration within R&D communities across HIV/AIDS, tuberculosis, malaria, NTDs, and childhood pneumonia and diarrhea.

Please note that the findings below reflect only the initial review, extraction, and synthesis of priorities identified in the domains of public health, implementation science, and innovative financing based on the reports reviewed for Working Paper 1. This paper is focused on applied research priorities that were identified within the context of a process that included the entire spectrum of research, from fundamental science to translation to implementation and financing. A more comprehensive analysis is currently underway.

## FINDINGS

### *Opportunities for Synergistic Research on Public Health and Implementation Science*

A total of 96 research activities were identified as common priorities across all disease areas and fell within 12 broad categories.

#### PUBLIC HEALTH AND IMPLEMENTATION RESEARCH

1. Develop new methods to evaluate and quantify the impact of new interventions (e.g. diagnostic, drug, vaccine, vector control and public health strategies), alternative control measures and combined strategies on rates of disease incidence, mortality and global burden
2. Find ways to scale-up global disease surveillance systems to fill current gaps of knowledge, particularly in the most endemic countries
3. Identify and evaluate how various biological, environmental, population-based and social factors influence infection rates
4. Develop methods to provide access to information, services and treatment coverage to the most at-risk and hardest-to-reach groups
5. Investigate ways to overcome health systems' human resource constraints on product development, lab capacity and service delivery
6. Assess the impact of, and determine how to best integrate, disease-specific interventions within existing health systems' capacity

7. Determine how to expand health systems research capacity through increased training, research and laboratory infrastructure, good clinical practice standards, general institutional capacities and strong national regulatory environments
8. Find ways to integrate quality assurance and user needs assessments into the R&D pipeline
9. Determine which actors should collaborate, and how, to regularly produce, review and verify target product profiles (TPPs) that can guide manufacturers' development specifications and suit country needs
10. Investigate linkages fully between specific diseases, sectors and other global health and development issues, and the contributions that new interventions and collaborations with key global networks could make to advance the global health and development agenda
11. Find ways to foster a culture of open innovation for sharing knowledge across different industries and sectors
12. Gather better data on the market for neglected disease R&D products (size, supply, demand, private and public sector variations) to reduce risk associated with investing in R&D

First, it was commonly identified that new methods to evaluate and quantify the impact of new interventions (e.g. diagnostic, drug, vaccine, vector control and public health strategies), alternative control measures and combined strategies (i.e. involving multiple interventions) on rates of disease incidence, mortality and global burden are urgently needed. This includes activities such as evaluating how assays with different speed, accuracy, price and technical specifications (e.g. which drugs) achieve the most desirable population-level health effects for the least cost, and what the trade-offs may be between different specifications. In the absence of such data, the relative impact of new interventions compared to alternative or conventional strategies remains unknown.

Second, research investigating how to scale-up global disease surveillance systems to fill current gaps of knowledge concerning the global burden of disease, and develop methods to give better global estimates was a common priority need across all disease areas. This was identified as particularly relevant in the most disease-endemic countries given the need to better identify the causes of low case detection and underreporting. Activities include developing tools to enhance monitoring capacity for real-time disease surveillance via collaboration with clinicians, and determining how to enable or strengthen health reporting systems' ability to monitor disease burden, incidence and treatment retention rates by patient age and gender.

Third, the need for research to better evaluate how various biological, environmental and social factors influence infection rates was common across all disease areas. This includes mustering better data on how the social and environmental determinants of health influence the spread and distribution of disease (e.g. processes involved in natural resource extraction and urban planning).

Fourth, collaboration in public health and implementation science was identified as crucial for learning how to rapidly scale-up the delivery of existing interventions using equitable and cost-effective approaches. Research into the development of new methods and tools is urgently needed to provide greater access to information and services, especially to the most at-risk and hardest-to-reach groups. This includes research to better understand disease transmission and patient health-seeking and provider behaviors in high-risk communities from theoretical, behavioral and social science perspectives. It also includes calls for determining why treatment discrepancies exist between urban and rural areas, and between wealth quintiles, in the uptake of various treatment programs (e.g. intermittent preventative treatment among pregnant women) in some countries, and how the approach for a more equitable scale-up of treatment can be replicated across countries.

Fifth, several priorities were related to how R&D efforts can enhance the performance of health systems in under-resourced, disease-endemic countries. For example, investigating ways to overcome health systems'

human resource constraints on product development, laboratory capacity and service delivery was a common priority across all disease areas. Assessing the impact of, and determining how to best integrate, disease-specific interventions and care programs within existing health systems' capacities was also identified as central to the successful scale-up of existing tools. This includes conducting urgently needed operational research to map out where individuals in the population seek care, where health care services are available, what resources (including laboratory capacity) exist at each level of health care, what fraction of patients with suspected infection access each level of health care, where treatment is available, and where technology deployment is likely to capture the largest fraction of patients with infection early in the infectious period.

Reports in all disease areas called for increased efforts towards expanding health systems' research capacity through developing mechanisms to increase training for health workers, research and laboratory infrastructure, clinical practice standards, general institutional capacities and/or strong national regulatory environments. This includes identifying methods to encourage LMICs to develop research priorities congruent with the burden of infectious diseases of poverty in their own populations, find ways to increase their own research activities to improve research leadership, and develop regional partnerships to build research infrastructure (including human resources and technical capacity). There were also calls for R&D to determine how to translate research into health strategies and create policies and development plans to guide national and international investments towards identified research priorities.

Reports in most disease areas called for increased research to determine how multi-stakeholder platforms for R&D can be coordinated to regularly produce, review and verify target product profiles that can guide manufacturers' development specifications and suit country needs. A key activity includes finding ways to bring public and private healthcare actors together to select the appropriate characteristics a product should possess to warrant its effective, widespread, and sustained use in local settings. Similarly, reports called for investigations to determine how to integrate quality assurance and user needs assessments into the R&D pipeline. The development of stronger incentives for upstream quality assurance (e.g. via site visits, stepped up lot testing, or changes to the WHO Product Testing program) was identified as a common priority across disease areas, as was the need to better define and evaluate the performance of new R&D products in terms of feasibility, cost-effectiveness, reduced diagnostic delay and impact on clinical decision-making and patient benefit.

Reports in all disease areas called for identifying mechanisms for fostering open innovation and knowledge sharing across different industries and sectors. This includes determining the best open-access models for the sharing of new knowledge and products, and the delivery of new interventions (e.g. designing a library of compounds with known infectious activity for academic research purposes). It also includes efforts to design and create an open innovation platform that brings together independent but cooperating agencies and consortia, including networks of researchers, community members and health workers that can help progress research, monitor health indices, undertake community audits and evaluation, better manage intellectual property and distribute financing. This was also correlated with numerous calls to gather better data on the market for neglected disease R&D products (e.g. size, supply, demand, private and public sector variations) to reduce donor risk associated with investing in R&D for neglected diseases.

Finally, the need to investigate mechanisms for strengthening linkages across specific disease communities, sectors and issues was a common priority. Reinforced relationships across diverse fields and disciplines were identified as key factors that could enhance the contributions made by new interventions to advance global health and the greater development agenda. This includes determining how to best involve sectors other than health in neglected disease research and control, including finance, education, agriculture, animal science, water, sanitation and environmental management. This could be established through the development of platforms for regular communication across sectors and industries, including integrated training modules and mechanisms for the exchange of information. The development of plans and strategies to overcome obstacles and risks to implementation (e.g. via the effects of natural disasters or conflict that results in the displacement of millions of people) was also identified as a priority across R&D communities in

all disease areas. Determining the short- and long-term economic costs of neglected disease burden on health and non-health industries such as education, trade, agriculture, livestock and tourism was also identified as a common priority area for R&D to encourage intersectoral participation in disease control and prevention.

### *Opportunities for Synergistic Research on Innovative Financing*

The 40 activities identified as priorities for R&D in innovative financing fell within 5 broad categories for synergistic collaboration.

#### **INNOVATIVE FINANCING**

1. Find innovative ways to reduce duplication and improve coordination of R&D financing by integrating goals and reducing overlap
2. Find ways to utilize innovative financing streams and regulatory tools to increase the availability of treatment options
3. Develop innovative funding platforms, incentive structures and mechanisms to engage/coordinate new partners in R&D for global health
4. Create innovative funding streams that link through a central clearinghouse for information regarding targets or compounds related to neglected disease research, funding sources, and services and skills offered to reduce risk and incentivize investments in R&D
5. Find ways to generate and sustain investments in the full spectrum of R&D for discovery, product development and implementation

First, a common priority was the need to find innovative ways of reducing duplication and improving coordination of R&D financing by integrating goals and reducing overlap. Activities related to this category include evaluating existing options to improve the coordination of priorities for action and harmonize approaches to R&D funding (e.g. using the proposed model of the WHO Consultative Expert Working Group on Research & Development: Financing & Coordination). This also includes developing methods to resolve issues related to the separation of the ultimate funders of R&D, recipients of funds, and intermediaries such as PDPs.

Second, determining how to utilize innovative financing streams and regulatory tools to increase the availability of treatment options in disease-endemic countries was identified as a common priority for R&D. Included in this second category were activities striving to develop methods to accurately anticipate demand, increase purchasing power through pooled procurement to reduce prices, or provide incentives to increase robust competition to ensure accessibility of quality treatment interventions.

Third, development of innovative funding platforms, incentive structures and mechanisms to engage and coordinate new partners in R&D for global health was a common priority. Activities identified under this category include identifying public-private partnerships (PPPs) that are willing to commit to a long-term funding mechanism (the entirety of the R&D process) and industry partners willing to collaborate with PPPs for neglected disease drug development. It also includes evaluating the potential for pooled funding mechanisms to encourage collaboration between academia, private industry, PDPs and PPPs for global health R&D, and investigating possible funding streams (e.g. incentives for G8 countries) to support the creation of pooled funding mechanisms that would provide secured funding to select PDPs.

Fourth, research on the design and operationalization of innovative funding streams that could link through a central clearinghouse for information regarding targets or compounds related to neglected disease research, and existing funding sources, services and skills was identified as a critical priority area that could yield benefits across diseases. Activities under this category include creating an easily accessible, online global platform that supports a database and detailed analysis of resources and financial investment in

health research that can provide policymakers, funders and researchers with information they need to guide their activities, identify funding gaps and mitigate duplicated efforts.

Finally, it was universally acknowledged that finding ways to generate and sustain long-term investments in discovery, development and delivery was critical to future R&D efforts of all disease areas. Activities supported in this R&D area include determining how to foster novel domestic resource streams for disease control (e.g. assessing the sustained funding potential of tourist taxes, community health insurance schemes, prize-linked savings, and modifications to national tax codes, endowment funds, and national health solidarity funds) and evaluating different approaches to overcoming financial barriers to R&D, such as research on the comparative effects of conditional cash transfers, vouchers and social insurance initiatives for households, or loan guarantees and fiscal strategies to encourage investment in infrastructure. It also includes developing innovative financing schemes to increase funding for operational research, support for research capacity-building, and a broader class of research activities that explore aspects of behaviour, economics, politics, trade and the environment as they apply to infectious diseases of poverty, along with means to monitor the impact of such funding.

## LIMITATIONS

Please note that the findings reported in this working paper reflect only the initial review, extraction, and synthesis of priorities identified in the domains of public health, implementation science, and innovative financing based on the reports that included the entire spectrum of research, from fundamental science to translation to implementation and financing. A more comprehensive analysis is currently underway.

**APPENDIX 1: EXPANDED VERSION: MAIN RECOMMENDATIONS OF WDR 1993**

*WDR 1993* pointed out the central role of governments in supporting essential national health research such as standardizing and financing the collection, analysis, and dissemination of health information (to guide program design, health policies and public spending); collecting and synthesizing epidemiological and other information necessary to monitor health status, detect disease outbreaks (i.e., surveillance), and guide public policy; conducting research on variations in clinical practice, equity, consumer satisfaction, and women's health. Several specific examples were provided, including improving research capacity through monitoring and evaluation at the district and facility levels. Suggestions were made to provide consumers, health researchers, and communities with information about the quality of care given by providers, both public and private, and about variations in medical practice.

*WDR 1993* suggested the international community had an important role in R&D which included supporting the collection of data for international comparisons, as well as studies that would target national action but require funding from a global community (e.g. standardized household survey programs). The report emphasized assisting local institutions to build capacity in epidemiology, health economics, health policy, and management including supporting international partnerships or networks; catalyzing technological development through basic research and product development, including (but not limited to) providing incentives to the commercial sector for developments related to diseases of the poor.

The *WDR 1993* suggested priorities for research for conditions that make the largest contributions to the global burden of disease, advocating for greater investment in research and product development if the disease burden is large, if no cost-effective interventions exist, and if experts believe that such interventions might be developed. They cited the priority of inexpensive, simple, and reliable diagnostics for respiratory infections as a good example of one meeting these criteria.

The *WDR 1993* generally advocated for greater investment in program development and operational research to guide implementation for problems that create a large burden of disease and for which cost-effective interventions already exist. They cited the example of intestinal parasitic worms posing questions such as “how can local programs be best designed to reach children? How can involvement of school officials be fostered?” *WDR 1993* pointed out that solutions to these problems are not universal and require contextualization and local engagement.

**Illustrative excerpt from *WDR 93*:** “Possible improvements in vaccine technology would reduce multidose vaccines to a single dose, improve the heat stability of vaccines, simplify administrative requirements (to permit greater use of oral vaccines as compared with injections, for example), create new combinations of vaccines to reduce patient contacts, integrate new vaccines into the immunization schedule, permit vaccination earlier in life to reduce infant deaths caused by vaccine-preventable diseases, and add to the menu of interventions new vaccines—for example, against diarrhea and pneumonia” (p.153).

**Illustrative excerpt from *WDR 93*:** *Another priority area for research and development is the development of low-cost and efficient diagnostic technologies for use in health centers in developing countries where sophisticated laboratories are unavailable. Examples of potentially important new technologies are visual methods of screening for cervical cancer, rapid plasma finger-stick diagnostic tools for syphilis, and new diagnostic tests for malaria for use at the local level. Rapid diagnostic tests avoid reliance on other levels of the health system because the health center, if supplied with the necessary drugs, can treat the problem on the spot. Innovations in medical equipment to reduce the cost or improve the effectiveness of preventing and treating problems at the health center level are high priorities for research and development.*

**Illustrative excerpt from WDR 1993 recommending specific top-burden investment targets:**

Tuberculosis	Methods of ensuring compliance; monitoring tools for drug resistance; simpler diagnostics; new/cheaper drugs
Diphtheria, polio, pertussis, measles, tetanus	Development of new and improved vaccines to reduce patient contacts, permit immunization at younger ages, and improve heat stability of some vaccines
Diarrheal diseases	Rotavirus & enterotoxigenic <i>E. coli</i> vaccines; improved cholera vaccine; improving hygiene and case management of persistent diarrhea; diarrhea prevention by breastfeeding promotion/improved weaning practices
Respiratory infections	Impact of indoor air pollution on pneumonia (to guide interventions such as improved stoves); inexpensive or simplified antibiotic regimens; inexpensive, simple, reliable diagnostics; pneumococcal vaccine
Perinatal & maternal causes	Methods of lowering costs of intervention and improving delivery in rural areas
Ischemic heart & cerebrovascular disease	Low-cost prevention, diagnosis, and management methods

The *WDR 1993* emphasized the importance of building capacity for research in countries, both from the perspective of deserving international support and the responsibility of national governments to invest in R&D. The report commented on the importance of developing partnerships across sectors, including commercial entities, national governments, scientists, and NGOs, to support research and drug development for diseases of the poor.

The *WDR 1993* highlighted in several of the above the importance of considering issues relevant to women, ranging from the disproportionate consequences of neglected tropical diseases on women, the need for clinical trials to more effectively include women and address gender-specific questions, and the need to design contextually-relevant gender-specific solutions.

**Illustrative excerpt from WDR 93:** *“Women spend up to half of their reproductive lives pregnant or lactating. Many protocols for treating tropical diseases exclude these women and sometimes even large numbers of women who might be pregnant (such as adolescent girls). Blanket exclusion of pregnant or lactating women has been the result not of clear evidence of problems but of reluctance to carry out appropriate drug trials on pregnant women. There is an urgent need to evaluate drug treatments for such women so that health services can offer them better treatment. This is part of a much broader problem of the common omission of women from medical studies and clinical trials in both developing and industrial countries.”*

**Illustrative excerpt from WDR 93:** *“This Report recommends that concerted efforts be made to develop or strengthen effective programs for control of STDs. Such efforts will be hampered by the challenges of diagnosing STDs, particularly in women, for whom the vast majority of infections are asymptomatic. Current methods are often unreliable and expensive, and their use requires refrigeration, electricity, and sophisticated equipment and training. In addition, certain tests require patients to return in one or two days, which is not feasible when, as is often the case, the patient must travel a long distance to receive health care. Even if patients return, the period of infectivity is prolonged by this delay in therapy. Syndromic-based approaches to treating STDs are currently being used to bridge this gap and are effective for men. For women, however, these approaches are less accurate.”*

**APPENDIX 2: INTERNATIONAL COMMISSIONS, INTELLECTUAL PROPERTY, WHA RESOLUTIONS**

**Since 1993: Selected International Health Commissions and Reports**

**Since 1993: Major International Health Commissions & Reports**

<p>Commission on Health Research for Development: "Health Research: Essential Link to Equity in Development" (1990)</p>	<p>World Development Report: "Investing in Health" (World Bank) (1993)</p>	<p>Ad hoc Committee on Health Research Relating to Future Intervention Options "Investing in Health Research &amp; Development" (WHO) (1996)</p>	<p>Commission on Macroeconomics and Health: "Macroeconomics and Health: Investing in Health for Economic Development" (WHO) (2001)</p>

**Since 1993: Selected Commissions on Health and Intellectual Property**

**Since 1993: Major Commissions on Health & Intellectual Property**

<p>Commission on Intellectual Property Rights: "Integrating IPR and Development Policy" (UK) (2002)</p>	<p>Commission on Intellectual Property Rights, Innovation &amp; Public Health: "Public Health, Innovation and IP 'rights'" (WHO) (2006)</p>	<p>Expert Working Group On Research and Development: Financing and Coordination (WHO) (2010)</p>	<p>Consultative Expert Working Group on R&amp;D: Financing and Coordination (WHO) (2012)</p>

## Since 1993: Selected WHA Resolutions Relevant to R&D

### Since 1993: Relevant WHA Resolutions

- 1996 WHA49.14: Revised drug strategy -1999, WHA52.19: Revised drug strategy
- 2000 WHA53.14: HIV/AIDS: confronting the epidemic
- 2001 WHA54.10: Scaling up the response to HIV/AIDS
- 2001 WHA54.11: WHO medicines strategy
- 2002 WHA55.14: Ensuring accessibility of essential medicines
- 2003 WHA56.27: Intellectual property rights, innovation and public health
- 2003 WHA56.30: Global health sector strategy for HIV/AIDS
- 2004 WHA57.14: Scaling up txt/care within coordinated & compresponse to HIV/AIDS
- 2006 WHA59.24: Public health, innovation, essential health research & IP rights
- 2006 WHA59.26: International trade and health
- 2007 WHA60.30: Public health, innovation and intellectual property
- 2008 WHA61.21: Global strategy & plan of action on public health, innovation and IP
- 2009 WHA62.16: Global strategy & plan of action on public health, innovation and IP
- 2011 WHA64.5: Pandemic influenza preparedness: sharing influenza viruses & access to vaccines
- 2011 WHA64.14: Global health sector strategy on HIV/AIDS, 2011-2015
- 2012 WHA65.22: Expert Working Group on R&D Financing and Coordination

### COMMISSION ON HEALTH RESEARCH FOR DEVELOPMENT<sup>27</sup>

The Commission on Health Research for Development included a review of the research literature over 24 months plus case studies in 10 developing countries, eight Commission meetings, meetings with WHO and UNICEF staff, multi-stakeholder regional workshops in Bangladesh, Zimbabwe, Brazil, Egypt and Mexico.

In 1990 the Commission on Health Research and Development (CHRD) estimated, on the basis of its own survey, that in 1986 out of US\$ 30 billion of health research worldwide, US\$ 1.6 billion was oriented to the needs of developing countries. Of this, US\$ 685 million was spent in and by developing country institutions, overwhelmingly funded by governments, and only eight countries accounted for three quarters of this spending. The balance of US\$ 950 million was provided by developed countries, of which industry contributed an estimated US\$ 300 million and governments (including through development assistance) contributed US\$ 590 million. Foundations and NGOs contributed just US\$ 60 million. The commission estimated that only 5%, or US\$ 1.6 billion, of total spending was devoted to the health problems of developing countries.

In 1990 the Commission on Health Research and Development (CHRD) estimated “93% of the world’s burden of preventable mortality (measured as years of potential life lost) occurs in the developing world... [yet] only 5% [of research] was devoted specifically to health problems of developing countries...For each year of potential life lost in the industrialized world, more than 200 times as much is spent on health research as is spent for each year lost in the developing world.”

In 1990 the Commission on Health Research and Development (CHRD) recommended that governments should spend 2% of their health budgets on what it called essential national health research and that donor nations should spend 5% of their aid for health in developing countries on research and the strengthening of

<sup>27</sup> Commission on Health Research for Development. Health Research: Essential Link to Equity in Development. New York, Oxford University Press, 1990.

research capacity. Specifically, (1) All countries should undertake essential national health research, (2) National efforts in developing countries should be supported by international partnerships that mobilize global scientific capacity towards highest-priority health problems, (3) Larger and sustained financial support from international sources needed, (4) An international monitoring system should be established to track progress.

#### **AD HOC COMMITTEE ON HEALTH RESEARCH RELATING TO FUTURE INTERVENTION OPTIONS<sup>28</sup>**

The Ad Hoc Committee on Health Research Relating to Future Intervention Options included a review of health needs and related priorities for R&D in LMICs.

In 1996, the Ad Hoc Committee on Health Research Relating to Future Intervention Options published another careful study of spending on health R&D in 1992. It calculated that total global investment had increased to US\$ 55.8 billion. It estimated that governments accounted for US\$ 28.1 billion of this expenditure, of which governments in developing countries provided US\$ 1.2 billion. The pharmaceutical industry contributed US\$ 24.7 billion, and the not-for profit sector US\$ 3 billion. The report also sought to estimate the amount of this spending devoted to the health problems of developing countries. Using a variety of approaches, it concluded that the amount was US\$ 2.4 billion (or 4.3% of global spending on health research). Of this amount, developing country governments spent US\$ 1.2 billion, US\$ 680 million came from developed country governments (of which US\$ 380 million was through development assistance), US\$ 400 million came from the pharmaceutical industry and US\$ 80 million from non-profit organizations.

Four key challenges the committee noted included (1) Traditional threats to maternal and child health, (2) Microbial evolution, (3) Emerging epidemics of non-communicable diseases, (4) Improving efficiency and equity in delivery of health services at the national level. The committee suggested a five step process: (1) Calculate global burden attributed to disease/condition, (2) Identify reasons for the persistence of the burden, (3) Judge adequacy of the current knowledge base, (4) Assess the promise of the R&D effort, (5) Assess current level of effort.

#### **COMMISSION ON MACROECONOMICS AND HEALTH**

The Commission on Macroeconomics and Health included extensive research and consultations conducted in two years, especially by the work of six Working Groups, which in total produced 87 background studies and six synthesis monographs. Hundreds of participants joined the analytical process. Commission was established by WHO under Brundtland and chaired by Jeff Sachs.

In 2001, the Commission on Macroeconomics and Health called for the establishment of a new Global Health Research Fund of US\$ 1.5 billion annually and for an equivalent increase in the amount of money going through existing channels to bodies such as WHO or public-private partnerships, making a total of US\$ 3 billion. As noted above, total public funding from developed countries has increased significantly but currently amounts to less than US\$ 2 billion annually. [The proposal for a Global Health Research Fund was not pursued when it was first proposed, but the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property considered in its deliberations in 2007 and 2008 the possibility of establishing a similar fund. This proposal did not encounter sufficient support, and the compromise reached was to recommend establishing the Expert Working Group.]

Recommendations included (1) LMICs should scale up access to essential health services and focus on specific interventions in partnership with high-income countries, (2) A global strategy for operational research

<sup>28</sup> Ad Hoc Committee on Health Research Relating to Future Intervention Options, Investing in health research and development, Geneva, 1996 (Document TDR/Gen/96.1).

regarding treatment protocols in low-income countries, (3) Investment in new and improved technologies to fight killer diseases of the poor, and (4) Endorsement of the Poverty Reduction Strategy Paper (PRSP) framework mechanism for donor financing.

Four main criteria in choosing these essential interventions were (1) Technically efficacious and can be delivered successfully, (2) Targeted diseases should impose a heavy burden on society, taking into account individual illness as well as social spill-overs (such as epidemics and adverse economic effects), (3) Social benefits should exceed costs of the interventions (with benefits including life-years saved and spill-overs such as fewer orphans or faster economic growth), (4) The needs of the poor should be stressed.

#### **COUNCIL ON HEALTH RESEARCH FOR DEVELOPMENT (COHRED)**

The Council on Health Research for Development (COHRED), founded in 1993 as the successor to the Commission's Task Force, has championed the evolution of Essential National Health Research (ENHR) and has supported work in more than 60 countries on the organization and prioritization of research to underpin health systems. COHRED's work on ENHR has stimulated greater attention to resourcing, managing and prioritizing health research and has led to the evolution of the concept of national health research systems (NHRS) as a comprehensive framework within which to analyze, develop and strengthen the capacities of countries to determine health research priorities and to decide on how to address them.

**APPENDIX 3: RESEARCH CATEGORIES FOR R&D**

WHO(2008)	Example of Framework used in Disease-Specific Effort TB Research Priority Effort (2011)			G FINDER (2012)	
Measuring the problem	➔	Epidemiology		Fundamental research	Basic research
Understanding its cause(s)	➔	Basic or fundamental research		R&D of new diagnostics	Product development <i>Diagnostics</i> <i>Drugs</i> <i>Vaccines</i> <i>Microbicides</i> <i>Vector control</i>
Elaborating solutions	⌋	R&D of new tools (diagnostics, drugs, vaccines)		R&D of new drugs	
Evaluating effectiveness of solutions	⌋			R&D of new vaccines	
Translating the solution(s) or evidence into policy, practice, products	➔	Operational research		Epidemiology, operational research & public health	Implementation research

There is currently no internationally agreed and recommended research classification system, in large part because reports generally focus on an aspect of research rather than the entire continuum. In 2008, WHO proposed a framework for describing research priorities covering five generic areas of activity: (1) measuring the problem; (2) understanding its cause(s); (3) elaborating solutions; (4) translating the solution(s) or evidence into policy, practice and products; and (5) evaluating the effectiveness of solutions (left column)<sup>29</sup>.

An example of research groupings used by a disease-specific priority report in TB is shown in the middle two columns). They outlined four general areas of TB research that cover the whole spectrum: (1) epidemiology (measuring the problem); (2) basic or fundamental research (understanding its causes); (3) research, development and evaluation of new tools, i.e. diagnostics, drugs and vaccines (elaborating solutions and evaluating the effectiveness of the solutions); (4) operational research (translating the solutions into practice, including better design of health systems and preparation of algorithms with existing and new tools). They chose to group epidemiological questions with public health and operational research questions but differentiated the control tools (shown in blue, third column from the left). Similar categories are used by G-FINDER<sup>30</sup> (shown in green, far right column), with the exception of two additional subcategories of microbicides and vector control products. Definitions used by G Finder may be found below.

BASIC RESEARCH AND FUNDAMENTAL SCIENCE*	
	<b>Basic research</b> “encompasses studies into the etiology of a disease or studies that increase scientific knowledge and understanding of a disease, disease processes or the pathogen or vector. They are not yet directed towards a specific intervention, product or health technology.” (G Finder, 2012) *

<sup>29</sup> World Health Organization/Stop TB Partnership. An international roadmap for tuberculosis research: towards a world free of tuberculosis. Geneva: World Health Organization; 2011.

<sup>30</sup> G-FINDER 2012. Moran M, Guzman J, Henderson K, Liyanage R, Wu L, Chin E, Chapman N, Abela-Oversteegen L, Gouglas D, Kwong D. Neglected Disease Research And Development: A Five Year Review. Policy Cures December 2012.

	<b>Fundamental research</b> includes “experimental or theoretical work that aims to acquire new knowledge of the underlying phenomena and observable facts without any particular application or use in view” (Australian Research Council).
<b>PRODUCT DISCOVERY AND DEVELOPMENT**</b>	
	“Product development constitutes a second category of research and is characterized by the discovery and development of new products and interventions (including drugs, vaccines, diagnostics and vector control tools). This includes research activities and processes (including clinical trials) necessary to develop and improve new compounds or devices specifically designed to prevent, diagnose, treat or cure infectious diseases of poverty.” (G Finder, 2012) *
	<b>DIAGNOSTICS</b> “Research activities and processes necessary to develop, optimise, and validate diagnostic tests for use in resource-limited settings (cheaper, faster, more reliable, ease of use in the field); including discovery and design, preclinical and clinical evaluation, and other activities essential for successful deployment for public health use.” (G Finder, 2012) *
	<b>DRUGS</b> “Research activities and processes necessary to develop and improve new compounds specifically designed to cure or treat neglected diseases; including drug discovery or design, preclinical and clinical development and other activities essential for successful drug development and uptake” (G Finder, 2012) *
	<b>VACCINES</b> “Research activities and processes necessary to develop and improve investigational vaccines intended <b>to prevent or treat infection</b> ; including vaccine design, preclinical and clinical development and other activities essential for successful vaccine development and uptake.***” (G Finder, 2012) *
	<b>MICROBICIDES</b> “Research activities and processes necessary to develop and improve topical microbicides specifically intended to prevent HIV transmission; including microbicide discovery or design, preclinical and clinical development, and other activities essential for successful microbicide development and uptake.” (G Finder, 2012) *
	<b>VECTOR CONTROL</b> “This includes chemical pesticides to inhibit and kill vectors associated with transmitting poverty-related diseases, biological control products to kill or control vectors such as microbial/ bacteriological larvicides, sterilisation techniques, genetic modification measures, and veterinary vaccines targeting animal reservoirs to prevent animal to human transmission of neglected diseases.” (G Finder, 2012) *
<b>IMPLEMENTATION RESEARCH OR OPERATIONAL RESEARCH***</b>	
	Implementation research includes the “development of delivery mechanisms for existing and new products, including interventions aimed at the broader health system to decrease the burden of infectious diseases of poverty).” (G Finder 2012)
* includes immunology of disease, biology of disease, biochemistry of the pathogen, genetics of the pathogen, bioinformatics and proteomics, pathophysiology and disease symptoms, vector biology, biochemistry and genetics, epidemiology and natural history (G Finder, 2012) *	
**G Finder categorizes preventive and therapeutic vaccines separately	

**APPENDIX 4: SOURCES REVIEWED FOR IDENTIFICATION OF EXISTING R&D PRIORITIES****Malaria:**

- A. Program for Appropriate Technology in Health (PATH). *Staying the Course? Malaria Research and Development in a Time of Economic Uncertainty*. Seattle: PATH; 2011.
- B. Moran M, Guzman J, Ropars A, Jorgensen M, Potter S, Selassie H. *The Malaria Product Pipeline: Planning for the Future*. Sydney: The George Institute for International Health/Global Forum for Health Research; 2007.
- C. World Health Organization. *World Malaria Report 2012*. Geneva: World Health Organization; 2012.
- D. World Health Organization Global Malaria Programme. "Global Plan for Insecticide Resistance Management in Malaria Vectors." Geneva: World Health Organization; 2012.
- E. PLOS Medicine. "malERA: a Research Agenda for Malaria Eradication." Barcelona, Spain: The Barcelona Centre for International Health Research; 2011.
- F. European Commission. *Final Report: Challenges for the Future Research on HIV/AIDS, Malaria, and Tuberculosis*. Luxembourg: European Communities; 2009.
- G. Evidence to Policy Initiative. *Maintaining the Gains in Global Malaria Control: the Health and Economic Benefits of Sustaining Control Measures*. San Francisco: University of California San Francisco; October 2011.
- H. Policy Cures. *Saving Lives and Creating Impact: EU Investment in Poverty-Related Disease*. London: Policy Cures London; October 2012.
- I. Berger M, Murugi J, Buch E, IJsselmuiden C, Kennedy A, Moran M, Guzman J, Devlin M, Kubata B. *Strengthening pharmaceutical innovation in Africa*. Council on Health Research for Development (COHRED)/New Partnership for Africa's Development (NEPAD); 2009.
- J. The George Institute for International Health. *Registering New Drugs: The African Context*. London; The George Institute for International Health, January 2010.
- K. Moran M, Ropars A, Guzman J, Diaz J, Garrison C. *The New Landscape of Neglected Disease Drug Development*. London: The London School of Economics and Political Science; 2005.
- L. UNITAID. *Malaria Diagnostic Technology Landscape*. World Health Organization; Dec 2011.
- M. UNITAID. *Malaria Diagnostics Market Landscape*. World Health Organization; Dec 2012.
- N. World Health Organization/Foundation for Innovative New Diagnostics/Centers for Disease Control/Special Programme for Research and Training in Tropical Diseases. *Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs: round 4*. Geneva: World Health Organization; 2012.

**TB:**

- A. New diagnostics working group of the Stop TB Partnership. *Pathways to better diagnostics for tuberculosis: a blueprint for the development of TB diagnostics*. Geneva: World Health Organization; 2009.
- B. World Health Organization. *Global Tuberculosis Report 2012*. Geneva: World Health Organization; 2012.
- C. World Health Organization/Stop TB Partnership. *An international roadmap for tuberculosis research: towards a world free of tuberculosis*. Geneva: World Health Organization; 2011.
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- E. UNITAID. *Tuberculosis: Diagnostic Technology Landscape: Semi-Annual Update*. Geneva: World Health Organization; Dec 2012.
- F. UNITAID. *Tuberculosis: Medicines Technology Landscape*. Geneva: World Health Organization; 2012.
- G. Lawn S, Mwaba P, Bates M, Piatek A, Alexander H, Marais B, et al. *Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test*. *Lancet Infect Dis*. 2013;13:349-361.
- H. Wallis R, Kim P, Cole S, Hanna D, Andrade B, Maeuer M, et al. *Tuberculosis biomarkers diversity: developments, needs and challenges*. *Lancet Infect Dis*. 2013;13:362-372.

- I. Wells W, Boehme C, Cobelens F, Daniels C, Dowdy D, Gardiner E, et al. Alignment of new tuberculosis drug regimens and drug susceptibility testing: a framework for action. *Lancet Infect Dis*. 2013. Available from: [http://dx.doi.org/10.1016/S1473-3099\(13\)70025-2](http://dx.doi.org/10.1016/S1473-3099(13)70025-2).
- J. Brennan P, Robertson B. *Tuberculosis vaccines: a strategic blueprint for the next decade*. Elsevier. 2012. 92(1):S1-S35.

**HIV:**

- A. Joint United Nations Programme on HIV/AIDS (UNAIDS). *UNAIDS Report on the Global AIDS Epidemic*. Geneva: UNAIDS; 2012.
- B. Joint United Nations Programme on HIV/AIDS (UNAIDS). *World AIDS Day Report 2012*. Geneva: UNAIDS; 2012.
- C. European Commission. *Final Report: Challenges for the Future Research on HIV/AIDS, Malaria, and Tuberculosis*. Luxembourg: European Communities; 2009.
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- E. Smelyanskaya, Marina. *Global Investments in HIV Treatment Research and Development in 2010 and 2011*. New York: Treatment Action Group (TAG); March 2013.
- F. Policy Cures. *Saving Lives and Creating Impact: EU Investment in Poverty-Related Disease*. London: Policy Cures London; October 2012.
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- I. Moran M, Ropars A, Guzman J, Diaz J, Garrison C. *The New Landscape of Neglected Disease Drug Development*. London: The London School of Economics and Political Science; 2005.
- J. UNITAID. *HIV/AIDS Diagnostic Technology Landscape*. 2<sup>nd</sup> Edition. Geneva: World Health Organization; 2012.
- K. UNITAID. *HIV/AIDS Diagnostic Technology Landscape: Semi-Annual Update*. Geneva: World Health Organization; Oct 2012.
- L. Murtagh M. *UNITAID Technical Report: HIV/AIDS Diagnostic Landscape*. Geneva: World Health Organization; July 2011.
- M. UNITAID. *2011 HIV/AIDS Diagnostic Technology Landscape: Semi-Annual Update*. Geneva: World Health Organization; Oct 2011.
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- B. World Health Organization. *Sustaining the drive to overcome the global impact of neglected tropical diseases*. Second WHO report on neglected tropical diseases. Geneva: World Health Organization; 2013.

- C. World Health Organization. Research Priorities for Zoonoses and Marginalized Infections. Technical Report of the TDR Disease Reference Group for Zoonoses and Marginalized Infections. Technical Report Series No. 971. Geneva: World Health Organization; 2012.
- D. World Health Organization. Research Priorities for Chagas Disease, Human African Trypanosomiasis and Leishmaniasis. TDR Disease Reference Group for Chagas Disease, Human African Trypanosomiasis and Leishmaniasis. Technical Report Series No. 975. Geneva: World Health Organization; 2012.
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- F. Karesh W, Dobson A, Lloyd JO, et. al. Ecology of zoonoses: natural and unnatural histories. *Lancet*. 2012; 380:1936-45.
- G. Kilpatrick A, Randolph S. Drivers, dynamics, and control of emerging vector-borne zoonotic diseases. *Lancet*. 2012; 380:1946–55.
- H. Morse S, Mazet J, Woolhouse M, Parrish C, Carroll D, Karesh W, et al. Prediction and prevention of the next pandemic zoonosis. *Lancet*. 2012; 380:1956-65.
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- K. Glassman A, Chalkidou K. Priority setting in health: Building institutions for smarter public spending. Washington: Center for Global Development; 2012.

**Childhood Pneumonia & Diarrhea:**

- A. Bhutta Z, Das J, Walker N, Rizvi A, Campbell H, Rudan I, Black R. Interventions to address deaths from childhood pneumonia and diarrhea equitably: what works and at what cost? *The Lancet*. 2013 Apr [cited 2013 Apr 25]. Available from: [http://dx.doi.org/10.1016/S0140-6736\(13\)60648-0](http://dx.doi.org/10.1016/S0140-6736(13)60648-0).
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## APPENDIX 5: BRIEF SUMMARY OF POSSIBLE IMPACT OF LATEST TECHNOLOGY ON UNFINISHED AGENDA: VACCINES, GENOMICS & NANOTECHNOLOGY

Recent advances in knowledge and tools related to vaccine development, genomics and nanotechnology have strong potential for making headway in previously intractable challenges presented by the unfinished agenda of infectious disease.

With regard to vaccine development<sup>31</sup>, progress in the field of structural biology is leading to the identification of promising novel therapeutic targets. Potent broadly neutralizing antibodies for HIV and influenza have been identified, raising hopes for successful rational vaccine design efforts. New vectors for vaccine delivery, including DNA-expression vectors, replication-defective viruses, and prime-boost combinations, have been demonstrated to be effective in inducing broadly neutralizing antibodies, with the strongest proof of concept thus far in influenza. Advances in the study of mucosal immunity may lead to therapies that can be better targeted to portals of infection, such as respiratory and intestinal epithelial surfaces. Clinical translation efforts may be sped along by innovative testing strategies, including adaptive clinical trial designs in which multiple vaccine candidates can be evaluated in parallel.

Advances in genomics are impacting disease research at all levels—from basic science to clinical trial design to diagnostics<sup>32</sup>. Medical structural genomics<sup>33</sup>, transcriptomics<sup>34</sup>, and proteomics<sup>35</sup> are revealing new drug and vaccine targets through the enhanced study of both host and pathogen genetic and metabolic profiles. Together with clinical and epidemiological data, molecular fingerprinting and genomic epidemiology tools have greatly enhanced the study of disease outbreak mapping and response, including speeding diagnostic tool development<sup>36,37</sup>. With the cost of sequencing technologies dropping steadily, efforts are increasingly focusing on streamlining and standardizing the collection, storage, analysis, and sharing of data across research efforts<sup>38</sup>. In addition, the reduction of sequencing and reagent costs has permitted the adaptation of DNA technologies for case diagnosis, molecular epidemiology, and detection of drug resistance to existing infrastructure in low-resource settings<sup>39</sup>.

Nanotechnology broadly includes nanoparticles and nanocapsules, which can protectively enclose payloads such as drugs or vaccines<sup>40</sup>. Nanoprobes and nanodevices have the potential to revolutionize diagnostic approaches,

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<sup>38</sup> Brindley PJ, Mitreva M, Ghedin E, Lustigman S. Helminth genomics: The implications for human health. *PLoS neglected tropical diseases*. 2009;3(10):e538. Epub 2009/10/27.

<sup>39</sup> Coloma J, Harris E. Molecular genomic approaches to infectious diseases in resource-limited settings. *PLoS medicine*. 2009;6(10):e1000142. Epub 2009/10/27.

<sup>40</sup> Chadwick S, Kriegel C, Amiji M. Nanotechnology solutions for mucosal immunization. *Advanced drug delivery reviews*. 2010 Mar 18;62(4-5):394-407.

with the theoretical sensitivity to not only distinguish pathogens but also subtypes such as resistant variants<sup>41</sup>. Nanotechnology strategies have been considered for HIV<sup>42,43</sup>, malaria<sup>44,45,46</sup>, TB<sup>47,48</sup>, influenza<sup>49</sup>, and Chagas disease<sup>50</sup>, including approaches to enhance the development and delivery of efficacious vaccines, to increase the stability of therapeutic compounds, and to reduce drug toxicity through delayed release and improved targeting. In addition, nanotechnology may permit the development of new drug and vaccine formulations with increased shelf-life and resistance to temperature sensitivity<sup>51</sup>.

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<sup>41</sup> Kaittanis C, Santra S, Perez JM. Emerging nanotechnology-based strategies for the identification of microbial pathogenesis. *Advanced drug delivery reviews*. 2010 Mar 18;62(4-5):408-23.

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<sup>43</sup> Chadwick S, Kriegel C, Amiji M. Nanotechnology solutions for mucosal immunization. *Advanced drug delivery reviews*. 2010 Mar 18;62(4-5):394-407.

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[http://whqlibdoc.who.int/hq/1996/TDR\\_Gen\\_96.1\\_pp35-91.pdf](http://whqlibdoc.who.int/hq/1996/TDR_Gen_96.1_pp35-91.pdf)  
[http://whqlibdoc.who.int/hq/1996/TDR\\_Gen\\_96.1\\_pp93-194.pdf](http://whqlibdoc.who.int/hq/1996/TDR_Gen_96.1_pp93-194.pdf)  
[http://whqlibdoc.who.int/hq/1996/TDR\\_Gen\\_96.1\\_pp195-278.pdf](http://whqlibdoc.who.int/hq/1996/TDR_Gen_96.1_pp195-278.pdf). Accessed 15 April 2010.
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## Supplementary Material for Working Papers 1 & 2:

**Working Paper 1: Priority Research Areas for Basic Science and Product Development for Neglected Diseases.** Sue J. Goldie<sup>1,2</sup>, Jennifer S. Edge<sup>1</sup>, Christen Reardon<sup>1</sup>, Cherie L. Ramirez<sup>1,2</sup> \*

**Working Paper 2: An Initial Scan of Priority Research Areas for Public Health, Implementation Science and Innovative Financing for Neglected Diseases.** Jennifer S. Edge<sup>1\*\*</sup>, Steven J. Hoffman<sup>1,2,3</sup>, Cherie L. Ramirez<sup>1,2</sup>, Sue J. Goldie<sup>1,2</sup>

Available for download at: <http://investinginhealth2035.org/working-papers>

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**For Additional Samples of Extraction and Synthesis see Secondary Supporting Background Material**





















































































































































































































































































R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	R&D Priorities for Achieving Goals
	<p>in humans, wildlife, and livestock<sup>{F},{H},{U}</sup></p> <ul style="list-style-type: none"> <li>• Find ways to enhance multi-sectoral collaboration in prevention and response efforts for zoonotic diseases, and in the elimination or mitigation of transmission routes to prevent their emergence<sup>{F}</sup></li> <li>• Find ways to encourage collaboration between ministries of health, environment and agriculture, and inter-governmental agencies involved in health, trade, food production, and the environment on zoonotic control efforts given that zoonoses affect developed and developing countries alike and spread readily across national boundaries<sup>{F},{G},{H},{U}</sup></li> <li>• Better understand the mechanistic processes linking land use and socioeconomic conditions with disease to enable the prediction of future trends and control or mitigation of vector-borne pathogens<sup>{G},{U}</sup></li> <li>• Develop a new systematic, pre-emptive risk assessment approach that aims to prevent the spread, or even the initial emergence, of pandemics of zoonotic origin<sup>{H}</sup></li> <li>• Identify ways to foster closer collaboration between government, private sector, civil society and communities – in areas such as agriculture, technology, education, social welfare, transport and health – to better understand complex socio-ecological drivers which contribute to ill-health and</li> </ul>	<ul style="list-style-type: none"> <li>• Find ways to strengthen advocacy for control of neglected zoonoses among stakeholders via informing them about the societal burden of these diseases, and providing education to affected populations to create demand for control at all levels of society<sup>{B}</sup></li> <li>• Develop integrated approaches to eliminate Dracunculiasis by learning to improve surveillance, intensify case-containment measures, provide access to improved drinking-water sources and promote behavioural change and awareness via information dissemination and education<sup>{B}</sup></li> <li>• Determine ways to maintain and generate needed expertise at the national level and to improve programmes' abilities to adapt to local conditions<sup>{B}</sup></li> <li>• Develop methods to align improvements in sanitation together with delivering preventive chemotherapy and health education as a basis for sustaining reductions in the prevalence of helminthes<sup>{B}</sup></li> <li>• Find ways to scale-up environmental interventions for NTDs<sup>{B}</sup></li> <li>• Determine how to improve husbandry practice and upgrade abattoirs and meat inspection, particularly for echinococcosis, cysticercosis and bovine tuberculosis<sup>{B}</sup></li> <li>• Determine the economic cost of neglected zoonoses for both the human and animal populations involved<sup>{C},{U}</sup></li> <li>• Study the efficacy of integrated interventions that address more than one zoonotic disease and/or agent at the same time, and determine the cost effectiveness of these interventions<sup>{C}</sup></li> <li>• Investigate promotion of health literacy and social mobilization to ensure maximal engagement of the affected populations in the selected interventions<sup>{C}</sup></li> <li>• Develop audience-specific health education and behaviour change interventions for cysticercosis and taeniasis, and assess their effectiveness together with gender-related correlates in intervention studies<sup>{C}</sup></li> <li>• Conduct operational research on the cost-effectiveness of integrated control for Asian schistosomiasis to establish optimum approach at scale in different geographical settings, including the value of transmission-blocking vaccines for use in buffalo or other mammalian hosts<sup>{C}</sup></li> <li>• Conduct studies on the problems of coverage and compliance related to access to mass treatment in the Philippines (Samar province) for Asian schistosomiasis in relation to animal reservoir diversity to define which zoonotic sources have an impact on the incidence of human infections<sup>{C}</sup></li> </ul>

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	R&D Priorities for Achieving Goals
	<p>the spread of infectious diseases<sup>(J)</sup></p> <ul style="list-style-type: none"> <li>• Develop methods to ensure that research findings, clinical experience and learning from both human and veterinary domains are connected<sup>(J)</sup></li> <li>• Identify ways to target the education sector, especially universities, to play a bigger role in building capacity and fostering interdisciplinary learning and research among a new generation of scientists and policy-makers through encouraging interdisciplinary work<sup>(J)</sup></li> <li>• Develop research frameworks to assess the reciprocal impact of global initiatives, national health systems and intersectoral governance on infectious disease control<sup>(J)</sup></li> <li>• Develop methods to determine the optimal balance between health workforce options and requirements to attain disease control targets in the context of broader health systems strengthening<sup>(J)</sup></li> <li>• Learn how to improve access and appropriate use of quality medical technologies for infectious disease control<sup>(J)</sup></li> <li>• Determine how stand-alone disease control information systems be integrated into existing national health information systems and into general health decision-making processes<sup>(J)</sup></li> <li>• Investigate how to develop research frameworks to assess the interaction between Global Health Initiative-targeted</li> </ul>	<ul style="list-style-type: none"> <li>• Develop appropriate and gender-sensitive tools and methods to assess the health and socioeconomic impact of control programmes on individuals and households for Asian schistosomiasis<sup>(C)</sup></li> <li>• Find ways to increase interest in the discovery and development of new diagnostic tools, vaccines and new trematocidal drugs for foodborne trematodiasis<sup>(C)</sup></li> <li>• Determine how to improve access to clean water, adequate sanitation and sewage treatment, and enhanced food safety measures to have an impact on foodborne trematodiasis<sup>(C)</sup></li> <li>• Develop integrated control approaches and intersectoral collaboration between public health and veterinary medicine for foodborne trematodiasis, including collaboration on considerations of feasibility, efficacy and cost-effectiveness<sup>(C)</sup></li> <li>• Conduct operations research on integrated control (mass treatment, education and behaviour change communication, community-directed/led strategies for health, sanitation and aquaculture management) in endemic communities and intersectoral collaboration between public health and veterinary medicine and public and private sectors in planning implementation, including food safety issues for foodborne trematodiasis<sup>(C)</sup></li> <li>• Analyze gender (male and female) differentials on access to and compliance with FBT treatment for foodborne trematodiasis (FBT)<sup>(C)</sup></li> <li>• Develop appropriate and gender-sensitive tools and methods to assess the socioeconomic impact of FBT on individuals, households, communities and societies<sup>(C)</sup></li> <li>• Assess the impact of FBT and its control into the health education programmes for communities and schools, and its effect on the knowledge and practice of endemic communities to prevent and control FBT<sup>(C)</sup></li> <li>• Assess the cost-effectiveness of integration of existing serological test regimes for toxoplasmosis into antenatal care programmes in low-income settings<sup>(C)</sup></li> <li>• Develop culturally acceptable health education programmes to improve food hygiene in the home, especially for pregnant women, to prevent toxoplasmosis infection<sup>(C)</sup></li> <li>• Find ways to enhance the surveillance of cryptosporidiosis infection prevalence in humans and livestock, and determine the short- and longer-term health and economic consequences for both populations<sup>(C)</sup></li> <li>• Assess the impact of community-level water and sanitation improvements on the</li> </ul>

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	R&D Priorities for Achieving Goals
	<p>services and non-Global Health Initiative-targeted services so that overall service delivery is improved<sup>(j)</sup></p> <ul style="list-style-type: none"> <li>• Develop leadership strategies and mechanisms to share common values of equity and the right to health, community involvement and sustainability across diverse actors through an outcome-oriented approach<sup>(j)</sup></li> <li>• Adopt systems thinking to assess the impact of system changes as they are designed and implemented, e.g. to better understand the impact of decentralization on disease control interventions, or how the introduction of pay-for-performance schemes impacts the rest of the health system<sup>(j)</sup></li> <li>• Further investigate how health systems interact with the wider social system and institutions (e.g. understanding how governance and political systems, culture and globalization forces impact on the structure and functions of health systems)<sup>(j)</sup></li> <li>• Investigate critical research questions concerning the scaling-up of interventions (e.g. What is the opportunity cost of scaling-up a specific innovation on other forms of health care and disease control? How does it relate to equity and efficiency? What are the contextual determinants for success? What information is available to assess scaling-up strategies?)<sup>(j)</sup></li> <li>• Investigate the impact of product</li> </ul>	<p>prevalence of human cryptosporidiosis infection in both urban and rural settings<sup>(c)</sup></p> <ul style="list-style-type: none"> <li>• Find ways to strengthen laboratory capacity for the diagnosis and surveillance of rabies to generate accurate data on incidence and guide control strategies and estimates of disease burden<sup>(c)</sup></li> <li>• Find ways to establish prioritization and cooperation of rabies control between health, veterinary and wildlife agencies<sup>(c)</sup></li> <li>• Evaluate the cost-effectiveness of different WHO-recommended pre and post-exposure regimens or rabies, including indirect costs associated with hospital visits<sup>(c)</sup></li> <li>• Investigate the economics of dog oral vaccination strategies and identify appropriate settings for implementing oral vaccination campaigns in dogs<sup>(c)</sup></li> <li>• Conduct ethnographic and participatory research to design relevant and understandable criteria for measuring the impact of bacterial zoonoses, and that incorporates a broader consideration of burden with consideration of the value of livestock for human well-being and development<sup>(c)</sup></li> <li>• Design and evaluate cost-effective brucellosis livestock vaccination strategies and advocate “One Health” approaches to implementation at the policy-maker level through ministries of health and agriculture<sup>(c),(f),(g)</sup></li> <li>• Develop approaches to raise awareness among physicians of the need for differential diagnosis of <i>Brucella</i> in cases of non-specific febrile illness<sup>(c)</sup></li> <li>• Conduct applied research on the development, implementation and evaluation of appropriate preventive health educational measures that are likely to provide a cost-effective means of reducing the burden of a wide range of bacterial zoonotic infections<sup>(c)</sup></li> <li>• Develop infrastructure and capacity to identify zoonotic enteric pathogens in the relevant animal populations<sup>(c)</sup></li> <li>• Determine the economic burden resulting from infections in livestock, including illness and loss of markets and income from animals and the direct and indirect economic costs of foodborne illnesses<sup>(c),(j)</sup></li> <li>• Develop ways to improve the communications between veterinary and human health professionals, to include integrated training modules and mechanisms for exchange of information<sup>(c),(j)</sup></li> <li>• Identify how to create joint veterinary/human health outbreak investigation teams, with access to quality laboratory capacity for diagnosis allied to</li> </ul>

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	R&D Priorities for Achieving Goals
	<p>development partnerships (PDPs) and incentives on developing country innovation systems, and identify the most effective partnerships to encourage health innovation for the poor while minimizing risks<sup>(j)</sup></p> <ul style="list-style-type: none"> <li>• Determine the most effective ways to implement the criteria for innovation (effectiveness, affordability, acceptability and sustainability) in national and global innovation systems<sup>(j)</sup></li> <li>• Develop platforms for innovative systems in Brazil, China, Indian and South Africa to be scaled-up, better integrated with other capacity building initiatives and more effectively globalized to assist smaller LMICs to create similar innovative environments<sup>(j)</sup></li> <li>• Identify strategies and social entrepreneurship models that are available for local communities to innovate in the prevention, control and treatment of infectious diseases<sup>(j)</sup></li> <li>• Find innovative methods to translate and customize health interventions and products to local settings in order to overcome cultural and social barriers (e.g. stigma, social norms) and sustain interventions over the long term<sup>(j)</sup></li> <li>• Develop systems to continually monitor and evaluate centers of excellence in LMICs to ensure their capacity in research innovation (e.g. they do not bias the national science and technology landscape)<sup>(j)</sup></li> </ul>	<p>enhancement of veterinary and human grassroots public health educational services (educational extension model) to improve animal and human health outcomes<sup>(c),(j)</sup></p> <ul style="list-style-type: none"> <li>• Develop strategies to control the delivery of drugs used for enteric infections without restricting access when these medications are urgently needed in order to increase appropriate use and delay the emergence and spread of drug resistance<sup>(c)</sup></li> <li>• Identify the optimal investments in livestock animal and human primary health care capacity to ensure appropriate treatment as well as the use of effective prevention modalities<sup>(c)</sup></li> <li>• Create new approaches to community sanitation measures and the provision of clean water supplies<sup>(c)</sup></li> <li>• Estimate the duration of “open defecation free” (ODF) status following CLTS<sup>(c)</sup></li> <li>• Estimate the cost–benefit of CLTS as compared with other approaches<sup>(c)</sup></li> <li>• Study the human-animal interface to clarify the social, cultural, behavioural, economic and gender dimensions of improving community access to proper sanitation through CLTS<sup>(c),(j)</sup></li> <li>• Evaluate the impact of CLTS on specific communities dependent on equines and camelines, smallholder pig farmers and those dependent on aquaculture<sup>(c)</sup></li> <li>• Further study mechanisms for coordinated public and animal health action within national government systems that comprise both the public health and animal health systems as a single entity on an equal partner basis<sup>(c)</sup></li> <li>• Find ways to increase the level of priority accorded to zoonotic diseases by increasing advocacy and undertaking research to underpin the importance of zoonotic infections as drivers of poverty<sup>(c)</sup></li> <li>• Find ways to extend the concept of zoonoses to cover diagnosis, data-sharing, monitoring and surveillance systems, training, interventions and delivery<sup>(c)</sup></li> <li>• Conduct long-term (longitudinal) studies assessing health education “multipacks”, i.e. for diseases with similar or overlapping bio-social determinants<sup>(c)</sup></li> <li>• Find ways to integrate a gender-sensitive approach to health education/promotion and behaviour change, e.g. the role of women, as they more often tend to be small livestock keepers<sup>(c)</sup></li> <li>• Organize and conduct comparative studies on traditional versus participatory research for zoonoses and marginalized infections<sup>(c)</sup></li> <li>• Conduct evaluation research (assessment of methodologies for</li> </ul>

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	R&D Priorities for Achieving Goals
	<ul style="list-style-type: none"> <li>• Determine the most effective way to link the local milieu of innovation in the public and private sectors in LMICs with international partners<sup>{J}</sup></li> <li>• Develop sophisticated regulatory and intellectual policies to provide the framework for an open innovative platform<sup>{J}</sup></li> <li>• Develop and refine processes to assess health interventions and technologies as inputs to budget decision making and the design of publicly subsidized health benefits<sup>{K}</sup></li> </ul>	<p>programme/project evaluation) for zoonotic diseases<sup>{C}</sup></p> <ul style="list-style-type: none"> <li>• Assess the specific contribution of educational components within integrated interventions<sup>{C}</sup></li> <li>• Expand systems research to determine how best the different sectors can interact<sup>{C}</sup></li> <li>• Find ways to integrate animal and human disease expertise with social science perspectives<sup>{C}</sup></li> <li>• Find ways to scale up research training to increase human resources in the area of public health, including veterinary and livestock services, for addressing zoonoses<sup>{C}</sup></li> <li>• Create opportunities to evaluate and modify zoonotic control strategies as experience is gained in implementation<sup>{C}</sup></li> <li>• Determine how to combine interventions allied to improved water and sanitation, and health education and promotion, and deploy them for the human and animal diseases in parallel<sup>{C}</sup></li> <li>• Expand research on the use of new communication technologies such as smart phones to enhance surveillance, reporting and evaluation of zoonoses<sup>{C}</sup></li> <li>• Find ways to ensure at-risk communities take precautions against CCHF by wearing protective clothing and getting health professionals to ensure that safety measures are adhered to within hospitals, most crucially when they encounter haemorrhaging patients<sup>{E}</sup></li> <li>• Determine how to enhance international disease-prevention efforts by identifying ways to advance implementation of WHO's International Health Regulations and international standards for animal health and zoonoses produced by the World Organization for Animal Health<sup>{F}</sup></li> <li>• Investigate how to improve veterinary services in many low-income and middle-income countries to increase detection, quantification, reporting and prevention of zoonotic infection in animals<sup>{F}</sup></li> <li>• Find ways to enhance the role ecologists play in zoonotic control programmes to produce more accurate mathematical model outputs via collaboration with clinicians with real-time data, participation in both prospective and retrospective study design, and field studies to identify key risk factors to target surveillance and interventions<sup>{F}</sup></li> <li>• Develop guidelines for safe or best practices that include ecological knowledge to</li> </ul>

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	R&D Priorities for Achieving Goals
		<p>reduce the risk of zoonotic disease emergence or occurrence among industries based on the extraction of natural resources, and find ways to mandate these guidelines through the funding mechanisms that support large-scale development projects or find ways for mandated guidelines to be required by financial insurers<sup>{F}</sup></p> <ul style="list-style-type: none"> <li>• Investigate correlations that exist between land use and disease incidence or measures of risk, and develop rigorous and mechanistic analyses that identify causal factors that are needed for intelligent urban planning to anticipate and avoid future vector-borne pathogen-based epidemics<sup>{G}</sup></li> <li>• Develop behavioural change strategies promoting personal protective behaviours to prevent the emergence of endemic or exotic pathogens<sup>{G}</sup></li> <li>• Develop effective ways to build capacity among human and veterinary pathologists, including the integration of disease-surveillance, shared animal-human epidemiological studies, and best ways to develop health services able to deal with animal and human health<sup>{J}</sup></li> <li>• Determine the best open-access models for sharing of new knowledge and products, and the delivery of new innovations<sup>{J}</sup></li> <li>• Find ways to highlight the importance of innovation by engaging key players in global networks<sup>{J}</sup></li> <li>• Develop and work towards a “one world-one research” community agenda<sup>{J}</sup></li> <li>• Learn how to foster a culture of open innovation for sharing knowledge, technology and repositories (e.g. demographic and biological database, bio-banks, biomarker banks, standard libraries and databases for traditional knowledge, social science data, etc.)<sup>{J}</sup></li> <li>• Create an open innovation platform that brings together independent but cooperating agencies and consortia, including networks of researchers, community members and health workers can help progress research, monitor health indices, undertake community audits and evaluation, better manage intellectual property, and distribute financing<sup>{J}</sup></li> <li>• Create monitoring systems to track pharmacological side effects and community attitudes towards health technologies and to strengthen capability to translate technologies into local solutions<sup>{J}</sup></li> <li>• Develop methods to implement a cross-disciplinary “One Health, One World” strategy in relation to research for infectious diseases of poverty that includes champions from government, civil society, education and the private sector,</li> </ul>

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	R&D Priorities for Achieving Goals
		<p>particularly in disease endemic countries<sup>(1)</sup></p> <ul style="list-style-type: none"> <li>• Develop mechanisms through which researchers in different countries can learn from one another (e.g. the BRICS countries), possibly through regional partnerships, new networks, online forums, exchange programmes and collaborations<sup>(1)</sup></li> </ul>
<b>INNOVATIVE FINANCING</b>	<ul style="list-style-type: none"> <li>• Identify how to expand support from Member States and their partners to ensure that new products are developed for preventing, diagnosing and controlling NTDs, and to ensure that access to services continues to expand<sup>(B)</sup></li> <li>• Find ways to advance political will and commitment to increase the capacity of helminth disease research in disease-endemic countries<sup>(A),(B)</sup></li> <li>• Determine how to generate investments in South-South collaborations for helminth R&amp;D<sup>(A)</sup></li> <li>• Determine how to increase investments in new drug and diagnostic test research and development programmes for enteric infections<sup>(C)</sup></li> <li>• Determine how to increase R&amp;D funding available for trypanosomatid diseases so that it is comparable with malaria, tuberculosis and HIV/AIDS<sup>(D)</sup></li> <li>• Determine how to fill the funding gap for NTD product development within the US President's Global Health Initiative<sup>(1)</sup></li> <li>• Identify how to allocate greater funding priority to research that adopts interdisciplinary approaches that encourage collaboration between government ministries and agencies, and</li> </ul>	<ul style="list-style-type: none"> <li>• Determine how to encourage Member States of the African, American (Latin America and Caribbean Islands), and South-East Asia Regions to promote and support the development of regional policies supporting the development of effective linkages and partnerships with international health research agencies<sup>(A)</sup></li> <li>• Find ways to gain regional commitment and strong advocacy to strengthen policies on health research aimed at providing evidence to justify health actions and practices that are flexible and responsive to the short- and long-term national needs<sup>(A)</sup></li> <li>• Find ways to encourage African countries to put in place research-friendly legislative reforms that facilitate exchange of expertise and data whilst ensuring protection of intellectual property rights<sup>(A)</sup></li> <li>• Develop comprehensive policies and strategies for supervision across all sectors in the regional and national innovation sector to foster transparency in terms of funding and its disbursement, strategic planning, priority-setting, knowledge management and demand creation<sup>(A)</sup></li> <li>• Develop innovative strategies for funding integrated and sustainable dog vaccination programmes, including education and social mobilization campaigns<sup>(C)</sup></li> <li>• Test simple cost-effective farming methods to prevent transmission of zoonotic infection to animals, crops and water supplies, and to humans, which will be applicable to small- and large-scale producers alike<sup>(C)</sup></li> <li>• Develop a highly efficient and collaborative environment to optimize effort and the use of funding for trypanosomatid diseases that engages the academic community, public institutes and the pharmaceutical/biotech sector in a unified effort<sup>(D)</sup></li> <li>• Develop strategies to increase the diagnostic and vaccine market for Crimean-Congo haemorrhagic fever<sup>(E)</sup></li> <li>• Find ways to incentivize greater investments in NTD product development from the GHI through a model of "vaccine diplomacy" that will inspire the next generation of poverty-reducing biotechnologies and also strengthens US foreign relations in NTD-endemic countries<sup>(1)</sup></li> </ul>

R&D Areas	NEGLECTED TROPICAL DISEASES	
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	<p>that better incorporate ecology into disciplines – including public health, medicine, social sciences, veterinary sciences and agriculture<sup>(1)</sup></p> <ul style="list-style-type: none"> <li>• Determine how to inspire greater investment in human capital and knowledge systems<sup>(1)</sup></li> <li>• Determine the best mix of infectious disease control funding mechanisms to strengthen health system financing, and in what contexts<sup>(1)</sup></li> <li>• Determine how global funding can be used to build mechanisms for innovation and health R&amp;D in the lowest income countries<sup>(1)</sup></li> <li>• Find ways to give LMICs with developing capacities more active roles in public–private PDPs that cater to long-term LMIC goals for product development<sup>(1)</sup></li> <li>• Create incentives to invest in implementation research to complement advances in product development for infectious diseases of poverty<sup>(1)</sup></li> <li>• Develop methods to avoid wastage and improve the efficiency of R&amp;D funding for infectious diseases of poverty<sup>(1)</sup></li> <li>• Find ways to strengthen the data reservoir concerning funding flows to infectious disease R&amp;D<sup>(1)</sup></li> <li>• Develop processes and methods to ensure that R&amp;D funding is relevant to the needs on the ground<sup>(1)</sup></li> <li>• Find ways to ensure that research capacity building activities are seen as integral to</li> </ul>	<ul style="list-style-type: none"> <li>• Determine how public–private partnerships can be expanded and scaled-up to include not only PDPs, but also the development of more basic research in the laboratory and the delivery of sustainable innovative products into the field<sup>(1)</sup></li> <li>• Find ways to reduce duplication and improve coordination of R&amp;D funding for priority conditions by integrating goals and reducing overlap<sup>(1)</sup></li> <li>• Find ways to reduce competition for funds as a source of wastage<sup>(1)</sup></li> <li>• Find ways to improve the coordination of priorities for action in order to harmonize approaches to R&amp;D funding e.g. through the proposed model of the WHO Expert Working Group on Research and Development Financing<sup>(1)</sup></li> <li>• Obtain funding data on implementation research, support for capacity building, and a broader class of research activities that explore aspects of behaviour, economics, politics, trade and the environment as they apply to infectious diseases of poverty<sup>(1)</sup></li> <li>• Develop a classification system to organize data on R&amp;D for health<sup>(1)</sup></li> <li>• Find ways to resolve the issue of separating ultimate funders from recipients of funds and from intermediaries (such as PDPs)<sup>(1)</sup></li> <li>• Develop information systems to help capture data on funding flows for R&amp;D on health<sup>(1)</sup></li> <li>• Investigate methods to build new funding capacity for supporting R&amp;D in emerging economies such as Brazil, China and India<sup>(1)</sup></li> <li>• Identify high-level actions on which policy-makers, funders and researchers should focus when developing their health research related strategies</li> <li>• Create and use a new index of infectious diseases of poverty to serve as a surrogate marker of national socioeconomic development<sup>(1)</sup> <ul style="list-style-type: none"> <li>○ Establishment of a framework of indicators for the index, based on a series of commissioned reviews and other research<sup>(1)</sup></li> <li>○ Identify institutions and other stakeholders, and provide funding to support development, piloting and small scale validation, in partnership with relevant stakeholders for the index<sup>(1)</sup></li> <li>○ Develop a stakeholders’ platform to review, agree and recommend a strategy and framework for scale-up and implementation of the index<sup>(1)</sup></li> </ul> </li> <li>• Create platforms to engage policy-makers with research entrepreneurship in endemic countries to demonstrate commitment to health research that could allow them to fund research and, in turn, use research outputs to underpin other</li> </ul>

R&D Areas	NEGLECTED TROPICAL DISEASES	
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	<p>the funding agenda<sup>(J)</sup></p> <ul style="list-style-type: none"> <li>• Develop a strategic approach to the funding and support of research and to the generation and use of research outputs<sup>(J)</sup></li> <li>• Find ways to reallocate part of public and donor monies toward the most cost-effective and equity-enhancing health interventions and technologies<sup>(K)</sup></li> <li>• Design and implement a systematic process for health priority-setting within “health technology assessment systems” at national and global levels to increase the value for money of donor investments<sup>(K)</sup></li> </ul>	<p>policies<sup>(J)</sup></p> <ul style="list-style-type: none"> <li>• Develop means to engage stakeholders in long-term partnerships with universities, public health and research institutes and health care systems in LMICs to facilitate LMIC health research ownership<sup>(J)</sup></li> <li>• Find ways to encourage funders to provide a framework that will allow leading research institutions and policy-makers in disease endemic countries to acquire expertise and capacity for priority setting, policy formulation and monitoring and evaluation of the effectiveness of actions<sup>(J)</sup></li> <li>• To facilitate LMIC health research ownership and strengthen partnerships with international donors, LMICs could:<sup>(J)</sup> <ul style="list-style-type: none"> <li>○ develop research priorities congruent with the burden of infectious diseases of poverty in their own populations;</li> <li>○ find ways to increase their own research activity and improve research leadership;</li> <li>○ develop regional partnerships to build research infrastructure, human resources and research capacity;</li> <li>○ create policies and develop plans to guide national and international investments towards the identified research priorities;</li> <li>○ develop plans to increase their national support for research and translation of research to strategies for health<sup>(J)</sup></li> </ul> </li> <li>• Create an innovation platform to foster a culture of innovation to benefit public health<sup>(J)</sup> <ul style="list-style-type: none"> <li>○ Develop a new paradigm of an “open innovation culture”, with a broader definition of innovation, through the collaboration of research and development agencies, industry and academia – both “north” and “south” – with disease endemic countries</li> <li>○ Find ways to strengthen the research, development and implementation capacity of disease endemic countries through the use of roadmaps for innovative development, partnerships with BRIC countries, etc.</li> <li>○ Create and expand an “open access innovation platform” comprising of open access to research information and to raw data, and mechanisms for joint ownership and sharing of intellectual property rights through fair and legal frameworks<sup>(J)</sup></li> </ul> </li> <li>• Create an easily accessible, online global platform that supports a database and detailed analysis of resources and financial investment in health research that can</li> </ul>

R&D Areas	NEGLECTED TROPICAL DISEASES	
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		<p>provide policy-makers, funders and researchers with information they need to guide their activities, identify funding gaps and mitigate duplicated efforts<sup>(1)</sup></p> <ul style="list-style-type: none"> <li>• Create a global health technology assessment facility to provide sustained technical and consultative support to global funding agencies and low- and middle-income country governments<sup>(K)</sup></li> <li>• Develop platforms to direct donor support to countries creating or developing their own health technology assessment systems<sup>(K)</sup></li> <li>• Find ways to accredit health technology assessment systems and institutions in LMICs (possibly through a self-assessment of competencies), and work to include phased accreditation requirements as conditions for external funding<sup>(K)</sup></li> <li>• Investigate ways to increase the allocative efficiency of both global health donors and national health systems<sup>(K)</sup></li> <li>• Examine the suitability of health technology assessment systems to serve as a hub of know-how, technical assistance, and knowledge brokerage on institutionalizing health technology assessment systems and on the design/adjustment of health benefits plans, defining best practices and evaluating results, at the service of LMIC governments and global health funding agencies through a practitioner-to-practitioner approach of knowledge sharing<sup>(K)</sup></li> <li>• Utilize health technology assessment systems to generate economies of scale in the generation and adaptation of evidence dossiers for specific LMICs, applying toolkits and glossaries already developed, in order to avoid duplication of effort and save money<sup>(K)</sup></li> <li>• Develop methods to benchmark and compare coverage decisions (through GDP per capita normalization, for example) on high-cost drugs and devices worldwide, as an input to decision making where local health technology assessment analysis is not possible<sup>(K)</sup></li> <li>• Build and find ways to support regional networks of policy makers and practitioners, such as HTAsiaLink<sup>(K)</sup></li> <li>• Investigate ways to maximize the consistency of the methods and evidence included in health technology assessment, in cooperation with existing networks working on harmonization, to reduce the burden to industry and to product development partnerships<sup>(K)</sup></li> <li>• Find ways to facilitate dialogue between health systems and industry to ensure that the benefits of new technology and system needs are mutually understood</li> </ul>

R&D Areas	NEGLECTED TROPICAL DISEASES	
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		<p>and reflected in price and availability<sup>{K}</sup></p> <ul style="list-style-type: none"> <li>• Develop methods to ensure that health technology assessment facilities are of use both to countries with health technology assessment agencies and those without them<sup>{K}</sup></li> <li>• Develop health technology assessments facilities' (HTAFs) ability to work with and mobilize expertise from health technology assessment agencies and academic institutions around the world, in order to allow for a practitioner-to-practitioner model of technical assistance and just-in-time support to decisions<sup>{K}</sup></li> <li>• Determine how HTAFs can attract and retain world-class health technology assessment experts to assist LMICs directly in accreditation or health technology assessment system development<sup>{K}</sup></li> <li>• Find ways to guarantee HTAFs' ability to ensure independence and transparency<sup>{K}</sup></li> <li>• Develop a financial model that is self-sustaining for HTAFs, although seeded by initial donations or support, ideally from health technology assessment pioneers in LMICs like Brazil, Poland, and Thailand or from countries that are investing heavily in their health care systems and are committed to evidence of return on investment, e.g. China and Turkey<sup>{K}</sup></li> <li>• Design a governance model that assures HTAFs' independence and rigor, while permitting engagement with governments and stakeholders involved in health technology assessment around the world<sup>{K}</sup></li> <li>• Develop methods to ensure HTAFs operate in close coordination with the WHO and the PAHO<sup>{K}</sup></li> </ul>

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