Research and Development Priorities to Achieve the "Grand Convergence"

Working Paper 1

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

Sue J. Goldie[1,2], Jennifer S. Edge[1], Christen Reardon[1], Cherie L. Ramirez[1,2] *

Working Paper 2

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

Jennifer S. Edge[1] **, Steven J. Hoffman[1,2,3], Cherie L. Ramirez[1,2], Sue J. Goldie[1,2]

Submitted: November 26, 2013

Affiliations:

[1] Harvard Global Health Institute, Harvard University, Cambridge, Massachusetts, USA.
[2] Harvard School of Public Health, Harvard University, Boston, Massachusetts, USA.
[3] Department of Epidemiology & Biostatistics and McMaster Health Forum, McMaster University, Hamilton, Ontario, Canada.

*Corresponding author: cramirez@hsph.harvard.edu
**Corresponding author: jennifer_edge@harvard.edu

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).

TABLE OF CONTENTS

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

Working Paper 1

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

Sue J. Goldie[1,2], Jennifer S. Edge[1], Christen Reardon[1], Cherie L. Ramirez[1,2]*

Acknowledgments:

Invaluable contributions to the discussions that motivated this paper and discussions about the insights that emerged from early efforts to review published data, and suggestions for future work have been made by Dr. Adel Mahmoud [Professor in Molecular Biology and Public Policy at Princeton University] and Dr. Jerry Keusch [Associate Provost for Global Health, Boston University, and Associate Dean for Global Health at Boston University School of Public Health].

Affiliations:

[1] Harvard Global Health Institute, Harvard University, Cambridge, Massachusetts, USA.
[2] Harvard School of Public Health, Harvard University, Boston, Massachusetts, USA.

*Corresponding author: cramirez@hsph.harvard.edu

INTRODUCTION

Research and development (R&D) is a critical contributor to improving health and therefore an essential component of investments in health[1]. 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[2]. 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)[3]. 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.

---

[1] 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.

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

[3] 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*.

Table 1. Selected Recommendations for R&D from *WDR 1993* – Estimated Investment and Progress		*Low to Modest Investment* Insufficient progress in most aspects	*Modest to Moderate Investment* Some progress in at least 1 aspect	*Moderate to High Investment* Some progress in most aspects
PRIORITIES FOR RESEARCH ACCORDING TO BURDEN OF DISEASE IN POOR				
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 *E. coli* 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		
BUILDING CAPACITY FOR RESEARCH & DEVELOPMENT IN POOR COUNTRIES				
Role of governments to support essential national health research in LIC and MIC				
	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		
Role of global community to support research capacity and attention to diseases afflicting LIC and MIC				
	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[4]. 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[5]. 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%[6]. 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[7].

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.

[4] 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.

[5] 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.

[6] Policy Cures 2012. G-FINDER 2012.

[7] Policy Cures 2012. G-FINDER 2012.

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

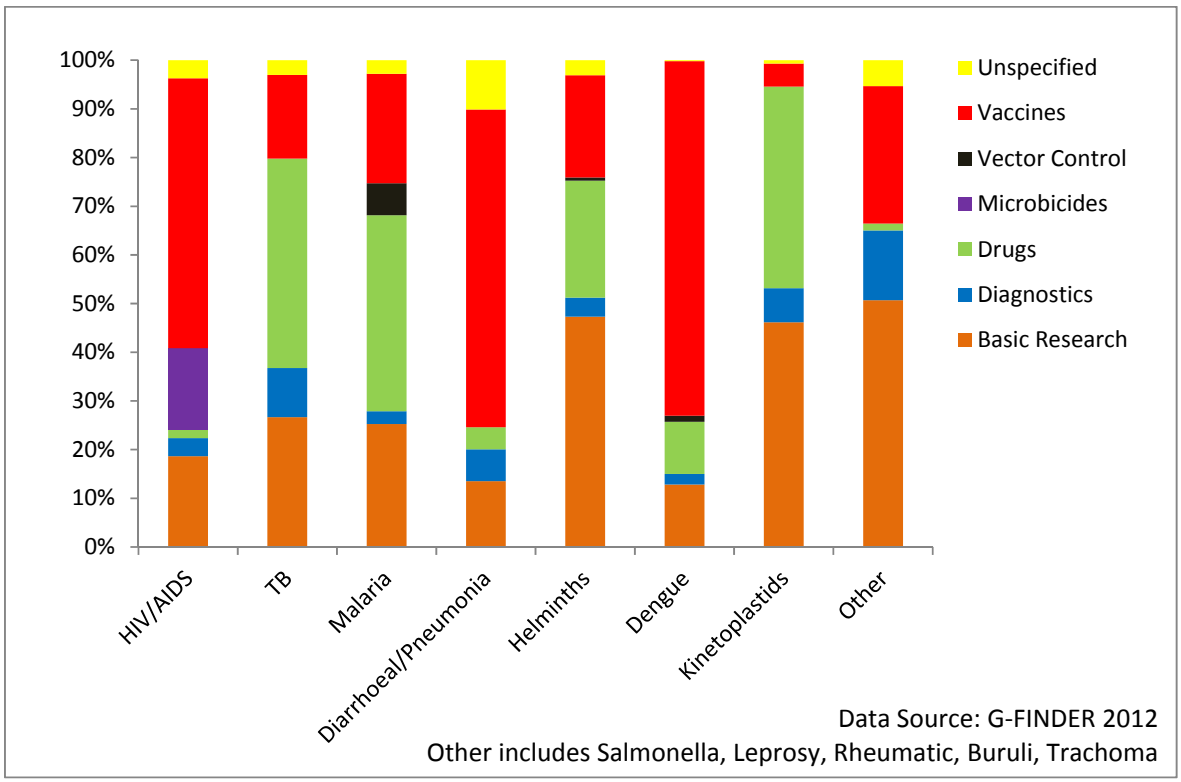
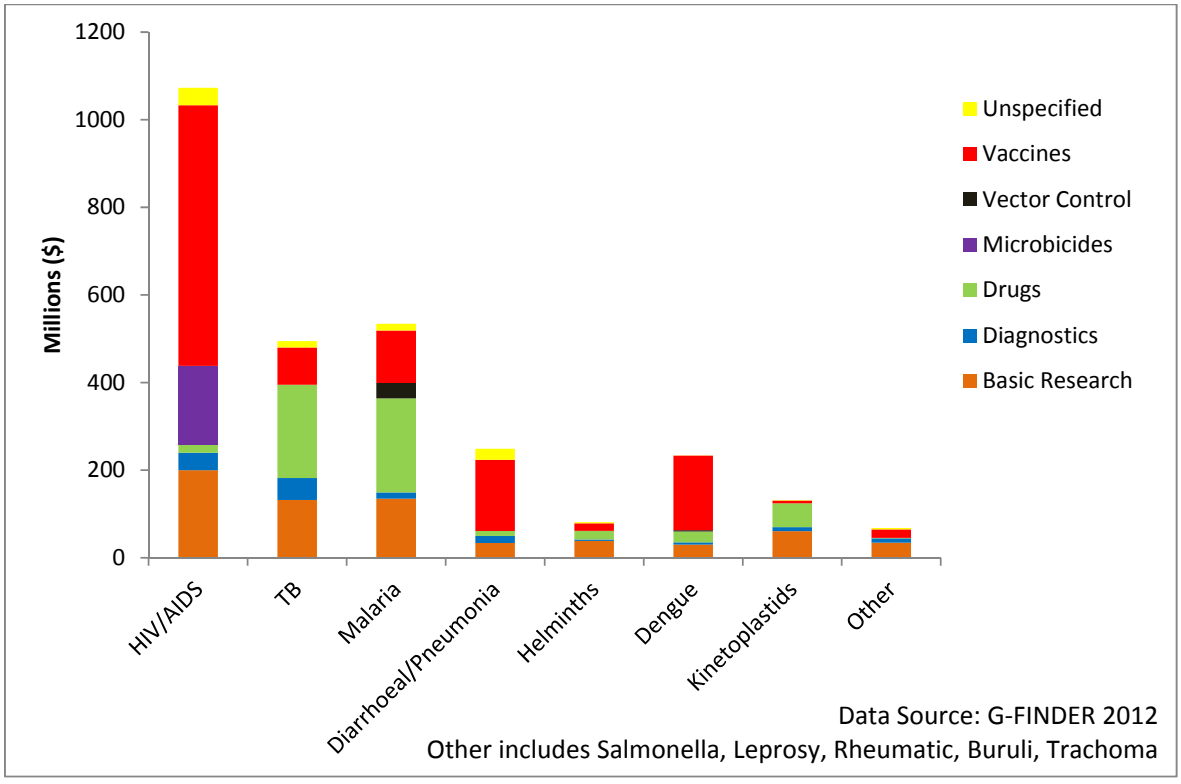


Figure 2: Allocation of investments in R&D by disease area and research type (2011)



We refer readers to another working paper produced for the *Lancet* Commission on Global Health[8] 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[9].

Funder-specific investments[10]

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

[8] 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.
[9] Policy Cures 2012. G-FINDER 2012.
[10] 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[11].

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[12].

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 [13]. 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

[11] http://www.gatesfoundation.org/; http://www.theglobalfund.org/en/; http://www.gavialliance.org/; http://www.who.int/alliance-hpsr/en/.
[12] Ad Hoc Committee on Health Research Relating to Future Intervention Options. Geneva: WHO; 1996.
[13] 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[14]. 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[15]. 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[16]. 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[17]. Following deliberation at the WHO Executive Board in January 2013[18], the CEWG resolution [A66/23] was approved at the 66th World Health Assembly[19]. 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[20]. 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[21]. 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.

[14] 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.
[15] Expert Working Group (EWG). (2008). R&D: Coordination and Financing. WHO, Geneva.
[16] Consultative Expert Working Group (CEWG). (2012). Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination. WHO, Geneva.
[17] 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.
[18] 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 132nd Session of the Executive Board. Paper EB132/21. WHO, Geneva.
[19] 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/.
[20] Commission on Health Research for Development. Health Research: Essential Link to Equity in Development. New York: Oxford University Press; 1990. p. 88.
[21] 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**[22]).

- *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**).

[22] **Working Paper 1 & 2 Supplementary Material** and **{ŜǑ2yŘI·Ǌè {ǆǇǇ2ǊǘʎyƎ .I·Ǒ]ƎǊ2ǆyŘ a I·ǘŜǊʎI·f** 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[23]	R&D Goals Identified as Priorities						
		Basic Science	Diagnostics	Drugs	Vaccines	Microbicides	Vectors	Total
Malaria*	14	26	24	22	15	N/A	14	***101***
Tuberculosis	10	31	47	18	51	N/A	N/A	***147***
HIV	15	31	11	25	31	9	N/A	***98***
Neglected Tropical Diseases**	11	18	22	21	24	N/A	21	***106***
Childhood Pneumonia and Diarrhea***	17	9	4	1	24	N/A	N/A	***38***
Total	**67**	**115**	**108**	**87**	**145**	**9**	**35**	**499**

*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 pneumonia* & *Neisseria meningitis.*

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.

[23] See **Appendix 4: Sources Reviewed for Identification of Existing R&D Priorities**.

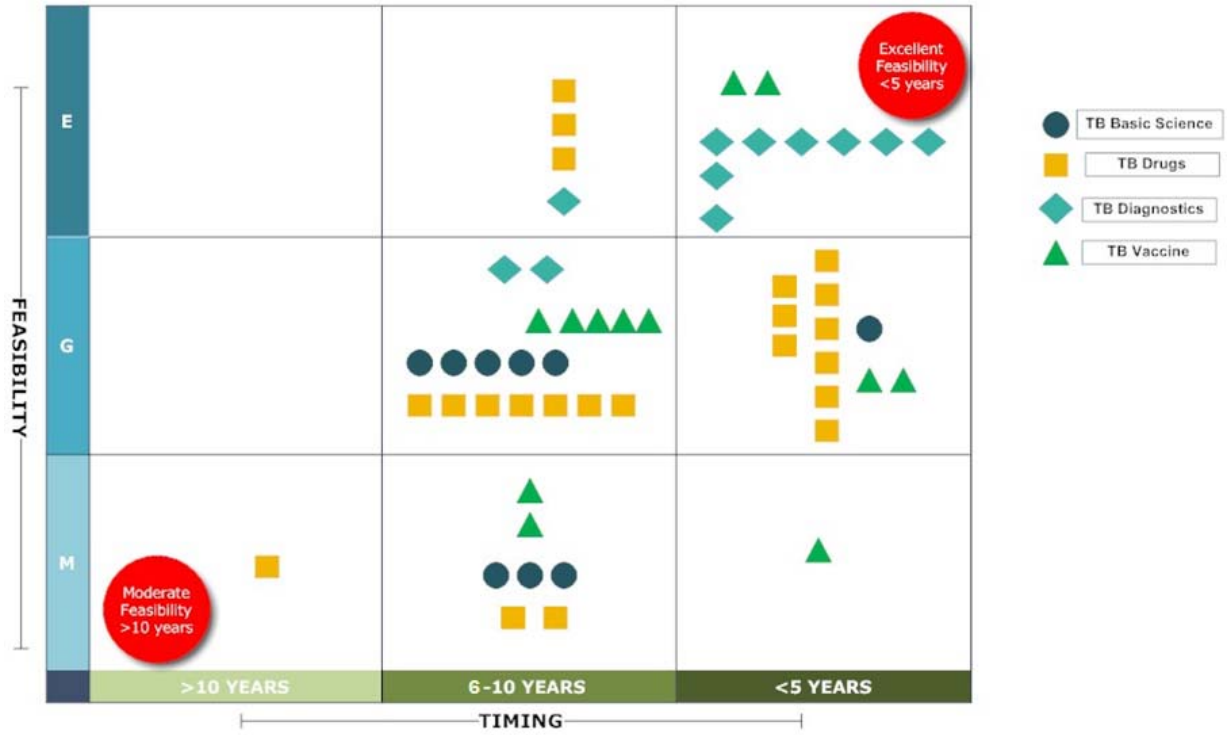
Comparison of disease-specific R&D priorities

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[24]. 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



[24] 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**[25]). 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

[25] **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 104 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 regiments 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 21st 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[26]. 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.

[26] Chadwick S, Kriegel 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

Jennifer S. Edge[1]*, Steven J. Hoffman[1,2,3], Cherie L. Ramirez[1,2], Sue J. Goldie[1,2]

Affiliations:

[1] Harvard Global Health Institute, Harvard University, Cambridge, Massachusetts, USA.
[2] Harvard School of Public Health, Harvard University, Boston, Massachusetts, USA.
[3] Department of Epidemiology & Biostatistics and McMaster Health Forum, McMaster University, Hamilton, Ontario, Canada.

*Corresponding author: jennifer_edge@harvard.edu

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 *E. coli* 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.

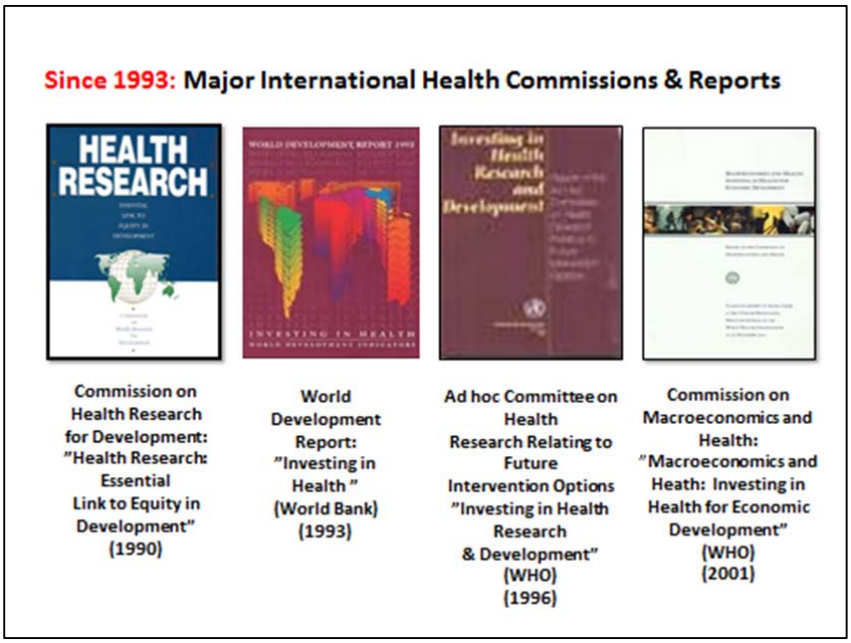
The *WDR 1993* highlighted in several of the above the importance of considering issues relevant to women, ranging from the disproportionate consequences of neglected tropical diseases on women, the need for clinical trials to more effectively include women and address gender-specific questions, and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

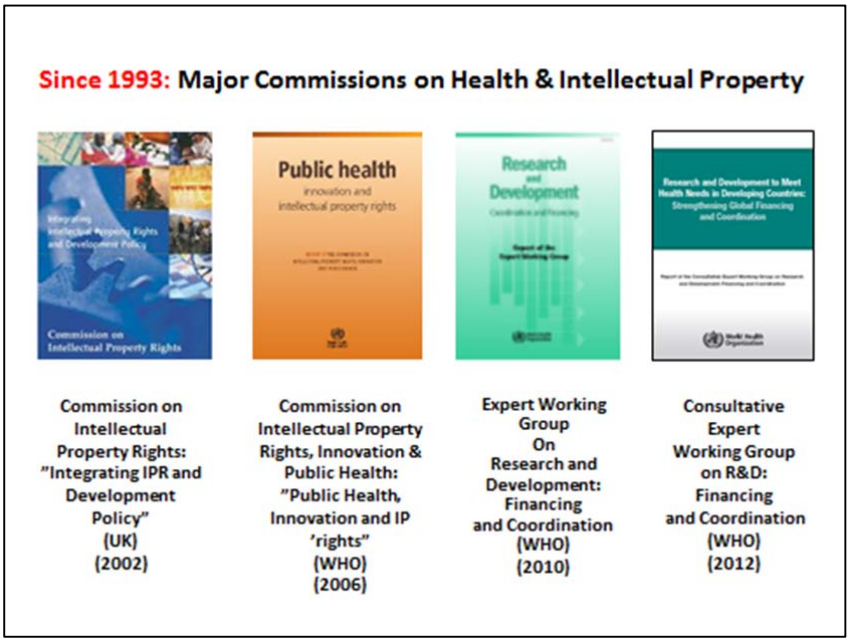
Illustrative excerpt from WDR 93: *"This Report recommends that concerted efforts be made to develop or strengthen effective programs for control of STDs. Such efforts will be hampered by the challenges of diagnosing STDs, particularly in women, for whom the vast majority of infections are asymptomatic. 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

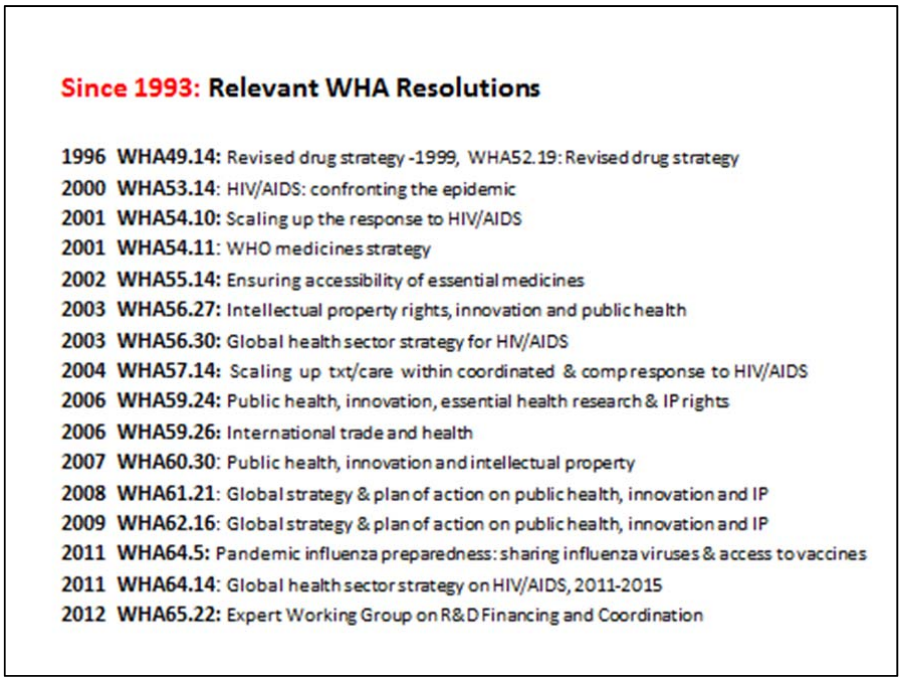
Since 1993: Selected International Health Commissions and Reports



Since 1993: Selected Commissions on Health and Intellectual Property



Since 1993: Selected WHA Resolutions Relevant to R&D



COMMISSION ON HEALTH RESEARCH FOR DEVELOPMENT[27]

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

[27] 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[28]

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

[28] 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 *Diagnostics* *Drugs* *Vaccines* *Microbicides* *Vector control*
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)[29].

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[30] (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*	
	Basic research "encompasses studies into the etiology of a disease or studies that increase scientific knowledge and understanding of a disease, disease processes or the pathogen or vector. They are not yet directed towards a specific intervention, product or health technology." (G Finder, 2012) *

[29] World Health Organization/Stop TB Partnership. An international roadmap for tuberculosis research: towards a world free of tuberculosis. Geneva: World Health Organization; 2011.
[30] 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.

	Fundamental research 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).	
PRODUCT DISCOVERY AND DEVELOPMENT**		
	"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) *	
		DIAGNOSTICS "*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) *
		DRUGS *"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) *
		VACCINES *"Research activities and processes necessary to develop and improve investigational vaccines intended **to prevent or treat infection**; including vaccine design, preclinical and clinical development and other activities essential for successful vaccine development and uptake.**"* (G Finder, 2012) *
		MICROBICIDES *"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) *
		VECTOR CONTROL "*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) *
IMPLEMENTATION RESEARCH OR OPERATIONAL RESEARCH***		
	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.
D. UNITAID. Tuberculosis Diagnostic Technology Landscape. Geneva: World Health Organization; 2012.
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.
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.
D. HIV Vaccines & Microbicides Resource Tracking Group (TWG). Investing to End the AIDS Epidemic: A New Era for HIV Prevention Research and Development. HIV Vaccines & Microbicides Resource Tracking Group; 2012.
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.
G. 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.
H. The George Institute for International Health. Registering New Drugs: The African Context. London; The George Institute for International Health, January 2010.
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. 2nd 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.
N. UNITAID. Diagnostic market analysis: HIV simple/rapid, enzyme immunoassay (EIA) and supplemental tests: available data and implications for future funding. Geneva: World Health Organization: July 2011.
O. Fauci A, Johnston M, Dieffenbach C, Burton D, Hammer S, Hoxie J, *et al*. HIV vaccine research: the way forward. Science. 2008; 321: 530-532.

Neglected Tropical Diseases:

A. World Health Organization. Research Priorities for Helminth Infections. Technical Report of the TDR Disease Reference Group on Helminth Infections (DRG4). Technical Report Series No. 972. Geneva: World Health Organization; 2012.
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.
E. Burki T. Ticks and Turkey. Lancet. 2012; 380:1897-98.
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.
I. Hotez P. New Antipoverty Drugs, Vaccines, and Diagnostics: A Research Agenda for the US President's Global Health Initiative (GHI). PLoS Negl Trop Dis. 2011;5(5): e1133. doi:10.1371/journal.pntd.0001133.
J. World Health Organization. Global Report for Research on Neglected Diseases of Poverty. Geneva: World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases; 2012.
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.
B. Chan M, Lake A. Integrated action for the prevention and control of pneumonia and diarrhoea. The Lancet. 2013 Apr [cited 2013 May 4]. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60692-3.
C. Chopra M, Mason E, Borrazzo J, Campbell H, Rudan I, Liu L, et al. Ending of preventable deaths from pneumonia and diarrhoea: an achievable goal. The Lancet. 2013 Apr [cited 2013 Apr 25]. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60319-0.
D. Fischer Walker C, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta Z, et al. Global burden of childhood pneumonia and diarrhea. The Lancet. 2013 Apr [cited 2013 Apr 25]. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60222-6.
E. Gill C, Young M, Schroder K, Carvajal-Velez L, McNabb M, Aboubaker S, Qazi S, Bhutta Z. Bottleneck, barriers, and solutions: results from multi-country consultations focused on reduction of childhood pneumonia and diarrhoea deaths. The Lancet. 2013 Apr [cited 2013 Apr 25]. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60314-1.
F. Kikwete J. Playing our part to save children's lives. The Lancet. 2013 Apr 12 [cited 2013 May 4]. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60719-9.
G. Samarasekera U, Horton R. Continuing the child survival revival. The Lancet. 2013 Apr 12 [cited 2013 May 4]. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60718-7.
H. World Health Organization/The United Nations Children's Fund (UNICEF). Ending preventable child deaths from pneumonia and diarrhoea by 2025: The integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD). Geneva: World Health Organization; 2013.
I. Huda T, Nair H, Theodoratou E, Zgaga L, Fattom A, El Arifeen S, et al. An evaluation of the emerging vaccines and immunotherapy against staphylococcal pneumonia in children. BMC Public Health. 2011; 11(Suppl 3):S27. Available from: http://www.biomedcentral.com/1471-2458/11/S3/S27.

J. Webster J, Theodoratou E, Nair H, Seong A, Zgaga L, Huda T, et al. An evaluation of emerging vaccines for childhood pneumococcal pneumonia. BMC Public Health. 2011; 11(Suppl 3):S27. Available from: http://www.biomedcentral.com/1471-2458/11/S3/S27.
K. Tate J, Patel M, Cortese M, Lopman B, Gentsch J, Fleming J, et al. Remaining issues and challenges for rotavirus vaccine in preventing global childhood diarrheal morbidity and mortality. Expert Rev Vaccines. 2012;11(2):211-220.
L. Patel M, Glass R, Desai R, Tate J, Parashar U. Fulfilling the promise of rotavirus vaccines: how fare have we come since licensure? Lancet Infectious Dis. 2012; 12: 561-70.
M. United Nations Children's Fund (UNICEF). Pneumonia and Diarrhoea: Tackling the Deadliest Diseases for the World's Poorest Children. New York: UNICEF; 2012.
N. United Nations Children's Fund (UNICEF). Update on Work on Medicines. Presentation. New York: UNICEF IPC; Dec 2012.
O. Ambroggio L, Thomson J, Kurowski E, Courter J, Statile A, Graham C, et al. Quality improvement methods increase appropriate antibiotic prescribing for childhood pneumonia. Official Journal of the American Academy of Pediatrics. 2013; 131:e1623. doi: 10.1542/peds.2012-2635.
P. Wazny K, Zipursky A, Black R, Curtis V, Duggan C, Guerrant R, et al. Setting research priorities to reduce mortality and morbidity of childhood diarrhoeal disease in the next 15 years. PLoS Med. 2013; 10(5): e1001446. doi:10.1371/journal.pmed.1001446.
Q. Scott J, Brooks A, Peiris J, Holtzman D, Mulholland E. Pneumonia research to reduce childhood mortality in the developing world. J Clin Invest. 2008; 118: 1291-1300. doi:10.1172/JCI33947.

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[31], 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[32]. Medical structural genomics[33], transcriptomics[34], and proteomics[35] 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[3637]. 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[38]. 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[39].

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

[31] Nabel GJ. Designing tomorrow's vaccines. The New England journal of medicine. 2013 Feb 7;368(6):551-60.
[32] Eisen JA, MacCallum CJ. Genomics of emerging infectious disease: A PLoS collection. PLoS biology. 2009;7(10):e1000224. Epub 2009/10/27.
[33] Van Voorhis WC, Hol WG, Myler PJ, Stewart LJ. The role of medical structural genomics in discovering new drugs for infectious diseases. PLoS computational biology. 2009;5(10):e1000530. Epub 2009/10/27.
[34] Seib KL, Dougan G, Rappuoli R. The key role of genomics in modern vaccine and drug design for emerging infectious diseases. PLoS genetics. 2009;5(10):e1000612. Epub 2009/10/27.
[35] Seib KL, Dougan G, Rappuoli R. The key role of genomics in modern vaccine and drug design for emerging infectious diseases. PLoS genetics. 2009;5(10):e1000612. Epub 2009/10/27.
[36] IOM (Institute of Medicine). 2013. The Science and Applications of Microbial Genomics: Workshop Summary. Washington, DC: The National Academies Press.
[37] Coloma J, Harris E. Molecular genomic approaches to infectious diseases in resource-limited settings. PLoS medicine. 2009;6(10):e1000142. Epub 2009/10/27.
[38] 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.
[39] Coloma J, Harris E. Molecular genomic approaches to infectious diseases in resource-limited settings. PLoS medicine. 2009;6(10):e1000142. Epub 2009/10/27.
[40] 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[41]. Nanotechnology strategies have been considered for HIV[4243], malaria[444546], TB[4748], influenza[49], and Chagas disease[50], 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[51].

[41] 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.
[42] Mahajan SD, Aalinkeel R, Law WC, Reynolds JL, Nair BB, Sykes DE, et al. Anti-HIV-1 nanotherapeutics: promises and challenges for the future. Int J Nanomedicine. 2012;7:5301-14.
[43] Chadwick S, Kriegel C, Amiji M. Nanotechnology solutions for mucosal immunization. Advanced drug delivery reviews. 2010 Mar 18;62(4-5):394-407.
[44] Chadwick S, Kriegel C, Amiji M. Nanotechnology solutions for mucosal immunization. Advanced drug delivery reviews. 2010 Mar 18;62(4-5):394-407.
[45] Santos-Magalhaes NS, Mosqueira VC. Nanotechnology applied to the treatment of malaria. Advanced drug delivery reviews. 2010 Mar 18;62(4-5):560-75.
[46] Look M, Bandyopadhyay A, Blum JS, Fahmy TM. Application of nanotechnologies for improved immune response against infectious diseases in the developing world. Advanced drug delivery reviews. 2010 Mar 18;62(4-5):378-93.
[47] Look M, Bandyopadhyay A, Blum JS, Fahmy TM. Application of nanotechnologies for improved immune response against infectious diseases in the developing world. Advanced drug delivery reviews. 2010 Mar 18;62(4-5):378-93.
[48] Chadwick S, Kriegel C, Amiji M. Nanotechnology solutions for mucosal immunization. Advanced drug delivery reviews. 2010 Mar 18;62(4-5):394-407.
[49] Kanekiyo M, Wei CJ, Yassine HM, McTamney PM, Boyington JC, Whittle JR, et al. Self-assembling influenza nanoparticle vaccines elicit broadly neutralizing H1N1 antibodies. Nature. 2013 Jul 4;499(7456):102-6.
[50] Romero EL, Morilla MJ. Nanotechnological approaches against Chagas disease. Advanced drug delivery reviews. 2010 Mar 18;62(4-5):576-88.
[51] Chadwick S, Kriegel C, Amiji M. Nanotechnology solutions for mucosal immunization. Advanced drug delivery reviews. 2010 Mar 18;62(4-5):394-407.

APPENDIX 6: MASTER REFERENCE LIST

Ad Hoc Committee on Health Research Relating to Future Intervention Options. Investing in Health Research and Development. Geneva: WHO; 1996. http://whqlibdoc.who.int/hq/1996/TDR_Gen_96.1_pp1-34.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_pp195-278.pdf. Accessed 15 April 2010.

Adams Jr. R. International Migration, Remittances and the Brain Drain: A Study of 24 Labor-Exporting Countries. Policy Research Working Paper 3069. World Bank. 2003.

Aggleton P. "Just a snip"?: a social history of male circumcision. Reproductive Health Matters. 2007; **15**(29): 15-21. http://www.hsph.harvard.edu/pihhr/files/RHM/RHM29%20-%20Aggleton.pdf. Accessed 14 May 2008.

Ahmedov M, Kennedy A, IJsselmuiden C. Governance and policy frameworks for health research in 38 countries. COHRED – Council on Health Research for Development. UNESCO Forum on Higher Education, Research and Knowledge: Global research seminar: sharing research agendas on knowledge systems; 2008; Paris: UNESCO. http://portal.unesco.org/education/en/files/58048/12246671755Ahmedov.pdf/Ahmedov.pdf. Accessed 29 April 2010.

Akhtar T, Khan J. Health research capacity in Pakistan: A country report prepared for the WHO and COHRED Regional Consultation on Health Research for Development. Council on Health Research for Development. 2000.

Albert E, Mickan S. Closing the gap and widening the scope. New directions for research capacity building in primary health care. Australian Family Physician. 2003; **32**(12): 1038-40, 43.

Aleta IR. A decade of health systems research: Lessons learnt and recasting the strategies for research capacity strengthening. Geneva: Alliance for Health Policy and Systems Research; 2000.

Alliance for Health Policy and Systems Research. HPSR capacity strengthening: Report on the consultation held in Bangkok, 14 October 2000, and implications for the Alliance. Geneva: Alliance for Health Policy and Systems Research; 2000.

Alliance for Health Policy and Systems Research. Strengthening health systems: the role and promise of policy and systems research. Geneva: Global Forum for Health Research; 2004.

Alliance for Health Policy and Systems Research. Sound Choices - Enhancing Capacity for Evidence-Informed Health Policy. Geneva: World Health Organization; 2007.

Ambroggio L, Thomson J, Kurowski EM, Courter J, Statile A, Graham C, et al. Quality Improvement Methods Increase Appropriate Antibiotic Prescribing for Childhood Pneumonia. Pediatrics. 2013; **131**(5): e1623-e31.

Andreano RL. An informal assessment of the international health policy programme. Working Paper. Geneva: Alliance for Health Policy and Systems Research; 2000.

Andruchow JE, Soskolne CL, Racioppi F, Bertollini R. Capacity building for epidemiologic research: a case study in the newly independent state of Azerbaijan. Annals of Epidemiology. 2005; **15**(3): 228-31.

Bates I, Akoto AYO, Ansong D, Karikari P, Bedu-Addo G, Critchley J, et al. Evaluating health research capacity building: an evidence-based tool. PLoS medicine. 2006; **3**(8): e299.

Bautista MCRB, Velho L, Kaplan D. Comparative Study of the Impacts of Donor-initiated Programmes on Research Capacity in the South: International Report. Report to the Directorate General of Development Cooperation (DGIS) Research and Developing Countries Division: Ministry of Foreign Affairs of The Netherlands; 2001.

Beaglehole R, Dal Poz MR. Public health workforce: challenges and policy issues. Human Resources for Health. 2003; **1**(1): 4.

Beattie P, Renshaw M, Davies CS. Strengthening health research in the developing world: malaria research capacity in Africa: Wellcome Trust for the Multilateral Initiative on Malaria; 1999.

Berger M, Murugi J, Buch E, IJsselmuiden C, Moran M, Guzman J, et al. Strengthening pharmaceutical innovation in Africa: Designing strategies for national pharmaceutical

innovation: choices for decision makers and countries: African Union, Council on Health Research for Development (COHRED), & New Partnership for Africa's Development (NEPAD); 2010.

Berglund EC, Nystedt B, Andersson SG. Computational resources in infectious disease: limitations and challenges. PLoS computational biology. 2009; **5**(10): e1000481. http://www.ncbi.nlm.nih.gov/pubmed/19855825.

Bhutta ZA, Das JK, Walker N, Rizvi A, Campbell H, Rudan I, et al. Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? The Lancet. 2013.

Binka F. Editorial: North–South research collaborations: a move towards a true partnership? Tropical Medicine & International Health. 2005; **10**(3): 207-9.

Binka F. Building national capacity for health research: the role of South-based networks such as INDEPTH. Global Forum for Health Research - Forum 9; 2005; Mumbai.

Blanchet N, Thomas M, Atun R, Jamison D, Knaul F, Hecht R. Global collective action in health: The WDR+ 20 landscape of core and supportive functions. Working paper: Lancet Commission on Investing in Health; 2013.

Boeren A, Alberts T, Alveteg T, Thulstrup EW, Trojer L. Sida/SAREC Bilateral Research Cooperation: Lessons Learned. Stockholm: Swedish International Development Cooperation Agency; 2006.

Brennan MJ, Thole J, Editors. Supplement: Tuberculosis Vaccines: A Strategic Blueprint for the Next Decade. Tuberculosis: Elsevier; 2012. p. S1–S35.

Brindley PJ, Mitreva M, Ghedin E, Lustigman S. Helminth genomics: The implications for human health. PLoS neglected tropical diseases. 2009; **3**(10): e538. http://www.ncbi.nlm.nih.gov/pubmed/19855829.

Bubela TM, Caulfield TA. Do the print media "hype" genetic research? A comparison of newspaper stories and peer-reviewed research papers. Canadian Medical Association Journal. 2004; **170**(9): 1399-407.

Bundred PE, Levitt C. Medical migration: who are the real losers? The Lancet. 2000; **356**(9225): 245-6.

Burke MA, de Francisco A, Moran M, Guzman J, Light D, Guimaraes R, et al. Monitoring financial flows for health research 2005: Behind the global numbers. Geneva: Global Forum for Health Research; 2006.

Burke MA, de Fransisco A. Monitoring financial flows for health research: Volume 2. Geneva: Global Forum for Health Research; 2004.

Burke MA, Matlin SA. Monitoring financial flows for health research 2008: prioritizing research for health and health equity. Geneva: Global Forum for Health Research; 2008.

Burki TK. Ticks and Turkey. The Lancet. 2012; **380**(9857): 1897-8.

Buse K, Mays N, Walt G. Making Health Policy. In: Black N, Raine R, editors. Understanding Public Health. Maidenhead, England: Open University Press; 2005. http://ssu.ac.ir/fileadmin/templates/fa/Moavenatha/Moavenate-Amozeshi/edicupload/modiriate_1/M__1_.pdf.

Campbell S, Schryer-Roy AM, Jessani N. The RM Knowledge Translation Toolkit: A Resource for Researchers. International Development Research Centre (IDRC) & Swiss Agency for Development and Cooperation (SDC); 2008. http://www.idrc.ca/uploads/user-S/12266886561Research_Matters_-_Knowledge_Translation_Toolkit_.pdf.

Canadian Institutes of Health Research. The CIHR Knowledge Translation Strategy 2004-2009: Innovation in Action; 2004. http://www.cihr-irsc.gc.ca/e/26574.html. Accessed 14 May 2007.

Cao X. Debating 'Brain Drain' in the Context of Globalisation. Compare: A Journal of Comparative and International Education 1996; **26**(3): 269–85.

Cardenas M, Perry G. Capacity Building in Economic Education and Research: A Note on the Experience of Latin America and the Caribbean (LAC). Budapest: World Bank & Central European University (CEU); 2005.

Carey-Burngarner E. Chapter 7: Capacity Development for Health Research. In: Secretariat of the Global Forum for Health Research (GFHR), editor. The 10/90 Report on Health Research 1999. Geneva: Global Forum for Health Research; 1999.

Carrington WJ, Detragiache E. How big is the brain drain? IMF Working Paper No. 98/102: International Monetary Fund; 1998. www.imf.org/external/pubs/ft/wp/wp98102.pdf.

Castanos LH. The brain drain from Mexico: the experience of scientists. Science and Public Policy. 1998; **25**(4): 247-53.

Castillo G. Revisiting capacity development: COHRED Learning Brief No. 2002/1. Geneva: Council on Health Research for Development; 2002.

Chadwick S, Kriegel C, Amiji M. Nanotechnology solutions for mucosal immunization. Advanced drug delivery reviews. 2010; **62**(4-5): 394-407. http://www.ncbi.nlm.nih.gov/pubmed/19931581.

Chan M, Lake A. Integrated action for the prevention and control of pneumonia and diarrhoea. The Lancet. 2013; **381**(9876): 1436-7.

Chopra M, Mason E, Borrazzo J, Campbell H, Rudan I, Liu L, et al. Ending of preventable deaths from pneumonia and diarrhoea: an achievable goal. The Lancet. 2013; **381**(9876): 1499-506.

Chowdhury SA, Block MAG, Harrison D. Health policy and systems research in Africa, Asia, and Latin America. Geneva: Alliance for Health Policy and Systems Research; 2000.

Clinton Health Access Initiative (CHAI), Evidence to Policy Initiative (E2Pi), African Leaders Malaria Alliance. Maintaining the Gains in Global Malaria Control: the Health and Economic Benefits of Sustaining Control Measures; 2011. http://globalhealthsciences.ucsf.edu/sites/default/files/content/ghg/e2pi-maintaining-the-gains.pdf.

Coloma J, Harris E. Molecular genomic approaches to infectious diseases in resource-limited settings. PLoS medicine. 2009; **6**(10): e1000142. http://www.ncbi.nlm.nih.gov/pubmed/19855820.

Comas I, Gagneux S. The past and future of tuberculosis research. PLoS pathogens. 2009; **5**(10): e1000600. http://www.ncbi.nlm.nih.gov/pubmed/19855821.

Commission on Health Research for Development. Health research: essential link to equity in development: Oxford University Press; 1990. http://www.cohred.org/downloads/open_archive/ComReports_0.pdf.

Conceição C, Leandro A, McCarthy M. National support to public health research: a survey of European ministries. BMC Public Health. 2009; **9**(1): 203.

Cook TE. Governing with the news: The news media as a political institution: University of Chicago Press; 1998.

Cooke A, Green B. Developing the research capacity of departments of nursing and midwifery based in higher education: a review of the literature. Journal of Advanced Nursing. 2000; **32**(1): 57-65.

Cooke J. A framework to evaluate research capacity building in health care. BMC Family Practice. 2005; **6**(1): 44.

Costello A, Zumla A. Moving to research partnerships in developing countries. BMJ: British Medical Journal. 2000; **321**(7264): 827.

Council on Health Research for Development (COHRED). International Conference on Health Research for Development, Bangkok 10–13 October 2000. Conference Report. Geneva: Council on Health Research for Development; 2001. http://www.cohred.org/downloads/708.pdf.

Council on Health Research for Development (COHRED). Health Research Web. http://www.healthresearchweb.org/.

Council on Health Research for Development (COHRED). Annual Report: Council on Health Research for Development (COHRED); 2012. http://www.cohred.org/wp-content/uploads/2013/03/COHRED_AR_web-copy-2012.pdf.

Council on Health Research for Development (COHRED). Beyond Aid: Research and innovation as key drivers for health, equity and development: Council on Health Research for Development (COHRED); 2012. http://www.cohred.org/wp-content/uploads/2011/05/COHRED_forum2012_web_NEW1.pdf1.pdf-low-res1.pdf.

Council on Health Research for Development (COHRED), The Lancet Commission on Investing in Health. Colloquium 2013 Report: Sustainable investments into research and innovation: COHRED; 2013. http://www.cohred.org/wp-content/uploads/2013/01/COHRED-Colloquium_Report_FINAL.pdf.

Crewe E, Young J. Bridging research and policy: context, evidence and links: Overseas Development Institute London; 2002.

Curat LJ, de Fransisco A, Al-Tuwaijri S, Ghaffar A, Jupp S. The 10/90 Report on Health Research, 2003-2004; 2004.

Currat LJ, de Fransisco A, Nchinda T. The 10/90 Report on Health Research 2000. Geneva: Global Forum for Health Research; 2000.

Currat LJ, de Fransisco A, Nchinda T. The 10/90 Report on Health Research 2001-2002; 2002.

Darby R. the sorcerer's apprentice: why can't we stop circumcising boys? contexts. 2005; **4**(2): 34-9.

de Fransisco A, Matlian S. Monitoring financial flows for health research 2006: the changing landscape of health research for development. Geneva: Global Forum for Health Research; 2006.

Dickson D. Nigeria, South Africa, and Uganda win academy funds. SciDevNet. http://www.scidev.net/global/capacity-building/news/nigeria-south-africa-and-uganda-win-academy-funds.html.

Docquier F, Rapoport H. Skilled migration: the perspective of developing countries: World Bank Publications; 2004.

Dorer MS, Talarico S, Salama NR. Helicobacter pylori's unconventional role in health and disease. PLoS pathogens. 2009; **5**(10): e1000544. http://www.ncbi.nlm.nih.gov/pubmed/19855816.

Dugger C. 'Brain drain' is damaging world's poorest countries, study shows. International Herald Tribune. 2005. http://www.highbeam.com/doc/1P1-114528888.html.

Eisen JA, MacCallum CJ. Genomics of emerging infectious disease: A PLoS collection. PLoS biology. 2009; **7**(10): e1000224. http://www.ncbi.nlm.nih.gov/pubmed/19855830.

El-Jardali F, Makhoul J, Jamal D, Ranson MK, Kronfol NM, Tchaghchagian V. Eliciting policymakers' and stakeholders' opinions to help shape health system research priorities in the Middle East and North Africa region. Health policy and planning. 2010; **25**(1): 15-27.

Entwistle VA, Watt IS. Judging journalism: how should the quality of news reporting about clinical interventions be assessed and improved? Quality in health care: QHC. 1999; **8**(3): 172.

Eskola J, Kilpi T. Public-private collaboration in vaccine research. Lancet. 2011; **378**(9789): 385-6. http://www.ncbi.nlm.nih.gov/pubmed/21664686.

European Commission. European Research: A Guide to Successful Communications. Luxembourg: European Commission; 2004. http://www.knowledgeboard.com/item/1866/23/5/3. Accessed 14 May 2008.

European Commission. Final Report: Challenges for the Future Research on HIV/AIDS, Malaria, and Tuberculosis. Luxembourg: Office for Official Publications of the European Communities; 2009. http://ec.europa.eu/research/conferences/2008/poverty-related-diseases/docs/conference-report-2008_en.pdf.

European Science Foundation. Policy Brief 43: Health Research Classification Systems - Current Approaches and Future Recommendations. Brussels: European Science Foundation; 2011. http://www.esf.org/fileadmin/Public_documents/Publications/spb43_Health_Research_Classification.pdf.

Evans DB, Marten R, Etienne C. Universal health coverage is a development issue. The Lancet. 2012; **380**(9845): 864-5.

Falush D. Toward the use of genomics to study microevolutionary change in bacteria. PLoS genetics. 2009; **5**(10): e1000627. http://www.ncbi.nlm.nih.gov/pubmed/19855823.

Fauci AS, Johnston MI, Dieffenbach CW, Burton DR, Hammer SM, Hoxie JA, et al. HIV vaccine research: the way forward. Science. 2008; 321(5888): 530-2. http://www.ncbi.nlm.nih.gov/pubmed/18653883.

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

Fleurence RL, Torgerson DJ. Setting priorities for research. Health Policy. 2004; **69**(1): 1-10.

Fogarty International Center. Review of the International Training and Research Program in Population and Health (ITRPH). Maryland: Fogarty International Center; 2005. http://www.fic.nih.gov/about/staff/policy-planning-evaluation/documents/itrph.pdf.

Frenk J, de Ferranti D. Universal health coverage: good health, good economics. The Lancet. 2012; **380**(9845): 862-4.

Fricke WF, Rasko DA, Ravel J. The role of genomics in the identification, prediction, and prevention of biological threats. PLoS biology. 2009; **7**(10): e1000217. http://www.ncbi.nlm.nih.gov/pubmed/19855827.

Ghaffar A. Three pillars of priority setting for health research: process, tools and values. London; 2006.

Ghaffar A, Collins T, Marlin SA, Olifson S. The 3D Combined Approach Matrix - An Improved Tool for Setting Priorities in Research for Health. Geneva: Global Health Forum for Health Research; 2009.

Ghaffar DA, IJsselmuiden C, Zicker F. Changing Mindsets: Research Capacity Strengthening in Low-and Middle-Income Countries: Council on Health Research for Development (COHRED), Global Forum for Health Research, & UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR); 2008.

Gill CJ, Young M, Schroder K, Carvajal-Velez L, McNabb M, Aboubaker S, et al. Bottlenecks, barriers, and solutions: results from multicountry consultations focused on reduction of childhood pneumonia and diarrhoea deaths. The Lancet. 2013.

Glassman A, Chalkidou K. Priority-setting in health: Building institutions for smarter public spending. health. 2012.

Global Forum for Health Research. Monitoring Financial Flows for Health Research: 2001. 2001: Global Forum for Health Research.

Global Strategy and Plan of Action on Public Health. Innovation and Intellectual Property. Sixty-first World Health Assembly 19–24 May 2008, Resolution WHA61.21. Geneva: World Health Organization; 2008.

Glynn C. Public Opinion. Boulder, United States: Westview Press; 1999.

Grilli R, Ramsay C, Minozzi S. Mass media interventions: effects on health services utilisation. Cochrane Database Syst Rev. 2002; **1**(1).

Güngör ND, Tansel A. Brain Drain from Turkey: an investigation of students' return intentions. Applied Economics. 2008; **40**(23): 3069-87.

Gupta R, Michalski MH, Rijsberman FR. Can an infectious disease genomics project predict and prevent the next pandemic? PLoS biology. 2009; **7**(10): e1000219. http://www.ncbi.nlm.nih.gov/pubmed/19855828.

Gyapong JO, Ofori-Adeji D. Capacity building for relevant health research in developing counties. Netherlands: Netherlands Organisation for International Cooperation in Higher Education. 2006.

Haagmans BL, Andeweg AC, Osterhaus AD. The application of genomics to emerging zoonotic viral diseases. PLoS pathogens. 2009; **5**(10): e1000557. http://www.ncbi.nlm.nih.gov/pubmed/19855817.

Halstead SB, Tugwell P, Bennett K. The international clinical epidemiology network (INCLEN): a progress report. Journal of clinical epidemiology. 1991; **44**(6): 579-89.

Henshall C, Oortwijn W, Stevens A, Granados A, Banta D. Priority Setting for Health Technology Assessment: Theoretical Considerations and Practical Approaches: A paper produced by the Priority Setting Subgroup of the EUR-ASSESS Project. International journal of technology assessment in health care. 1997; **13**(02): 144-85.

Hilderbrand ME, Grindle MS. Building sustainable capacity: challenges for the public sector: Prepared for the United Nations Development Programme, Pilot Study of Capacity Building by the Harvard Institute for International Development, Harvard University; 1994.

HIV Vaccines & Microbicides Resource Tracking Group (TWG). Investing to End the AIDS Epidemic: A New Era for HIV Prevention Research and Development: HIV Vaccines & Microbicides Resource Tracking Group; 2012. http://www.hivresourcetracking.org/sites/default/files/July%202012%20Investing%20to%20End%20the%20AIDS%20Epidemic-%20A%20New%20Era%20for%20HIV%20Prevention%20Research%20&%20Development.pdf.

Hoffman SJ, Røttingen J-A. Assessing implementation mechanisms for an international agreement on research and development for health products. Bulletin of the World Health Organization. 2012; **90**(11): 854-63.

Holmes EC, Grenfell BT. Discovering the phylodynamics of RNA viruses. PLoS computational biology. 2009; **5**(10): e1000505. http://www.ncbi.nlm.nih.gov/pubmed/19855824.

Horton D. Evaluating capacity development: experiences from research and development organizations around the world: IDRC; 2003.

Hotez PJ. New antipoverty drugs, vaccines, and diagnostics: a research agenda for the US President's Global Health Initiative (GHI). PLoS neglected tropical diseases. 2011; **5**(5): e1133.

Hovland I. Successful Communication: A toolkit for researchers and civil society organisations: Overseas development institute (ODI). Research and policy in development programme (RAPID); 2005.

Howitt P, Darzi A, Yang G-Z, Ashrafian H, Atun R, Barlow J, et al. Technologies for global health. The Lancet. 2012.

Huda T, Nair H, Theodoratou E, Zgaga L, Fattom A, El Arifeen S, et al. An evaluation of the emerging vaccines and immunotherapy against staphylococcal pneumonia in children. BMC public health. 2011; **11**(Suppl 3): S27.

Hyder AA, Akhter T, Qayyum A. Capacity development for health research in Pakistan: the effects of doctoral training. Health Policy and Planning. 2003; **18**(3): 338-43.

Ijsselmuiden C. Human resources for health research. Medicus Mundi Bulletin. 2007; **104**: 22-7.

Ijsselmuiden C, Marais D, Wassenaar D, Mokgatla-Moipolai B. Mapping African ethical review committee activity onto capacity needs: the MARC initiative and HRWeb's interactive database of RECs in Africa. Developing World Bioethics. 2012; **12**(2): 74-86.

IJsselmuiden C, Matlin S. Why health research?: Council on Health Research for Development; 2006.

Institute of Medicine. Genome-Based Therapeutics: Targeted Drug Discovery and Development: Workshop Summary; 2012; Washington (DC): Institute of Medicine. http://www.ncbi.nlm.nih.gov/pubmed/23346605.

International Development Research Centre. Capacity building strategic evaluation : summary of findings of phase 1 and 2. Ottawa: International Development Research Centre; 2006. http://idl-bnc.idrc.ca/dspace/bitstream/10625/33600/1/123661.pdf.

Jentsch B, Pilley C. Research relationships between the South and the North: Cinderella and the ugly sisters? Social Science & Medicine. 2003; **57**(10): 1957-67.

Johnson K, Kennedy SB, Harris AO, Lincoln A, Neace W, Collins D. Strengthening the HIV/AIDS service delivery system in Liberia: an international research capacity-building strategy. Journal of evaluation in clinical practice. 2005; **11**(3): 257-73.

Joint United Nations Programme on HIV/AIDS (UNAIDS). World AIDS Day Report 2012. Geneva: UNAIDS; 2012. http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/JC2434_WorldAIDSday_results_en.pdf.

Kaittanis C, Santra S, Perez JM. Emerging nanotechnology-based strategies for the identification of microbial pathogenesis. Advanced drug delivery reviews. 2010; **62**(4-5): 408-23. http://www.ncbi.nlm.nih.gov/pubmed/19914316.

Kanekiyo M, Wei CJ, Yassine HM, McTamney PM, Boyington JC, Whittle JR, et al. Self-assembling influenza nanoparticle vaccines elicit broadly neutralizing H1N1 antibodies. Nature. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23698367.

Kaplan W, Laing R. Priority medicines for Europe and the world: World Health Organization Geneva; 2004.

Kapur D, McHale J, McHale JF. Give us your best and brightest: The global hunt for talent and its impact on the developing world: Brookings Inst Press; 2005.

Karesh WB, Dobson A, Lloyd-Smith JO, Lubroth J, Dixon MA, Bennett M, et al. Ecology of zoonoses: natural and unnatural histories. The Lancet. 2012; **380**(9857): 1936-45.

Kazlauskienė A, Rinkevičius L. Lithuanian "Brain Drain" Causes: Push and Pull Factors. Engineering economics. 2006; (1 (46): 27-37.

Kazlauskienė A, Rinkevičius L. The role of social capital in the highly-skilled migration from Lithuania. Engineering economics. 2006; (4 (49): 69-75.

Kennedy A, IJsselmuiden C. Building & strengthening national health research systems. A manager's guide to developing and managing effective health research systems Geneva: Council on Health Research for Development. 2006.

Keusch GT, Scrimshaw NS. Selective primary health care: strategies for control of disease in the developing world. XXIII. Control of infection to reduce the prevalence of infantile and childhood malnutrition. Review of Infectious Diseases. 1986; **8**(2): 273-87.

KFPE (Commission for Research Partnerships with Developing Countries). Guidelines for research in partnership with developing countries. Berne: KFPE; 1998. http://www.kfpe.ch/download/Guidelines_e.pdf.

KFPE (Commission for Research Partnerships with Developing Countries). Enhancing research capacity in developing and transition countries: COHRED; 2001.

Kikwete J, Jenkins K, Whitbread J. Playing our part to save children's lives. The Lancet. 2013; **381**(9880): 1798-9.

Kilpatrick AM, Randolph SE. Drivers, dynamics, and control of emerging vector-borne zoonotic diseases. The Lancet. 2012; **380**(9857): 1946-55.

Kupfer L, Hoffman K, Jarawan R, McDermott J, Bridbord K. Strategies to discourage brain drain. Bulletin of the World Health Organization. 2004.

Kusimba S. Kenya: Elaborate Passages into Manhood. The Daily Nation. 2004. http://allafrica.com/stories/200408110450.html.

Ladi S, Pop D, Street N. Approaches to Measuring Capacity and Capacity-Building for Policy-Research. 2004.

Landriault E, Matlin SA. Monitoring financial flows for health research 2009: behind the global numbers. 2009: Global Forum for Health Research.

Lansang MA, Dennis R. Building capacity in health research in the developing world. Bulletin of the World Health Organization. 2004; **82**(10): 764-70.

Larsen PO, von Ins M. The rate of growth in scientific publication and the decline in coverage provided by Science Citation Index. Scientometrics. 2010; **84**(3): 575-603.

Larsson A, Oxman AD, Carling C, Herrin J. Medical messages in the media–barriers and solutions to improving medical journalism. Health Expectations. 2003; **6**(4): 323-31.

Latko B, Temporão JG, Frenk J, Evans TG, Chen LC, Pablos-Mendez A, et al. The growing movement for universal health coverage. The Lancet. 2011; **377**(9784): 2161-3.

Lawn SD, Mwaba P, Bates M, Piatek A, Alexander H, Marais BJ, et al. Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test. The Lancet infectious diseases. 2013; **13**(4): 349-61.

Lloyd LM. Tips for Using the Media. Communication & Information Management Resource Centre (CIMRC); 2005.

Logan BI. The Reverse Transfer of Technology from Sub-Saharan Africa: The Case of Zimbabwe. International Migration. 1999; **37**(2): 437-63.

Lomas J, Fulop N, Gagnon D, Allen P. On being a good listener: setting priorities for applied health services research. Milbank Quarterly. 2003; **81**(3): 363-88.

Look M, Bandyopadhyay A, Blum JS, Fahmy TM. Application of nanotechnologies for improved immune response against infectious diseases in the developing world. Advanced drug delivery reviews. 2010; **62**(4-5): 378-93. http://www.ncbi.nlm.nih.gov/pubmed/19922750.

Lowell BL. Policy responses to the international mobility of skilled labour. International Migration Branch, International Labour Office. 2001.

Lowell BL, Findlay A. Migration of highly skilled persons from developing countries: impact and policy responses. International Migration Papers. 2001; **44**.

Mackay R, Horton D, Dupleich L, Andersen A. Evaluating organizational capacity development. Canadian Journal of Program Evaluation. 2002; **17**(2): 121-50.

Maconick R, Morgan P. Capacity-building supported by the United Nations: some evaluations and some lessons: United Nations; 1999.

Mahajan SD, Aalinkeel R, Law WC, Reynolds JL, Nair BB, Sykes DE, et al. Anti-HIV-1 nanotherapeutics: promises and challenges for the future. Int J Nanomedicine. 2012; **7**: 5301-14. http://www.ncbi.nlm.nih.gov/pubmed/23055735.

Maina-Ahlberg B, Nordberg E, Tomson G. North-South health research collaboration: challenges in institutional interaction. Social Science & Medicine. 1997; **44**(8): 1229-38.

McCarthy FD, Bader W, Pleskovic B. Creating partnerships for capacity building in developing countries. World Bank Policy Research Working Paper. 2003; **3099**.

McHardy AC, Adams B. The role of genomics in tracking the evolution of influenza A virus. PLoS pathogens. 2009; **5**(10): e1000566. http://www.ncbi.nlm.nih.gov/pubmed/19855818.

Mervis JD, Normile D. Science in Southeast Asia: Getting ready for prime time. Science. 1998: 279.

Michaud C, Murray C. Resources for health research and development in 1992: a global overview. World Health Organization, Investing in Health Research and Development Geneva. 1996.

Montorzi G, De Haan S, Ijsselmuiden C. Priority setting for health research: A management process for countries. Council on Health Research Development (COHRED): http://www cohred ch/prioritysetting. 2010.

Montorzi G, de Haan S, Jsselmuiden C. Priority Setting for Health Research: Toward a management process for low and middle income countries. Geneva: COHRED; 2010. http://www.cohred.org/sites/default/files/WP1_PrioritySetting.pdf.

Moon S. Medicines as global public goods: The governance of technological innovation in the new era of global health. Global Health Governance. 2009; **2**(2).

Moon S, Bermudez J, Hoen Et. Innovation and access to medicines for neglected populations: could a treaty address a broken pharmaceutical R&D system? PLoS medicine. 2012; **9**(5): e1001218.

Moore M, Stewart S, Hudock A. Institution building as a development assistance method. A review of literature and ideas. Report September 1994: SIDA; 1995.

Moran M, Guzman J, Abela-Oversteegen L, Liyanage R, Omune B, Wu L, et al. Neglected disease research and development: is innovation under threat?: G-FINDER; 2011.

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.

Moran M, Guzman J, McDonald A, Wu L, Omune B. Registering New Drugs: The African Context. London: The George Institute for International Health; 2010.

Moran M, Guzman J, Ropars A, Jorgensen M, McDonald A, Potter S, et al. The malaria product pipeline: planning for the future. The George Institute for International Health; 2007.

Moran M, Ropars A-L, Guzman J, Diaz J, Garrison C. The new landscape of neglected disease drug development. The new landscape of neglected disease drug development. 2005.

Morgan P. An update on the performance monitoring of capacity development programs: What are we learning. Hull: Canadian International Development Agency. 1999.

Morse SS, Mazet JA, Woolhouse M, Parrish CR, Carroll D, Karesh WB, et al. Prediction and prevention of the next pandemic zoonosis. The Lancet. 2012; **380**(9857): 1956-65.

Murray C, Bell D, DeJonghe E, Zaidi S, Michaud C. A study of financial resources devoted to research on health problems of developing countries. The Journal of tropical medicine and hygiene. 1990; **93**(4): 229-55.

Murray CJ, Frenk J. A framework for assessing the performance of health systems. Bulletin of the World Health Organization. 2000; **78**(6): 717-31.

Murtagh MM. UNITAIDS Technical Report. HIV/AIDS diagnostic landscape. 2011.

Muthuri P, Wachira M. School where students have to be men. The Daily Nation. 2007.

Mwangi M. Circumcision comes of age. The Daily Nation.

Nabel GJ. Designing tomorrow's vaccines. The New England journal of medicine. 2013; **368**(6): 551-60. http://www.ncbi.nlm.nih.gov/pubmed/23388006.

Nchinda TC. Research capacity strengthening in the South. Social science & medicine. 2002; **54**(11): 1699-711.

Neilson S, Lusthaus C. IDRC-Supported capacity building: developing a framework for capturing capacity changes. Report by Universalia Consultants for IDRC Evaluation Unit. 2007.

NEPAD Planning and Coordinating Agency. NEPAD agency business plan 2012: NEPAD Planning and Coordinating Agency; 2012. http://www.nepad.org/system/files/NEPAD%20Planning%20and%20Coordinating%20Agency%20Business%20Plan%202012%20pdf.pdf.

New Diagnostics Working Group of the Stop TB Partnership. Pathways to better diagnostics for tuberculosis: a blueprint for the development of TB diagnostics. Geneva: WHO; 2009.

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/.

NIH News. Adult Male Circumcision Significantly Reduces Risk of Acquiring HIV. National Institute of Allergies and Infectious Diseases (NIAID). 2006. http://www.nih.gov/news/pr/dec2006/niaid-13.htm. Accessed 14 May 2008.

Nurse K, Wight D. Development assistance and research capacity strengthening: The commissioning of health social science research in East Africa. Journal of Eastern African Studies. 2011; **5**(2).

Nuyens Y. No development without research: a challenge for research capacity strengthening. 2005: Global Forum for Health Research Geneva.

Nuyens Y. Setting priorities for health research: lessons from low-and middle-income countries. Bulletin of the World Health Organization. 2007; **85**(4): 319-21.

Odhiambo E. The knife won't give us the President we desire. The East African Standard. 2007.

OECD. Frascati Manual 2002: Proposed Standard Practice for Surveys on Research and Experimental Development: OECD; 2002.

OECD. Paris Declaration on Aid Effectiveness and the Accra Agenda for Action. 2005.

Okello D, Chongtrakul P. COHRED Working Group on Priority Setting. A Manual for Research Priority Setting using the ENHR Strategy. 2000.

Onyango-Obbo C. Africans are Too Promiscuous for Monogamy, Let's Circumcise Them. The East African. 2007.

Overseas Development Institute (ODI), Chronic Poverty Research Center (CPRC). Getting into the kitchen: media strategies for research; 2005. http://panosrelay.org.uk/wp-content/static/getting_into_kitchen.pdf.

Overseas Development Institute (ODI), Chronic Poverty Research Centre (CPRC). A Researcher's Guide to Working with the Media. London: Panos. http://www.hedon.info/docs/relay_researchers_guide.pdf.

Oxman AD, Schünemann HJ, Fretheim A. Improving the use of research evidence in guideline development: 2. Priority setting. Health Research Policy and Systems. 2006; **4**(14): 14.

Pang T, Sadana R, Hanney S, Bhutta ZA, Hyder AA, Simon J. Knowledge for better health: a conceptual framework and foundation for health research systems. Bulletin of the World Health Organization. 2003; **81**(11): 815-20.

Paraje G, Sadana R, Karam G. Increasing international gaps in health-related publications. Science. 2005; **308**(5724): 959-60.

Patel MM, Glass R, Desai R, Tate JE, Parashar UD. Fulfilling the promise of rotavirus vaccines: how far have we come since licensure? The Lancet Infectious Diseases. 2012; **12**(7): 561-70.

Popescu D, Patrasca M, Chivu I. Tendencies of International Career of Romanian Researchers: Brain Drain? Journal of Applied Quantitative Methods. 2006; **1**(2): 194-209.

Potter C, Brough R. Systemic capacity building: a hierarchy of needs. Health Policy and Planning. 2004; **19**(5): 336-45.

Program for Appropriate Technology in Health (PATH). Staying the Course? Malaria Research and Development in a Time of Economic Uncertainty. Seattle: PATH; 2011.

Ranson MK, Bennett SC. Priority setting and health policy and systems research. Health Research Policy and Systems. 2009; **7**(27).

Rappuoli R, Black S, Lambert PH. Vaccine discovery and translation of new vaccine technology. The Lancet. 2011; **378**(9788): 360-8. http://www.ncbi.nlm.nih.gov/pubmed/21664687.

Rath A, Olry A, Dhombres F, Brandt MM, Urbero B, Ayme S. Representation of rare diseases in health information systems: the Orphanet approach to serve a wide range of end users. Human Mutation. 2012; **33**(5): 803-8.

Reddy P, Taylor SE, Sifunda S. Research capacity building and collaboration between South African and American partners: the adaptation of an intervention model for HIV/AIDS prevention in corrections research. AIDS Education and Prevention. 2002; **14**(5 Supplement B): 92-102.

Reich MR. Public-private partnerships for public health. In: Reich MR, editor. Cambridge: Harvard University Press; 2002. http://www.hsph.harvard.edu/michael-reich/files/2012/09/Partnerships_book.pdf.

Romero EL, Morilla MJ. Nanotechnological approaches against Chagas disease. Advanced drug delivery reviews. 2010; **62**(4-5): 576-88. http://www.ncbi.nlm.nih.gov/pubmed/19941920.

Røttingen J-A, Chamas C. A new deal for global health R&D? The recommendations of the Consultative Expert Working Group on Research and Development (CEWG). PLoS medicine. 2012; **9**(5): e1001219.

Røttingen J-A, Chamas C, Goyal L, Harb H, Lagrada L, Mayosi BM. Securing the public good of health research and development for developing countries. Bulletin of the World Health Organization. 2012; **90**(5): 398-400.

Røttingen JA, Regmi S, Eide M, Young AJ, Viergever RF, Ardal C, et al. 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; 382(9900): 1286-307. http://www.ncbi.nlm.nih.gov/pubmed/23697824.

Rudan I, Chopra M, Kapiriri L, Gibson J, Lansang MA, Carneiro I, et al. Setting priorities in global child health research investments: universal challenges and conceptual framework. Croatian Medical Journal. 2008; **49**(3): 307-17.

Rudan I, Gibson J, Kapiriri L, Lansang MA, Hyder AA, Lawn J, et al. Setting priorities in global child health research investments: assessment of principles and practice. Croatian Medical Journal. 2007; **48**(5): 595.

Ruffin J, Flagg-Newton JL. Building capacity for health disparity research at minority institutions. The American Journal of the Medical Sciences. 2001; **322**(5): 251-6.

Sadana R, Lee-Martin S-P, Lee J. Health Research System Analysis (HRSA) Initiative: Methods for Collecting Benchmarks and Systems Analysis Toolkit Tool #1. A brief overview of WHO Health Research System Analysis initiative and an overview of core indicators and descriptive variables. WHO. 2004. www.who.int/rpc/health_research/HRSA_brief_Aug06.pdf.

Sadana R, Pang T. Health research systems: a framework for the future. Bulletin of the World Health Organization. 2003; **81**(3): 159-.

Samarasekera U, Horton R. Continuing the child survival revival. The Lancet. 2013; **381**(9875): 1335-6.

Sander C. Development Research Impact: REACH. Paper for presentation at the ICRAF International Workshop, Nairobi, 27–29 April 1998. Ottawa: International Development Research Centre; 1998. http://idl-bnc.idrc.ca/dspace/bitstream/10625/48402/1/IDL-48402.pdf.

Santos-Magalhaes NS, Mosqueira VC. Nanotechnology applied to the treatment of malaria. Advanced drug delivery reviews. 2010; **62**(4-5): 560-75. http://www.ncbi.nlm.nih.gov/pubmed/19914313.

Schneider M. The setting of health research priorities in South Africa: South African Medical Research Council; 2001. http://www.mrc.ac.za/bod/healthpriorities.htm.

Schulz K, Gustafsson I, Illes E. Manual for Capacity Development: Sida; 2005. http://www.sida.se/Publications/Import/pdf/sv/Manual-for-Capacity-Development_1408.pdf.

Schulz-Baldes A, Vayena E, Biller-Andorno N. Sharing benefits in international health research. Research-capacity building as an example of an indirect collective benefit. EMBO Reports. 2007; **8**(1): 8.

Schwitzer G, Mudur G, Henry D, Wilson A, Goozner M, Simbra M, et al. What are the roles and responsibilities of the media in disseminating health information? PLoS medicine. 2005; **2**(7): e215.

Scott JAG, Brooks WA, Peiris JM, Holtzman D, Mulhollan EK. Pneumonia research to reduce childhood mortality in the developing world. The Journal of Clinical Investigation. 2008; **118**(4): 1291.

Seib KL, Dougan G, Rappuoli R. The key role of genomics in modern vaccine and drug design for emerging infectious diseases. PLoS genetics. 2009; **5**(10): e1000612. http://www.ncbi.nlm.nih.gov/pubmed/19855822.

Sen A. Development as Freedom. New York: Anchor Books; 1999.

Simon J. Commentary: Does strengthening research capacity improve health equity? British Medical Journal. 2000: 816-7.

Sitthi-amorn C, Somrongthong R. Strengthening health research capacity in developing countries: a critical element for achieving health equity. British Medical Journal. 2000; **321**(7264): 813.

Smelyanskaya M. Global Investments in HIV Treatment Research and Development in 2010 and 2011. New York: Treatment Action Group (TAG); 2013. http://www.treatmentactiongroup.org/hiv/publications/2013/hiv-treatment-rd-2010-2011.

Sosnik A, Amiji M. Nanotechnology solutions for infectious diseases in developing nations. Preface. Advanced drug delivery reviews. 2010; **62**(4-5): 375-7. http://www.ncbi.nlm.nih.gov/pubmed/19913580.

Start D, Hovland I. Tools for policy impact: a handbook for researchers: Overseas Development Institute London; 2004.

Stone D, Maxwell S, Keating M. Bridging research and policy. An International Workshop Funded by the UK Department for International Development Radcliffe House; 2001; Warwick University.

Tate J, Patel M, Cortese M, Lopman B, Gentsch J, Fleming J, et al. Remaining issues and challenges for rotavirus vaccine in preventing global childhood diarrheal morbidity and mortality. Expert Review of Vaccines. 2012; **11**(2): 211-20.

TDR Disease Reference Group for Zoonoses and Marginalized. Research Priorities for Zoonoses and Marginalized Infections. Geneva: WHO; 2012.

Terry RF, Allen L, Gardner CA, Guzman J, Moran M, Viergever RF. Mapping global health research investments, time for new thinking–a Babel Fish for research data. Health Research Policy and Systems. 2012; **10**: 28.

Terry RF, van der Rijt T. Overview of research activities associated with the World Health Organization (2007): results of a survey covering 2006/07. Health Research Policy and Systems. 2010; **8**(25).

Thorn K, Holm-Nielsen L. International mobility of researchers and scientists: Policy options for turning a drain into a gain. WIDER Research Paper. UNU-WIDER. 2006. Sect. 145-67. http://www.wider.unu.edu/publications/working-papers/research-papers/2006/en_GB/rp2006-83/.

UNDP, Bank W, Diseases WSPfRaTiT. Tropical disease research : a global partnership at work, new approaches to research capability strengthening
Tropical disease research : a global partnership at work, new approaches to research capability strengthenin - See more at: http://apps.who.int/iris/handle/10665/62745#sthash.CzulHLbB.dpuf. Geneva: WHO; 2005.

UNICEF, UNDP, World Bank, WHO Special Programme for Research and Training in Tropical Diseases. Tropical disease research: progress 2003–2004. Geneva: WHO; 2005.

UNICEF, UNDP, World Bank, WHO Special Programme for Research and Training in Tropical Diseases. TDR Business Plan 2008–2013. Geneva: WHO; 2007.

UNICEF, UNDP, World Bank, WHO Special Programme for Research and Training in Tropical Diseases. TDR Ten Year Vision and Strategy. Geneva: WHO; 2007.

UNITAID. HIV/AIDS Diagnostic Technology Landscape: Semi-Annual Update. Geneva: WHO; 2011.

UNITAID. HIV/AIDS Diagnostic Technology Landscape. 2nd Edition. Geneva: WHO; 2012.

UNITAID. Malaria Diagnostic Technology Landscape. Geneva: WHO; 2012.

UNITAID. Malaria Diagnostics Market Landscape. Geneva: WHO; 2012.

UNITAID. Tuberculosis Diagnostic Technology Landscape. Geneva: WHO; 2012.

UNITAID. Tuberculosis: Diagnostic Technology Landscape: Semi-Annual Update. Geneva: WHO; 2012.

UNITAID. Tuberculosis: Medicines Technology Landscape. Geneva: WHO; 2012.

United Kingdom Evaluation Forum. Medical Research: Assessing the benefits to society: The Academy of Medical Sciences, Medical Research Council, & Wellcome Trust; 2006. http://www.wellcome.ac.uk/stellent/groups/corporatesite/@msh_publishing_group/documents/web_document/wtx031817.pdf.

United Nations Children's Fund (UNICEF). Update on Work on Medicines (Presentation). New York: UNICEF IPC; 2012.

United Nations Children's Fund (UNICEF). Pneumonia and Diarrhoea: Tackling the Deadliest Diseases for the World's Poorest Children. New York: UNICEF; 2012. http://www.unicef.org/media/files/UNICEF_P_D_complete_0604.pdf.

United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS Report on the Global AIDS Epidemic. Geneva: UNAIDS; 2013.

http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf.

United States Census Bureau. 1990 Population Census. 2002. http://www.census.gov/main/www/cen1990.html. Accessed 14 May 2008.

Van Voorhis WC, Hol WG, Myler PJ, Stewart LJ. The role of medical structural genomics in discovering new drugs for infectious diseases. PLoS computational biology. 2009; **5**(10): e1000530. http://www.ncbi.nlm.nih.gov/pubmed/19855826.

Varkevisser CM, Mwaluko GM, Le Grand A. Research in action: the training approach of the Joint Health Systems Research Project for the Southern African Region. Health Policy and Planning. 2001; **16**(3): 281-91.

Velho L. Research capacity building for development: from old to new assumptions. Science Technology & Society. 2004; **9**(2): 171-207.

Viergever RF, Terry RF, Karam G. Use of data from registered clinical trials to identify gaps in health research and development. Bulletin of the World Health Organization. 2013; **91**(6): 416-25C.

Waddell C, Lomas J, Lavis J, Abelson J, Shepherd C, Bird-Gayson T. Joining the conversation: Newspaper journalists' views on working with researchers. Politiques de Santé. 2005; **1**(1): 123-39.

Walker CLF, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. Global burden of childhood pneumonia and diarrhoea. The Lancet. 2013; **381**(9875): 1405-16.

Wallis R, Kim P, Cole S, Hanna D, Andrade B, Maeuer M. Tuberculosis biomarkers diversity: developments, needs and challenges. The Lancet Infectious Diseases. 2013; **13**: 362-72.

Walsh JA, Warren KS. Selective primary health care: an interim strategy for disease control in developing countries. New England Journal of Medicine. 1979; **301**(18): 967-74.

Wazny K, Zipursky A, Black R, Curtis V, Duggan C, Guerrant R, et al. Setting research priorities to reduce mortality and morbidity of childhood diarrhoeal disease in the next 15 years. PLoS medicine. 2013; **10**(5): e1001446.

Webster J, Theodoratou E, Nair H, Seong AC, Zgaga L, Huda T, et al. An evaluation of emerging vaccines for childhood pneumococcal pneumonia. BMC public health. 2011; **11**(Supplement 3): S26.

Weigold MF. Communicating Science A Review of the Literature. Science Communication. 2001; **23**(2): 164-93.

Wellcome Trust. Strategic Plan 2005-2010: Making a Difference: Wellcome Trust; 2005.

Wells WA, Boehme CC, Cobelens FG, Daniels C, Dowdy D, Gardiner E, et al. Alignment of new tuberculosis drug regimens and drug susceptibility testing: a framework for action. The Lancet Infectious Diseases. 2013; **13**(5): 449-58.

WHO Advisory Committee on Research. A research policy agenda for science and technology to support global health development. Geneva: WHO; 1998. http://apps.who.int/iris/handle/10665/65483. Accessed 15 April 2010.

WHO Commission on Macroeconomics and Health. Macroeconomics and Health: Investing in Health for Economic Development. Geneva: WHO; 2001. http://www.cid.harvard.edu/cidcmh/CMHReport.pdf.

WHO Commission on Social Determinants. Closing the gap in a generation: Health equity through action on the social determinants of health. Geneva: WHO; 2008.

WHO Expert Working Group on Research and Development Financing. Research and development: coordination and financing. Geneva: WHO; 2010. http://www.who.int/phi/documents/ewg_report/en/.

WHO Secretariat. Defining disease types I, II, and III; 2012 November 14, 2012. http://www.who.int/phi/3-background_cewg_agenda_item5_disease_types_final.pdf. Accessed November 20, 2012.

WHO Special Programme for Research and Training in Tropical Diseases. Global Report for Research on Neglected Diseases of Poverty. Geneva: WHO; 2012.

World Bank. World Development Report 1993: Investing in Health. Washington D.C.: World Bank; 1993.

World Health Organization. Categorization of WHO information products. World Health Organization. http://intranet.who.int/homes/whp/whopublishingpolicies/pubpolicyplanning/initialclearance.shtml. Accessed 15 April 2010.

World Health Organization. World Health Report 1999: making a difference. Geneva: WHO; 2000.

World Health Organization. Public Health-Innovation and Intellectual Property Rights: Report of the Commission on Intellectual Property Rights, Innovation and Public Health: WHO; 2006.

World Health Organization. Communiqué of the High Level Ministerial Meeting on Health Research for Developing Countries: Accra, Ghana, 14–17 June 2006. Geneva: WHO; 2006.

World Health Organization. The global burden of disease: 2004 update. Geneva: WHO; 2008.

World Health Organization. Report of the World Health Organization Expert Working Group on Research and Development Financing. Geneva: WHO; 2010.

World Health Organization. The World Health Report - Health systems financing: the path to universal coverage. Geneva: WHO; 2010.

World Health Organization. Research and development to meet health needs in developing countries: strengthening global financing and coordination. Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination. Geneva: WHO; 2012.

World Health Organization. Global Plan for Insecticide Resistance Management in Malaria Vectors. Geneva: WHO; 2012.

World Health Organization. Global Tuberculosis Report 2012. Geneva: WHO; 2012.

World Health Organization. Research Priorities for Helminth Infections. Technical Report of the TDR Disease Reference Group on Helminth Infections (DRG4). Geneva: WHO; 2012.

World Health Organization. World Malaria Report 2012. Geneva: WHO; 2012.

World Health Organization. Changing Mindsets: Strategy on health policy and systems research. Geneva: WHO; 2012.

World Health Organization. Follow-up of the report of the Consultative Expert Working Group on Research and Development (2012): financing and coordination. Report No.: EB 132/21. Geneva: WHO; 2012.

World Health Organization. Sustaining the drive to overcome the global impact of neglected tropical diseases. Geneva: WHO; 2013.

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: WHO; 2012.

World Health Organization, Stop TB Partnership. An international roadmap for tuberculosis research: towards a world free of tuberculosis. Geneva: WHO; 2011.

World Health Organization, The United Nations Children's Fund (UNICEF). Ending preventable child deaths from pneumonia and diarrhoea by 2025: The integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD). Geneva: WHO; 2013.

World Health Organization, WHO Special Programme for Research and Training in Tropical Diseases (TDR). Research Priorities for Chagas Disease, Human African Trypanosomiasis and Leishmaniasis. Geneva: WHO; 2012.

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[1,2], Jennifer S. Edge[1], Christen Reardon[1], Cherie L. Ramirez[1,2] *

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

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

Affiliations:
[1] Harvard Global Health Institute, Harvard University, Cambridge, Massachusetts, USA.
[2] Harvard School of Public Health, Harvard University, Boston, Massachusetts, USA.
[3] Department of Epidemiology & Biostatistics and McMaster Health Forum, McMaster University, Hamilton, Ontario, Canada.
*Corresponding author: cramirez@hsph.harvard.edu
**Corresponding author: jennifer_edge@harvard.edu

Table of Contents for Working Paper 1 & 2 Supplementary Material:

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

Malaria Report Overview

Source: PLOS Medicine. malERA: a Research Agenda for Malaria Eradication. Barcelona: The Barcelona Centre for International Health Research; 2011.

Attachment 1: Description of Report[1]

This report provides a series of publications for PLOS that address the research agenda to eradicate malaria globally. Sponsored by The Malaria Education Research Agenda (malERA), an initiative that complements the current research agenda by identifying key knowledge gaps and defines the strategies and tools that will result in malaria eradication, this report identifies multiples aspects of the research agenda, including: basic science, drugs, vaccines, vector control, diagnostics, health systems and operational research, and monitoring and evaluation.

[1] **Source:** PLOS Medicine. malERA: a Research Agenda for Malaria Eradication. Barcelona: The Barcelona Centre for International Health Research; 2011.

Attachment 2: Table of Contents[2]

[2] **Source:** PLOS Medicine. malERA: a Research Agenda for Malaria Eradication. Barcelona: The Barcelona Centre for International Health Research; 2011.

Attachment 3: Executive Summary *(No Executive Summary provided; abstracts from chapters provided below)*[3]

A Research Agenda to Underpin Malaria Eradication

The interruption of malaria transmission worldwide is one of the greatest challenges for international health and development communities. The current expert view suggests that, by aggressively scaling up control with currently available tools and strategies, much greater gains could be achieved against malaria, including elimination from a number of countries and regions; however, even with maximal effort we will fall short of global eradication. The Malaria Eradication Research Agenda (malERA) complements the current research agenda—primarily directed towards reducing morbidity and mortality—with one that aims to identify key knowledge gaps and define the strategies and tools that will result in reducing the basic reproduction rate to less than 1, with the ultimate aim of eradication of the parasite from the human population. Sustained commitment from local communities, civil society, policy leaders, and the scientific community, together with a massive effort to build a strong base of researchers from the endemic areas will be critical factors in the success of this new agenda.

A Research Agenda for Malaria Eradication: Basic Science and Enabling Technologies

Today's malaria control efforts are limited by our incomplete understanding of the biology of Plasmodium and of the complex relationships between human populations and the multiple species of mosquito and parasite. Research priorities include the development of in vitro culture systems for the complete life cycle of P. falciparum and P. vivax and the development of an appropriate liver culture system to study hepatic stages. In addition, genetic technologies for the manipulation of Plasmodium need to be improved, the entire parasite metabolome needs to be characterized to identify new druggable targets, and improved information systems for monitoring the changes in epidemiology, pathology, and host-parasite-vector interactions as a result of intensified control need to be established to bridge the gap between bench, preclinical, clinical, and population-based sciences

A Research Agenda for Malaria Eradication: Drugs

Antimalarial drugs will be essential tools at all stages of malaria elimination along the path towards eradication, including the early control or ''attack'' phase to drive down transmission and the later stages of maintaining interruption of transmission, preventing reintroduction of malaria, and eliminating the last residual foci of infection. Drugs will continue to be used to treat acute malaria illness and prevent complications in vulnerable groups, but better drugs are needed for elimination-specific indications such as mass treatment, curing asymptomatic infections, curing relapsing liver stages, and preventing transmission. The ideal malaria eradication drug is a coformulated drug combination suitable for mass administration that can be administered in a single encounter at infrequent intervals and that result in radical cure of all life cycle stages of all five malaria species infecting humans. Short of this optimal goal, highly desirable drugs might have limitations such as targeting only one or two parasite species, the priorities being Plasmodium falciparum and Plasmodium vivax. The malaria research agenda for eradication should

[3] **Source:** PLOS Medicine. malERA: a Research Agenda for Malaria Eradication. Barcelona: The Barcelona Centre for International Health Research; 2011.

include research aimed at developing such drugs and research to develop situation-specific strategies for using both current and future drugs to interrupt malaria transmission.

A Research Agenda for Malaria Eradication: Vaccines

Vaccines could be a crucial component of efforts to eradicate malaria. Current attempts to develop malaria vaccines are primarily focused on Plasmodium falciparum and are directed towards reducing morbidity and mortality. Continued support for these efforts is essential, but if malaria vaccines are to be used as part of a repertoire of tools for elimination or eradication of malaria, they will need to have an impact on malaria transmission. We introduce the concept of ''vaccines that interrupt malaria transmission'' (VIMT), which includes not only ''classical'' transmission-blocking vaccines that target the sexual and mosquito stages but also pre-erythrocytic and asexual stage vaccines that have an effect on transmission. VIMT may also include vaccines that target the vector to disrupt parasite development in the mosquito. Importantly, if eradication is to be achieved, malaria vaccine development efforts will need to target other malaria parasite species, especially Plasmodium vivax, where novel therapeutic vaccines against hypnozoites or preventive vaccines with effect against multiple stages could have enormous impact. A target product profile (TPP) for VIMT is proposed and a research agenda to address current knowledge gaps and develop tools necessary for design and development of VIMT is presented.

A Research Agenda for Malaria Eradication: Vector Control

Different challenges are presented by the variety of malaria transmission environments present in the world today. In each setting, improved control for reduction of morbidity is a necessary first step towards the long-range goal of malaria eradication and a priority for regions where the disease burden is high. For many geographic areas where transmission rates are low to moderate, sustained and well-managed application of currently available tools may be sufficient to achieve local elimination. The research needs for these areas will be to sustain and perhaps improve the effectiveness of currently available tools. For other low-to-moderate transmission regions, notably areas where the vectors exhibit behaviours such as outdoor feeding and resting that are not well targeted by current strategies, new interventions that target predictable features of the biology/ecologies of the local vectors will be required. To achieve elimination in areas where high levels of transmission are sustained by very efficient vector species, radically new interventions that significantly reduce the vectorial capacity of wild populations will be needed. Ideally, such interventions should be implemented with a one-time application with a long-lasting impact, such as genetic modification of the vectorial capacity of the wild vector population.

A Research Agenda for Malaria Eradication: Diagnoses and Diagnostics

Many of malaria's signs and symptoms are indistinguishable from those of other febrile diseases. Detection of the presence of Plasmodium parasites is essential, therefore, to guide case management. Improved diagnostic tools are required to enable targeted treatment of infected individuals. In addition, field-ready diagnostic tools for mass screening and surveillance that can detect asymptomatic infections of very low parasite densities are needed to monitor transmission reduction and ensure elimination. Antibody-based tests for infection and novel methods based on biomarkers need further development and validation, as do methods for the detection and treatment of Plasmodium vivax. Current

rapid diagnostic tests targeting P. vivax are generally less effective than those targeting Plasmodium falciparum. Moreover, because current drugs for radical cure may cause serious side effects in patients with glucose-6- phosphate dehydrogenase (G6PD) deficiency, more information is needed on the distribution of G6PD-deficiency variants as well as tests to identify at-risk individuals. Finally, in an environment of very low or absent malaria transmission, sustaining interest in elimination and maintaining resources will become increasingly important. Thus, research is required into the context in which malaria diagnostic tests are used, into diagnostics for other febrile diseases, and into the integration of these tests into health systems.

A Research Agenda for Malaria Eradication: Health Systems and Operational Research

Health systems research and development is needed to support the global malaria eradication agenda. In this paper, we (the malERA Consultative Group on Health Systems and Operational Research) focus on the health systems needs of the elimination phase of malaria eradication and consider groupings of countries at different stages along the pathway to elimination. We examine the difference between the last attempt at eradication of malaria and more recent initiatives, and consider the changing health system challenges as countries make progress towards elimination. We review recent technological and theoretical developments related to health systems and the renewed commitment to strengthening health systems for universal access and greater equity. Finally, we identify a number of needs for research and development, including tools for analyzing and improving effective coverage and strengthening decision making and discuss the relevance of these needs at all levels of the health system from the community to the international level.

A Research Agenda for Malaria Eradication: Monitoring, Evaluation, and Surveillance

Monitoring, evaluation, and surveillance measure how well public health programs operate over time and achieve their goals. As countries approach malaria elimination, these activities will need to shift from measuring reductions in morbidity and mortality, to detecting infections (with or without symptoms) and measuring transmission. Thus, the monitoring and evaluation and surveillance research and development agenda needs to develop the tools and strategies that will replace passive surveillance of morbidity with active and prompt detection of infection, including confirmation of interruption of transmission by detecting present and past infections, particularly in mobile populations. The capacity to assess trends and respond without delay will need to be developed, so that surveillance itself becomes an intervention. Research is also needed to develop sensitive field tests that can detect low levels of parasitaemia, together with strategies for their implementation. Other areas to explore include the rigorous evaluation of the utility of more detailed maps of disease and infection incidence and prevalence, the development of new maps to inform programmatic responses and the use of surveillance technologies based on cell phone or real-time internet Web-based reporting. Because any new strategies for monitoring and evaluation and surveillance for eradication have major implications for program implementation, research is also needed to test systems of delivery for acceptability, feasibility, efficiency, cost effectiveness, and community engagement. Finally, there is a clear need to systematically review the information from past elimination efforts for malaria and other infectious diseases.

A Research Agenda for Malaria Eradication: Modeling

Malaria modeling can inform policy and guide research for malaria elimination and eradication from local implementation to global policy. A research and development agenda for malaria modeling is proposed, to support operations and to enhance the broader eradication research agenda. Models are envisioned as an integral part of research, planning, and evaluation, and modelers should ideally be integrated into multidisciplinary teams to update the models iteratively, communicate their appropriate use, and serve the needs of other research scientists, public health specialists, and government officials. A competitive and collaborative framework will result in policy recommendations from multiple, independently derived models and model systems that share harmonized databases. As planned, modeling results will be produced in five priority areas: (1) strategic planning to determine where and when resources should be optimally allocated to achieve eradication; (2) management plans to minimize the evolution of drug and pesticide resistance; (3) impact assessments of new and needed tools to interrupt transmission; (4) technical feasibility assessments to determine appropriate combinations of tools, an associated set of target intervention coverage levels, and the expected timelines for achieving a set of goals in different socio-ecological settings and different health systems; and (5) operational feasibility assessments to weigh the economic costs, capital investments, and human resource capacities required.

A Research Agenda for Malaria Eradication: Cross Cutting Issues for Eradication

Discipline-specific Malaria Eradication Research Agenda (malERA) Consultative Groups have recognized several cross-cutting issues that must be addressed to prevent repetition of some of the mistakes of past malaria elimination campaigns in future programs. Integrated research is required to develop a decision-making framework for the switch from malaria control to elimination. Similarly, a strong economic case is needed for the very long-term financial support that is essential for elimination. Another cross-cutting priority is the development of improved measures of intensity of transmission, especially at low and nonrandom levels. Because sustained malaria elimination is dependent on a functioning health system, a further key cross-cutting research question is to determine how inputs for malaria can strengthen health systems, information systems, and overall health outcomes. Implementation of elimination programs must also be accompanied by capacity building and training to allow the assessment of the impact of new combinations of interventions, new roles for different individuals, and the operational research that is needed to facilitate program expansion. Finally, because community engagement, knowledge management, communication, political, and multisectoral support are critical but poorly understood success factors for malaria elimination, integrated research into these issues is vital.

Some Lessons for the Future from the Global Malaria Eradication Programme

Discipline-specific Malaria Eradication Research Agenda (malERA) Consultative Groups have recognized several cross-cutting issues that must be addressed to prevent repetition of some of the mistakes of past malaria elimination campaigns in future programs. Integrated research is required to develop a decision-making framework for the switch from malaria control to elimination. Similarly, a strong economic case is needed for the very long-term financial support that is essential for elimination. Another cross-cutting priority is the development of improved measures of intensity of transmission, especially at low and nonrandom levels. Because sustained malaria elimination is dependent on a functioning health system, a further key cross-cutting research question is to determine how inputs for malaria can strengthen health systems, information systems, and overall health outcomes. Implementation of elimination programs must also be accompanied by capacity building and training to allow the assessment of the impact of new combinations of interventions, new roles for different individuals, and the operational research that

is needed to facilitate program expansion. Finally, because community engagement, knowledge management, communication, political, and multisectoral support are critical but poorly understood success factors for malaria elimination, integrated research into these issues is vital.

The Role of Research in Viral Disease Eradication and Elimination Programs: Lessons for Malaria Eradication

By examining the role research has played in eradication or regional elimination initiatives for three viral diseases—smallpox, poliomyelitis, and measles—we derive nine cross-cutting lessons applicable to malaria eradication. In these initiatives, some types of research commenced as the programs began and proceeded in parallel. Basic laboratory, clinical, and field research all contributed notably to progress made in the viral programs. For each program, vaccine was the lynchpin intervention, but as the programs progressed, research was required to improve vaccine formulations, delivery methods, and immunization schedules. Surveillance was fundamental to all three programs, whilst polio eradication also required improved diagnostic methods to identify asymptomatic infections. Molecular characterization of pathogen isolates strengthened surveillance and allowed insights into the geographic source of infections and their spread. Anthropologic, sociologic, and behavioural research were needed to address cultural and religious beliefs to expand community acceptance. The last phases of elimination and eradication became increasingly difficult, as a nil incidence was approached. Any eradication initiative for malaria must incorporate flexible research agendas that can adapt to changing epidemiologic contingencies and allow planning for post eradication scenarios.

Attachment 4: Methodology[4]

[No defined methodology provided]

[4] **Source:** PLOS Medicine. malERA: a Research Agenda for Malaria Eradication. Barcelona: The Barcelona Centre for International Health Research; 2011.

Attachment 5: Additional Selected Passages Relevant to R&D Priority Setting[5]

KEY SUMMARY POINTS ACROSS ALL ARTICLES:

Basic Research

- Leading the charge are new molecular, chemical, immunological, and epidemiological research tools that, whilst requiring adaptation to malaria, have realizable rewards in the near future. In particular, developments in systems biology, metabolomics, glycomics, and lipid metabolism and new high-throughput approaches involving chemical biology are likely to be of great use in the field of malaria eradication.
- At the basic science level, we specifically identified a deeper understanding of the whole parasitic life cycle and the interaction of the parasite with human and vector hosts at different stages as a high priority. In addition, a life cycle–based perspective will provide insights into the transitions from one host to another and highlight key points, triggers, decisions, and co-incident events as the parasite moves from one life stage to the next that could prove crucial in malaria eradication attempts.
- A research paradigm shift away from the ''parasite-first'' approach to an examination of what the human and mosquito host cells provide to the developing parasite is needed to complement on-going approaches
- Many roadblocks that prevent scale-up of genetic manipulation and functional analysis of essential genes need to be overcome. These roadblocks include the low frequency of homologous recombination in Plasmodium, difficulties associated with the manipulation of large fragments of AT-rich and repetitive genomic DNA, and the lack of robust and scalable systems for conditional gene expression. In addition, there are no practical strategies for achieving saturation mutagenesis. Technologies to tackle some of these roadblocks are available for other organisms and need to be introduced to the malaria research agenda
- Systematic mutagenesis on a genome-wide scale will allow us to distinguish essential from redundant metabolic pathways and will be critical to obtaining a comprehensive picture of the stage-specific biology of the parasite that could be targeted with drugs or vaccines.
- Finally, the recent completion of several parasite and mosquito genomes [50–54] and new insights into the contribution of human and mosquito host genotype to transmission have radically changed how researchers approach malaria.
- New technological platforms that permit the deep characterization of the metabolome (complete set of small-molecule metabolites) of Plasmodium will identify new potentially druggable targets. Metabolomic studies of such samples may not only provide information about the state of the host, but also about the interaction between the host and the parasite.
- As increasing parts of the world move towards elimination, a deeper understanding of the basic science of host-parasite-vector population interactions in disease transmission and of the changes in these interactions that result from intensified control and elimination efforts will be increasingly important
- Research that investigates the parasite stages that develop within the mosquito and their transmission through the vector is likely to be of great use, therefore, in malaria control and eradication.

[5] **Source:** PLOS Medicine. malERA: a Research Agenda for Malaria Eradication. Barcelona: The Barcelona Centre for International Health Research; 2011.

- Focused research efforts designed to understand the epidemiology of the gametocyte and how it varies with species, with host, and with the environment are required.
- The development of an efficient inexpensive, automated P. vivax blood-stage culture system would undoubtedly enhance the study of this parasite's biology
- The development of in vitro systems to understand hypnozoite biology as it relates to liver-stage biology is a clear priority
- Desired target product profiles need to be defined without preferred technological approaches being suggested to create opportunities for lateral thinking by experts bringing new approaches from different fields
- Careful evaluation and appropriate use of today's technologies from the physical, chemical, and biomedical engineering sciences is needed to improve the molecular understanding of parasite developmental biology and of the mammalian host-parasite-vector interactions
- Mechanism of action studies for drugs and vaccines in the current pipeline are also needed to inform future strategies for the development of the next generation of interventions and therapeutics
- The study of human host and vector factors in large-scale, long-term population-based field studies and the use of appropriate technologies in translation applications is also essential.
- Key research priorities include: the development of in vitro culture systems for all life stages of P. falciparum and P. vivax, in particular, hepatic stages; improved genetic technologies for the manipulation of Plasmodium; and systems-based approaches incorporating cutting-edge technologies such as metabolomics

Drugs

KNOWLEDGE GAPS AND RESEARCH PRIORITIES FOR OPTIMIZING CURRENT DRUGS

- Pharmacology studies to optimize dosing regimens of 8-aminoquinolines for gametocytocidal and anti-relapse efficacy and safety
- Rapid and robust point-of-care glucose-6-phosphate dehydrogenase (G6PD) test to improve safety of 8-aminoquinoline use
- Tests that can detect resistance to artemisinins and ACT partner drugs
- Determine gametocytocidal and anti-relapse activity of current drugs and those in the pipeline

KNOWLEDGE GAPS AND RESEARCH PRIORITIES FOR DEVELOPING NEW DRUGS FOR MALARIA ERADICATION

- Drugs that prevent transmission by killing or preventing development of gametocytes, or blocking sporozoite development in the mosquito
- Drugs that cure liver stages of vivax (and ovale) malaria
- Ideally, drugs that can be administered in a single encounter at infrequent intervals, and that result in radical cure of all parasite stages (Single Encounter Radical Cureand Prophylaxis, see Box 1)
- Sustained or pulsed release formulations

- Exceptionally safe schizonticidal drugs for curing asymptomatic falciparum infection

Fundamental research questions aimed towards developing desired drugs

- Fundamental studies of liver and sexual stage biology (in both host and mosquito)
- Mechanisms of resistance and pharmacological strategies to deter resistance
- In vitro culture of P. vivax to understand parasite biology

Tools and capacities

- Increased capacity for clinical pharmacology research including pharmacokinetics/pharmacodynamics studies in populations targeted for malaria elimination
- Increased capacity for human challenge studies for early go/no go decisions on drug candidates
- Assays to measure transmission-blocking activity
- Assays to measure activity against liver stages
- In vitro culture of P. vivax and other non-falciparum species for drug screening
- Genomic and proteomic approaches to identify transmission-blocking and liver-stage activity

KNOWLEDGE GAPS AND RESEARCH PRIORITIES FOR DRUG TREATMENT AND PREVENTION STRATEGIES FOR ERADICATION

- Field studies to evaluate new drugs and approaches in a variety of epidemiological settings
- Robust and highly sensitive malaria diagnostics for malaria infection and especially for carriage of infectious gametocytes
- Measures to monitor and improve adherence and safety
- How must drug treatment and prevention strategies change as elimination proceeds?
- Strategies to deter resistance

ADDITIONAL NOTES

- New and better drugs for intermittent preventive treatment (IPT) of malaria in pregnancy and molecular markers that can be used as surveillance tools for monitoring artemisinin-resistant malaria are both critically important research priorities,
- Another creative approach from the past that may hold promise for the future is the use of long-acting formulations. ‘‘Repository’’ formulations of malaria drugs to provide prolonged protection were extensively researched in the early 1960s [27], and oil-based depot injections of cycloguanil pamoate provided more than 1 year of protection against experimental challenge with P. falciparum sporozoites
- Notable examples are the emergence of artemisinin resistance and the consequent need for improved strategies to contain dissemination of resistant parasite strains coupled with accelerated research into potential new drugs for first-line treatment

- Similarly, new insecticides are urgently needed to replace those threatened by increased mosquito resistance [11], and accelerated development of vaccines that can impact on malaria incidence, disease, and death remains a high priority
- Single Encounter Radical Cure and Prophylaxis (SERCaP) has a target product profile (TPP) that includes radical cure, defined as elimination of all parasites (including the long-lived hypnozoites of P. vivax or P. ovalein the liver), suitability for mass administration (including administration to healthy subjects and the consequent need of a very good safety profile), and prophylaxis for at least 1 month after treatment
- For example, development of new safe and effective drugs that block the infectivity of the mature sexual forms of P. falciparum gametocytes and/or the dormant hepatic forms (hypnozoites) of P. vivax could have a profound impact on transmission rates and would be valuable tools in the efforts to contain and eliminate parasite strains resistant to first line treatment drugs.

Vaccine

- Development and application of novel vaccine delivery approaches and/or adjuvants to elicit long-lasting protective efficacy that makes significant impact on malaria transmission rates under diverse epidemiological settings.
- Expansion of vaccine development efforts to cover Plasmodium species other than P. falciparum, especially P. vivax (including hypnozoites).
- Understanding the dynamics between multiplication of asexual stage parasites, gametocytogenesis, and malaria transmission rates at the population level.
- Development of robust assays to study functional immune responses at the individual level that can predict effect on malaria transmission at the population level and allow decision making in product development.
- Development of tools to measure malaria transmission rates, thereby facilitating clinical development of vaccines that reduce malaria transmission.
- The broader concept of ‘‘vaccines that interrupt malaria transmission (VIMT)’’ is introduced by the malERA Consultative Group on Vaccines to replace the term ‘‘transmission blocking vaccines’’ (TBVs), which has been used widely to refer to vaccines that target only the sexual and mosquito stages of the parasite
- VIMT could include antivector vaccines that target mosquito molecules essential for parasite development, highly effective pre-erythrocytic or erythrocytic stage vaccines, and vaccines targeting parasite antigens of sexual and mosquito stages of the infection. The desired TPP identified by the Consultative Group for VIMT indicates that they should be effective against both P. falciparum and P. vivax,suitable for administration to all age groups, and should impact transmission
- Other issues discussed by the group in their article include the need for validated functional assays that measure the reduction in infectivity at the individual level after vaccination that could be used as surrogate measures to predict reductions in transmission rates at the community level.

Vector control

- Development of an analytic framework that can bring together existing and new information on all aspects of malaria and malaria transmission through a public portal designed to facilitate decision making by the malaria research, control, and tool development communities.
- An improved choice of insecticides, and formulations coupled with improved methods to reduce the risk of resistance to ensure that the availability of effective insecticides does not become the limiting factor in our ability to reduce transmission to levels where local elimination can be attempted.
- Better understanding of the ecology, behaviour, and genetic population structure of malaria vectors, particularly outdoor biting and resting species that escape current vector control tools.
- Development of innovative new technologies that can:
  - Educate the community effectively and engage the consumer market
  - Control outdoor biting and resting mosquito vectors
  - Simply and rapidly measure transmission
- Sustained commitment to the long-term development of novel approaches like the genetic manipulation of natural vector populations that will permanently reduce the very high vectorial capacities of dominant malaria vectors in sub-Saharan Africa and some parts of Asia.
- The most pressing challenge is the development of a coherent research agenda for discovering and developing a broader range of insecticides, with novel modes of action that can circumvent emerging resistance to existing insecticides, in particular, pyrethroid-based insecticides
- The second challenge is the development of interventions that affect vectors that do not rest or feed indoors and are therefore not susceptible to current tools
- The final critical challenge is the development of novel approaches that permanently reduce the high vectorial capacities of the dominant malaria vectors in sub-Saharan Africa

<u>Diagnostics</u>

Programmatic issues

- Further data on thresholds of (i) parasite density likely to cause symptoms in low-transmission settings with variable or waning immunity, and (ii) transmission potential of cases with parasitemia below the threshold of microscopy and RDTs
- Diagnostic tests for nonmalarial febrile illness in malaria endemic and malaria-elimination settings
- Distribution of severe G6PD variants

<u>Technical issues: case-management tools</u>

High priority

Stable tests for case management in low-training, low technology settings with sensitivity sufficient for community level case management, including

- Antigen-detecting RDTs
    - Greater consistency in P. falciparum detection, particularly in the case of nonpersistent antigens
    - More sensitive and stable tests to detect non-P.falciparum parasites
    - Clarification of the programmatic/implementation requirements that will ensure good impact in the field
    - Standardized low-cost positive controls for antigen detecting RDTs suitable for field use
    - Sustainable tools for quality control of RDTs at a country level.
- Further investigation of nonblood sampling to determine the potential for detecting recoverable antigen in these samples.
- More consistent, reliable staining methods for microscopy
- G6PD deficiency mapping and identification (if 8-aminoquinolones are to be used)

Medium priority

- Multiplexing: Other diseases, markers of severity
- Field G6PD detection (may be more important if tafenoquine approved), or raised priorities for P. vivax relapse prevention
- Tools to standardize and improve microscopy interpretation

Low priority

- Hypnozoite detection (becomes a high priority if feasibility can be demonstrated through further research on hypnozoite biology, identifying good biomarkers).

<u>Technical issues: surveillance tools</u>

High priority

- Field-applicable tools for detection of low-density parasitemia in a high-throughput manner, suitable for surveys and active detection of parasite carriage in time to allow management of positive cases
- Tools for minimally invasive, very rapid detection of low density parasite infections suitable for screening of migrants/travelers
- Innovation with potential for major operational impact
- Non-invasive, low-density parasite detection

Low-hanging fruit with immediate application for elimination

- High-throughput field molecular detection, capable of use at district level or below
- Positive control methods for RDTs

ADDITIONAL NOTES

- The main challenge identified by the malERA Consultative Group on Diagnoses and Diagnostics is to find a robust, sensitive, and specific standardized method for assessment of transmission intensity in the intervening period when transmission continues at low and non-random levels. Improved serological tests have been suggested, but other minimally invasive biomarkers could be considered.
- Other challenges for diagnostics include the need for tools that can rapidly detect and monitor unexpectedly high transmission that leads to outbreaks and that can identify reintroduction of infections that may be asymptomatic

<u>Operational Research</u>

- Overarching issue: Development and validation of a tool kit for the national and subnational level, comparable to rapid assessment procedures, allowing (i) effectiveness decay analysis for identifying bottlenecks for effective coverage of malaria interventions and (ii) decisions on the degree of integration of interventions into existing and strengthened health systems.
- Priority health systems research questions:
    - At the health facility level, how can health worker performance and compliance with best practice be monitored, enhanced, and sustained?
    - At the district level, what are the factors impeding greater application of existing tools and approaches to district health system strengthening including surveillance?
    - At the national level, what experience is there of strengthening health system components using disease-specific programmes?

<u>Monitoring, Evaluation, and Surveillance</u>

- Update the malaria monitoring and evaluation Framework to include transmission reduction, and develop key data elements for a surveillance system from a systematic review of previous elimination attempts
- Systematically review lessons learned from experiences with surveillance as an intervention to determine how it can be tailored to various programmatic settings
- Identify appropriate program time points for introduction of malaria infection detection in active or passive modes
- Develop improved diagnostic tools for use in monitoring and evaluation and surveillance, focusing on practical field-ready tools for detection of asymptomatic infection
- Develop information systems to monitor malaria infections, facilitate timely local program decisions and responses to reduce transmission
- Develop methods, indicators, and shareable databases for parasite strain information to better track transmission

- Develop methods for accessing and tracking population movements and quantifying their contribution and risk of malaria transmission
- Explore how maps can be constructed to: show the probability of a threshold of transmission being exceeded; incorporate a wider range of metrics such as serological and entomological data; assess cost-effectiveness of national stratification initiatives based on remotely sensed satellite data
- Perform a systematic review to assess and compare metrics of malaria transmission at near zero transmission levels; research the validity of novel metrics to measure transmission at near zero levels, and to measure transmission potential within areas where transmission has been eliminated
- Assess the precision, bias, feasibility, and cost-effectiveness of novel sampling methods for routine monitoring of present and past infections in target populations, including mobile populations
- Conduct research to develop biomarkers such as DNA based methods or serology as monitoring and evaluation and surveillance tools

ADDITIONAL NOTES

- At the regional/global level, what are the strengths and weaknesses of current malaria surveillance and patient management practices in malaria-endemic countries and what are the likely determinants of success of intercountry collaboration for disease elimination?
- As discussed by the malERA Consultative Group on Modeling [16], a significant research challenge for malaria eradication will be to integrate these new approaches into the planning of elimination, surveillance, monitoring, and evaluation, and to create appropriate interfaces for different user communities, including researchers, global and national policy makers, and local-level planners.
- We believe there are at least two potentially transformative developments that need to be pursued. First, continuous laboratory culture of P. vivax, P. ovale, and P. malariae needs to be developed to provide an essential platform for studying the biology of the liver stages and sexual forms of these parasites.
- Second, systems analyses of transcription, proteome, and metabolome libraries, rapid screening of drug libraries, high-throughput approaches to antigen identification, and the functional definition of gene products are all feasible but not yet fully exploited, but would bring important new tools to the bench scientist and to field operations.
- It is now clear that the long-term solution to malaria elimination and eradication will require a systems approach in which malaria specific interventions and actions are integrated into existing health systems [34]. To achieve this, research is needed into health systems, their readiness to optimize novel programs, systems, tests, or other interventions, and their continuing performance
- During their deliberations, the malERA Consultative Group on Health Systems and Operational Research identified the need for a substantial research approach to establish and validate a tool kit that allows effectiveness-decay analysis of health system impediments to effective and equitable coverage of malaria interventions and that allows decisions to be made on the degree of possible integration of interventions into an existing health system
- A further critical component of the research agenda identified by this Consultative Group is the development and validation of a decision-making framework to guide the move from control to elimination

- The need to investigate the performance of surveillance, monitoring, and evaluation by new and old technologies [39,40] and to evaluate optimal strategies for implementation of surveillance as an active responsive intervention to further reduce transmission

---

RELEVANT PASSAGES FROM ARTICLES

Drugs: Single Encounter Radical Cure and Prophylaxis (p. 3)

In the recent past, drug development efforts were guided by the need for first-line drugs to treat P. falciparum infections with an increasing emphasis on drugs with a short half-life that potentially minimize the risk of development of resistance rather than on drugs with a long half-life that have benefits for dosing and post-treatment prophylaxis [13]. Treatment of infected individuals with a variety of drug regiments has been used successfully in combination with intensive vector control to eliminate malaria from areas with relatively strong health systems and stable populations. However, interruption of malaria transmission is likely to require a new set of drugs and formulations.

As described in more detail in the article by the malERA Consultative Group on Drugs [14], such drugs will need to be used both in stable transmission areas and in complex urban or remote rural areas, with poorly functioning health systems where concerted campaigns may be the only way of achieving high coverage or preventing reintroduction by migrants or travelers from endemic regions. For such campaigns to impact effectively on inaccessible populations, a single encounter between health providers and target populations is critical. Single Encounter Radical Cure and Prophylaxis (SERCaP) has a target product profile (TPP) that includes radical cure, defined as elimination of all parasites (including the long-lived hypnozoites of P. vivax or P. ovale in the liver), suitability for mass administration (including administration to healthy subjects and the consequent need of a very good safety profile), and prophylaxis for at least 1 month after treatment, to outlast the typical development period of Plasmodia parasites in Anopheline mosquitoes. A drug with this profile would perform in a similar way to a highly efficacious pre-erythrocytic (infection-preventing) vaccine.

A drug with this TPP may take a long time to develop, but the development of new drugs that meet some of these essential requirements could dramatically improve chances of eradication. For example, development of new safe and effective drugs that block the infectivity of the mature sexual forms of P. falciparum gametocytes and/or the dormant hepatic forms (hypnozoites) of P. vivax could have a profound impact on transmission rates and would be valuable tools in the efforts to contain and eliminate parasite strains resistant to first line treatment drugs. Presently, only the 8-aminoquinolines are known to be effective against both P. vivax hypnozoites and P. falciparum stage-five gametocytes. Unfortunately this class of drugs has significant side-effects in some individuals, particularly hemolysis in those with G6PD deficiency, that compromise their widespread use in mass administration for elimination [14].

Diagnostics (p. 4)

Methods for measuring transmission are central to an elimination agenda. Current methods for measuring transmission that may be applied in endemic areas are time-consuming, expensive, and too insensitive for use in conditions of low and non-uniform infection [21,22]. Some years after regional elimination, as immunity declines, infection is likely to be symptomatic and may become the best marker of resumed transmission. However, during the early elimination phase in regions previously experiencing high transmission, populations will retain clinical immunity and will not experience symptomatic disease with every infection [23]. Thus, the main challenge identified by the malERA Consultative Group on Diagnoses and Diagnostics and discussed in detail in their article and in the article on Cross-cutting Issues for Eradication [24,25] is to find a robust, sensitive, and specific standardized method for assessment of transmission intensity in the intervening period when transmission continues at low and nonrandom levels. Improved serological tests have been suggested [26], but other minimally invasive biomarkers could be considered. This information will be essential for modeling potential effects of various interventions alone, or in combination, and for assessing efficacy of transmission–reducing vaccines and drugs. Other challenges for diagnostics discussed by the Consultative Group include the need for tools that can rapidly detect and monitor unexpectedly high transmission that leads to outbreaks and that can identify reintroduction of infections that may be asymptomatic [16,24].

Enabling technologies and platforms (p. 5)

The development of new tools for elimination is critically dependent on a vibrant and coherent agenda for basic sciences. We believe there are at least two potentially transformative developments that need to be pursued. First, continuous laboratory culture of P. vivax, P. ovale, and P. malariae needs to be developed to provide an essential platform for studying the biology of the liver stages and sexual forms of these parasites. These forms could be important targets of intervention strategies with drugs, vaccines, or other biological or chemical agents aimed at interrupting transmission. Second, systems analyses of transcription, proteome, and metabolome libraries, rapid screening of drug libraries, high-throughput approaches to antigen identification, and the functional definition of gene products are all feasible but not yet fully exploited, but would bring important new tools to the bench scientist and to field operations. These and other aspects of enabling technologies and platforms are considered in detail in the articles prepared by the malERA Consultative Groups on Basic Science and Enabling Technologies and on Cross-cutting Issues for Eradication [25,31].

Health Systems Integration, Operational Research, and Effectiveness-Decay Analysis (p. 6)

The previous formal attempt at global eradication of malaria (1955–1969) depended largely on vertical operations that often bypassed health systems and their health services because it was assumed that eradication operations could be run most efficiently in this way. Many of the elimination efforts failed, because the health systems failed, leading to a pessimistic view that malaria can only be eliminated where economic progress, governance, and efficient health systems are in place to support maintenance of conditions necessary to block transmission [32,33].

It is now clear that the long-term solution to malaria elimination and eradication will require a systems approach in which malaria specific interventions and actions are integrated into existing health systems [34]. To achieve this, research is needed into health systems, their readiness to optimize novel programs, systems, tests, or other interventions, and their continuing performance [35–37]. During their deliberations, the malERA Consultative Group on Health Systems and Operational Research identified the need for a substantial research approach to establish and validate a tool kit that allows effectiveness-decay analysis of health system impediments to effective and equitable coverage of malaria interventions and that allows decisions to be made on the degree of possible integration of interventions into an existing health system [16,38]. A further critical component of the research agenda identified by this Consultative Group is the development and validation of a decision-making framework to guide the move from control to elimination.

Finally, but equally importantly, the article by the malERA Consultative Group on Monitoring, Evaluation, and Surveillance considers the need to investigate the performance of surveillance, monitoring, and evaluation by new and old technologies [39,40] and to evaluate optimal strategies for implementation of surveillance as an active responsive intervention to further reduce transmission [41].

Liver-Stage Cultures (p. 10)

Our current understanding of the biology of the parasite's liver stage (the hypnozoite stage) suggests this stage will be an important target in efforts to eradicate malaria [20]. Specifically, hepatic development occupies a critical position in mediating the establishment of blood-stage infection and, consequently, the transmission of malaria. Moreover, in the case of P. vivax, the dormant hypnozoite stages remain in the liver for a variable and protracted period before leading to relapse. Clearly, eradication of P. vivax (and P. ovale) is unlikely to be attained without developing effective hypnozoiticides.

The availability of a Plasmodium liver-stage model would allow the investigation of the host factors that are involved in primary and latent intrahepatic development and of the metabolic pathways that regulate development of this parasitic stage. In addition, the existence of such a model would allow the development of much needed drug screens for this stage that could, like the recently available drug screens for asexual blood stage infections [21–27], take advantage of the unprecedented access to the three chemical compound libraries—GlaxoSmithKline's Tres Cantos Antimalarial TCAMS dataset [24], the Novartis-GNF Malaria Box Dataset, and the St. Jude Children's Hospital Malaria dataset [25]—that are hosted at ChEMBL-NTD (www.ebi.ac.uk/chemblntd), an Open Access repository of primary screening and medicinal chemistry data.

Finally, with the resurgence in interest in genetically attenuated or irradiated sporozoite-based, pre-erythrocytic vaccines [28,29], a liver-stage model would permit investigation of the molecular basis of their developmental arrest—an understanding that will be critical in both the licensing of such vaccines and in ensuring that breakthrough infections do not arise.

Thus, the development of in vitro systems to understand hypnozoite biology as it relates to liver-stage biology is a clear priority. However, the culture of parasites through the liver stage is likely to be a significant challenge given the intractability of this stage relative to other life stages.

Such an endeavour will require a highly collaborative and interdisciplinary approach that includes specialists in the fields of hepatocyte and stem cell biology as well as biomedical engineering. The development of hepatocytes that maintain their polarity and normal trafficking properties is a necessary step towards this kind of model, as is development of primary or immortalized hepatocyte cultures with sufficient life span to allow hypnozoite formation and survival [30–34]. Cell lines that allow high infectivity and that can yield high parasite numbers would be especially valuable for generating more useful quantities of parasite material with which to work. Moreover, a single hepatocyte line may not be amenable or useful to all the different subdisciplines present in the malaria community. Some may be appropriate for immunological studies, while others may be suited to drug studies against primary or relapse infection from hypnozoites [1,2]. Finally, it should be noted that the possibility of using humanized mouse models engrafted with functional human cells and tissues, including human hepatocytes or human hematolymphoid cells, presents a unique in vivo approach that could also facilitate our understanding of Plasmodium liver-stage biology [35].

Development of Genetic Tools for P. vivax and Approaches for Systematic Mutagenesis in Plasmodium (p. 11)

Major advances towards understanding fundamental aspects of model organisms inherently follow technological innovations that move fields in new directions. Thus, the ability to manipulate the genomes of different Plasmodium species has revolutionized malaria research. Nevertheless, we are still a long way from the systematic use of reverse genetics seen in other model systems such as yeast. For example, although the P. falciparum genome was completed more than 5 years ago, as many as half of the annotated genes are still listed as having a hypothetical or unknown function; around 90% of the genes have little biological evidence for function. Furthermore, little is being done currently to coordinate the study of individual genes or gene families, with the exception of recent efforts to systematically define the function of proteins involved in erythrocyte remodeling and export [40].

Despite many recent improvements to genetic technologies in Plasmodium, many roadblocks that prevent scale-up of genetic manipulation and functional analysis of essential genes need to be overcome [41–44]. These roadblocks include the low frequency of homologous recombination in Plasmodium, difficulties associated with the manipulation of large fragments of AT-rich and repetitive genomic DNA, and the lack of robust and scalable systems for conditional gene expression. In addition, there are no practical strategies for achieving saturation mutagenesis. Technologies to tackle some of these roadblocks are available for other organisms [45,46] and need to be introduced to the malaria research agenda.

If these technical limitations can be overcome, systematic mutagenesis on a genome-wide scale will allow us to distinguish essential from redundant metabolic pathways and will be critical to obtaining a comprehensive picture of the stage-specific biology of the parasite that could be targeted with drugs or vaccines. Stable, conditional knock-out approaches for genes that are essential in one life stage but not in another would also identify potential drug targets. Improved genetic technologies will also enable the systematic production of large-scale repositories of gene knockout or epitope-tagged versions for every plasmodial gene. Such community resources would avoid duplication and benefit from the economy of scale. More importantly, easy access to large numbers of mutants would inspire new experimental approaches, as they have in the yeast field [47–49], and widen access to genetic technology.

Finally, the recent completion of several parasite and mosquito genomes [50–54] and new insights into the contribution of human and mosquito host genotype to transmission have radically changed how researchers approach malaria. This information, together with an internationally accessible repository of transgenic lines for every Plasmodium gene, will change the way that the research community approaches the most basic and relevant questions related to Plasmodium biology (of all species) and interactions of the various Plasmodium species with their hosts.

Metabolomics (p. 11)

As with genomic innovations, new technological platforms that permit the deep characterization of the metabolome (complete set of small-molecule metabolites) of Plasmodium will identify new potentially druggable targets [55,56]. Indeed, analysis of the parasite's metabolome is already revealing profound new insights into parasite biology that were not amenable to or that were missed by genomic approaches [57–59]. For metabolites that are readily identifiable, differences among parasite strains, under varying drug conditions, or in mutant backgrounds will enhance understanding of the known metabolic pathways present in Plasmodium spp. However, many of the measurable compounds are likely to derive from previously undetected novel metabolites (including the products of poorly understood lipid and carbohydrate metabolism). The identification of these compounds could yield key insights for the development of new antimalarial drugs or the control of drug resistance. Moreover, the identification of the metabolic similarities between different parasite stages could provide new approaches to the development of drugs with potential to kill the parasites at many points in their life cycle, possibly in both the human host and the mosquito vector [58–61].

Metabolomic approaches should also enable identification of metabolic differences between, for example, patients who are asymptomatic and those with advanced stage cerebral malaria (or other severe syndromes). Metabolomic studies of such samples may not only provide information about the state of the host, but also about the interaction between the host and the parasite. The Consultative Group felt that such studies, which bring together bench scientists and field clinicians, should be encouraged as the true picture of the diversity of metabolic effects can only be fully appreciated from field-derived samples. Finally, the group noted that the application of metabolomic technology will be particularly powerful in unraveling the biochemical strategies of parasites with no or poor genomic resources such as P. ovale or P. malariae.

Box 2. Summary of the Research and Development Agenda for Basic Science Research (p. 12)

- A research paradigm shift away from the ''parasite-first'' approach to an examination of what the human and mosquito host cells provide to the developing parasite is needed to complement on-going approaches
- A new approach is needed to support collaborative and truly cross-disciplinary arrangements among scientists to bridge the gap between basic laboratory and clinical/ population-based sciences and to meet the scientific benchmarks outlined by malERA
- Desired target product profiles need to be defined without preferred technological approaches being suggested to create opportunities for lateral thinking by experts bringing new approaches from different fields
- Careful evaluation and appropriate use of today's technologies from the physical, chemical, and biomedical engineering sciences is needed to improve the molecular understanding of parasite developmental biology and of the mammalian host-parasite-vector interactions

- Mechanism of action studies for drugs and vaccines in the current pipeline are also needed to inform future strategies for the development of the next generation of interventions and therapeutics
- The study of human host and vector factors in large-scale, long-term population-based field studies and the use of appropriate technologies in translation applications is also essential.

Long-Acting Formulations (p. 19)

Another creative approach from the past that may hold promise for the future is the use of long-acting formulations. ''Repository'' formulations of malaria drugs to provide prolonged protection were extensively researched in the early 1960s [27], and oil-based depot injections of cycloguanil pamoate provided more than 1 year of protection against experimental challenge with P. falciparum sporozoites [28]. These injections were evaluated in at least 15,000 people, but never deployed as a tool for elimination because of the attendant pain and local abscesses.

Box 2. A Draft Research and Development Agenda for Drugs for Malaria Eradication (p. 19)

KNOWLEDGE GAPS AND RESEARCH PRIORITIES FOR OPTIMIZING CURRENT DRUGS

- Pharmacology studies to optimize dosing regimens of 8-aminoquinolines for gametocytocidal and anti-relapse efficacy and safety
- Rapid and robust point-of-care glucose-6-phosphate dehydrogenase (G6PD) test to improve safety of 8-aminoquinoline use
- Tests that can detect resistance to artemisinins and ACT partner drugs
- Determine gametocytocidal and anti-relapse activity of current drugs and those in the pipeline

KNOWLEDGE GAPS AND RESEARCH PRIORITIES FOR DEVELOPING NEW DRUGS FOR MALARIA ERADICATION

Desired products

- Drugs that prevent transmission by killing or preventing development of gametocytes, or blocking sporozoite development in the mosquito
- Drugs that cure liver stages of vivax (and ovale) malaria
- Ideally, drugs that can be administered in a single encounter at infrequent intervals, and that result in radical cure of all parasite stages (Single Encounter Radical Cure and Prophylaxis, see Box 1)
- Sustained or pulsed release formulations
- Exceptionally safe schizonticidal drugs for curing asymptomatic falciparum infection

Fundamental research questions aimed towards developing desired drugs

- Fundamental studies of liver and sexual stage biology (in both host and mosquito)
- Mechanisms of resistance and pharmacological strategies to deter resistance

- In vitro culture of P. vivax to understand parasite biology

Tools and capacities

- Increased capacity for clinical pharmacology research including pharmacokinetics/pharmacodynamics studies in populations targeted for malaria elimination
- Increased capacity for human challenge studies for early go/no go decisions on drug candidates
- Assays to measure transmission-blocking activity
- Assays to measure activity against liver stages
- In vitro culture of P. vivax and other non-falciparum species for drug screening
- Genomic and proteomic approaches to identify transmission-blocking and liver-stage activity

KNOWLEDGE GAPS AND RESEARCH PRIORITIES FOR DRUG TREATMENT AND PREVENTION STRATEGIES FOR ERADICATION

- Field studies to evaluate new drugs and approaches in a variety of epidemiological settings
- Robust and highly sensitive malaria diagnostics for malaria infection and especially for carriage of infectious gametocytes
- Measures to monitor and improve adherence and safety
- How must drug treatment and prevention strategies change as elimination proceeds?
- Strategies to deter resistance

Rationale of the Proposed malERA Approach to Development of Malaria Vaccines (p. 24)

First, we introduce the broad concept of VIMT (Vaccines that interrupt malaria transmission). VIMT may be composed of one or more of the following components: classical TBVs that target sexual and mosquito stage parasite antigens; highly effective pre-erythrocytic vaccines that reduce asexual and sexual stage parasite prevalence rates; highly effective asexual erythrocytic stage vaccines that inhibit multiplication of asexual stage parasites efficiently to reduce blood-stage parasite densities and have an impact on malaria transmission; and vaccines that target vector antigens to disrupt parasite development in the vector. It seems obvious that a highly effective pre-erythrocytic vaccine that prevents erythrocytic stage infection will reduce transmission, but the effect of partially effective pre-erythrocytic or asexual blood-stage vaccines on individual infectivity needs investigation. A successful VIMT must primarily reduce malaria transmission. However, VIMTs that include pre-erythrocytic and/ or asexual blood-stage vaccine components may also provide individuals with protection against malaria. Such VIMT would also protect the population against epidemic spread following reintroduction of malaria after elimination, an important characteristic given that the gains accrued through many years of elimination can be rapidly reversed if malaria is reintroduced to a population with no antimalarial immunity [10].

Second, the observed impact of concerted nonvaccine malaria control efforts on transmission dynamics in several malaria endemic regions has shown that high-intensity transmission settings (entomological inoculation rate, EIR .50) can be converted to low-to-moderate intensity

transmission settings (EIR ,10) [11,12]. Implementation of VIMT together with such control efforts may successfully drive down transmission rates to reduce the effective reproduction rate (Reffective) to below 1.0.

Third, the consultative group introduces the concept of a detailed TPP for this class of vaccines and urges that novel clinical development methods and approaches be considered to shorten the time to VIMT registration and implementation.

Fourth, the consultative group lays out a detailed research agenda that must be developed, funded, and implemented in parallel with VIMT development efforts. This agenda includes development of critical tools that will be required to register and implement such a vaccine. In particular, we identify the need to develop robust assays to measure biologically relevant transmission- blocking activities at the individual level that are validated as surrogates of reductions in transmission rates at the population level. If this goal is achieved, such assays could become the key tool for measurement of primary vaccine efficacy endpoints in conditional registration trials, thereby simplifying the clinical development program.

Finally, the consultative group considers that interested industrial partners should be identified early on in development, because expertise in applied immunology, vaccinology, product development, manufacturing, and regulatory activities is concentrated within industry and will play an essential role in the successful development of VIMT. In addition, it will be important to engage with regulatory agencies to define efficient yet sound regulatory strategies to develop and register new tools that can meet the needs of global malaria elimination and eradication efforts.

Box 1. Summary of the Research and Development Agenda for Vaccines (p. 31)

A prioritized research and development agenda to enable the development of VIMT for use as critical components in malaria elimination efforts includes:

- Development and application of novel vaccine delivery approaches and/or adjuvants to elicit long-lasting protective efficacy that makes significant impact on malaria transmission rates under diverse epidemiological settings.
- Expansion of vaccine development efforts to cover Plasmodium species other than P. falciparum, especially P. vivax (including hypnozoites).
- Understanding the dynamics between multiplication of asexual stage parasites, gametocytogenesis, and malaria transmission rates at the population level.
- Development of robust assays to study functional immune responses at the individual level that can predict effect on malaria transmission at the population level and allow decision making in product development.
- Development of tools to measure malaria transmission rates, thereby facilitating clinical development of vaccines that reduce malaria transmission.

Vector Control: Current Tools and Resource Gaps (p. 35)

The key goal of the malERA Consultative Group on Vector Control was to help define the research and development agenda that will be required to sustain and improve the effectiveness of currently available tools like LLINs and IRS and to develop new vector-targeted tools that can be used to interrupt transmission in environments or at intensities that these existing tools cannot reach. It is clear that new technology will be required in very high transmission areas to reduce vectorial capacity and achieve even effective control, let alone elimination. The main aim of this paper is to define a research and development agenda that focuses on those new research questions and knowledge gaps that arise specifically in response to the call for malaria eradication, and that would not otherwise be at the top of the agenda (Table 1). It is particularly important to recognize that this operationally specified goal significantly limits the scope of research and development under consideration, and this document should not be the basis for all vector research related to malaria. Our article does, however, describe the challenges for vector control methodology in the elimination phase, for detecting and monitoring areas of persistent transmission, and for detecting and monitoring nonrandom transmission leading to outbreaks. We also discuss the requirements for rapid and urgent intervention when outbreaks occur (see also [8]).

The Consultative Group identified four key components to successful vector control within an eradication agenda. First, the ecology of vectors responsible for malaria transmission in those regions of the world where current tools are insufficient for elimination needs to be understood. Second, sets of synergistic or complementary interventions tools need to be developed and applied through rationally designed programs that can be spatially and temporally combined into effective intervention programs.

Third, appropriate monitoring and evaluation tools that can guide the application and evolution of control and elimination programs as malaria endemicity is pushed towards local elimination need to be developed and applied. Finally, there is a critical need for built-in flexibility in programs so that where initial efforts fail, they can adapt to circumstances by incorporating and implementing new approaches. Thus, as malaria programs are scaled up, vector control will have a major role in disease burden reduction but, as programs become increasingly successful in reducing transmission, accurate estimation of the point at which large-scale vector control activities can be relaxed will become critical. Premature removal of mainstream vector control, either through planned reductions in activities or through failure of long-lasting interventions like LLINs or IRS as resistance evolves, is likely in many instances to lead to a catastrophic increase in morbidity and mortality because of resurgent malaria in a non-immune population [8,9].

The exact role of vector control as countries enter the elimination phase of activities will be situation specific. However, valuable lessons can be drawn from the WHO Global Malaria Eradication Program (GMEP) of the 1950s and 1960s [10], in which vector control alone was considered to be enough in many situations to eliminate malaria. Although this approach was successful in some cases, success was often short-lived [11,12]. Another valuable lesson can be learned from current efforts to eradicate filariasis. For this vector-borne disease, multiple rounds of mass drug administration in many countries divorced from targeted vector control have not achieved the predicted interruption in transmission [13].

Indeed, there is now a consensus that malaria elimination with current tools is far more likely if the best available tools are used in combinations. In the past two decades, especially in an African context, the combination of drugs and vector control with impregnated nets has been highlighted for its role in the reduction of morbidity and mortality [14]. However as malERA sets out a research and development agenda for elimination/eradication and vector control, other interventions must be considered primarily in terms of their impact on malaria infection and transmission, not instead of, but in addition to, their role in prevention and modification of disease.

We highlight the research and development areas identified as priority areas by the Consultative Group before providing a summary research and development agenda that draws together the various strands of our discussions.

Box 1. Summary of the Research and Development Agenda for Vector Control (p. 40)

- Development of an analytic framework that can bring together existing and new information on all aspects of malaria and malaria transmission through a public portal designed to facilitate decision making by the malaria research, control, and tool development communities.
- An improved choice of insecticides, and formulations coupled with improved methods to reduce the risk of resistance to ensure that the availability of effective insecticides does not become the limiting factor in our ability to reduce transmission to levels where local elimination can be attempted.
- Better understanding of the ecology, behaviour, and genetic population structure of malaria vectors, particularly outdoor biting and resting species that escape current vector control tools.
- Development of innovative new technologies that can:
    - Educate the community effectively and engage the consumer market
    - Control outdoor biting and resting mosquito vectors
    - Simply and rapidly measure transmission
- Sustained commitment to the long-term development of novel approaches like the genetic manipulation of natural vector populations that will permanently reduce the very high vectorial capacities of dominant malaria vectors in sub-Saharan Africa and some parts of Asia.

Box 1. Summary of the Research and Development Agenda for Diagnosis and Diagnostics (p. 51)

Overarching questions

- What proportion of effort should be directed to screening and surveillance versus early case detection at various time points in elimination? Question to be addressed by modeling and validated in different areas.
- Do we need microscopy for elimination, or can other tests replace it?

Programmatic issues

- Further data on thresholds of (i) parasite density likely to cause symptoms in low-transmission settings with variable or waning immunity, and (ii) transmission potential of cases with parasitemia below the threshold of microscopy and RDTs
- Diagnostic tests for nonmalarial febrile illness in malaria endemic and malaria-elimination settings
- Distribution of severe G6PD variants

Technical issues: case-management tools

High priority

Stable tests for case management in low-training, low technology settings with sensitivity sufficient for community-level case management, including:

- Antigen-detecting RDTs
    - Greater consistency in P. falciparum detection, particularly in the case of non-persistent antigens
    - More sensitive and stable tests to detect non-P. falciparum parasites
    - Clarification of the programmatic/implementation requirements that will ensure good impact in the field
    - Standardized low-cost positive controls for antigen-detecting
    - RDTs suitable for field use
    - Sustainable tools for quality control of RDTs at a country level.
- Further investigation of nonblood sampling to determine the potential for detecting recoverable antigen in these samples.
- More consistent, reliable staining methods for microscopy
- G6PD deficiency mapping and identification (if 8-aminoquinolones are to be used)

Medium priority

- Multiplexing: Other diseases, markers of severity
- Field G6PD detection (may be more important if tafenoquine approved), or raised priorities for P. vivax relapse prevention
- Tools to standardize and improve microscopy interpretation

Low priority

- Hypnozoite detection (becomes a high priority if feasibility can be demonstrated through further research on hypnozoite biology, identifying good biomarkers).

Technical issues: surveillance tools

High priority

- Field-applicable tools for detection of low-density parasitemia in a high-throughput manner, suitable for surveys and active detection of parasite carriage in time to allow management of positive cases

- Tools for minimally invasive, very rapid detection of low-density parasite infections suitable for screening of migrants/travelers

Innovation with potential for major operational impact

- Non-invasive, low-density parasite detection

Low-hanging fruit with immediate application for elimination

- High-throughput field molecular detection, capable of use at district level or below
- Positive control methods for RDTs

Box 2. Summary of the Research and Development Agenda for Monitoring, Evaluation, and Surveillance (p. 67)

- Update the malaria monitoring and evaluation Framework to include transmission reduction, and develop key data elements for a surveillance system from a systematic review of previous elimination attempts
- Systematically review lessons learned from experiences with surveillance as an intervention to determine how it can be tailored to various programmatic settings
- Identify appropriate program time points for introduction of malaria infection detection in active or passive modes
- Develop improved diagnostic tools for use in monitoring and evaluation and surveillance, focusing on practical field-ready tools for detection of asymptomatic infection
- Develop information systems to monitor malaria infections, facilitate timely local program decisions and responses to reduce transmission
- Develop methods, indicators, and shareable databases for parasite strain information to better track transmission
- Develop methods for accessing and tracking population movements and quantifying their contribution and risk of malaria transmission
- Explore how maps can be constructed to: show the probability of a threshold of transmission being exceeded; incorporate a wider range of metrics such as serological and entomological data; assess cost-effectiveness of national stratification initiatives based on remotely sensed satellite data
- Perform a systematic review to assess and compare metrics of malaria transmission at near zero transmission levels; research the validity of novel metrics to measure transmission at near zero levels, and to measure transmission potential within areas where transmission has been eliminated
- Assess the precision, bias, feasibility, and cost-effectiveness of novel sampling methods for routine monitoring of present and past infections in target populations, including mobile populations
- Conduct research to develop biomarkers such as DNA-based methods or serology as monitoring and evaluation and surveillance tools

Attachment 6: Selected Key Figures[6]

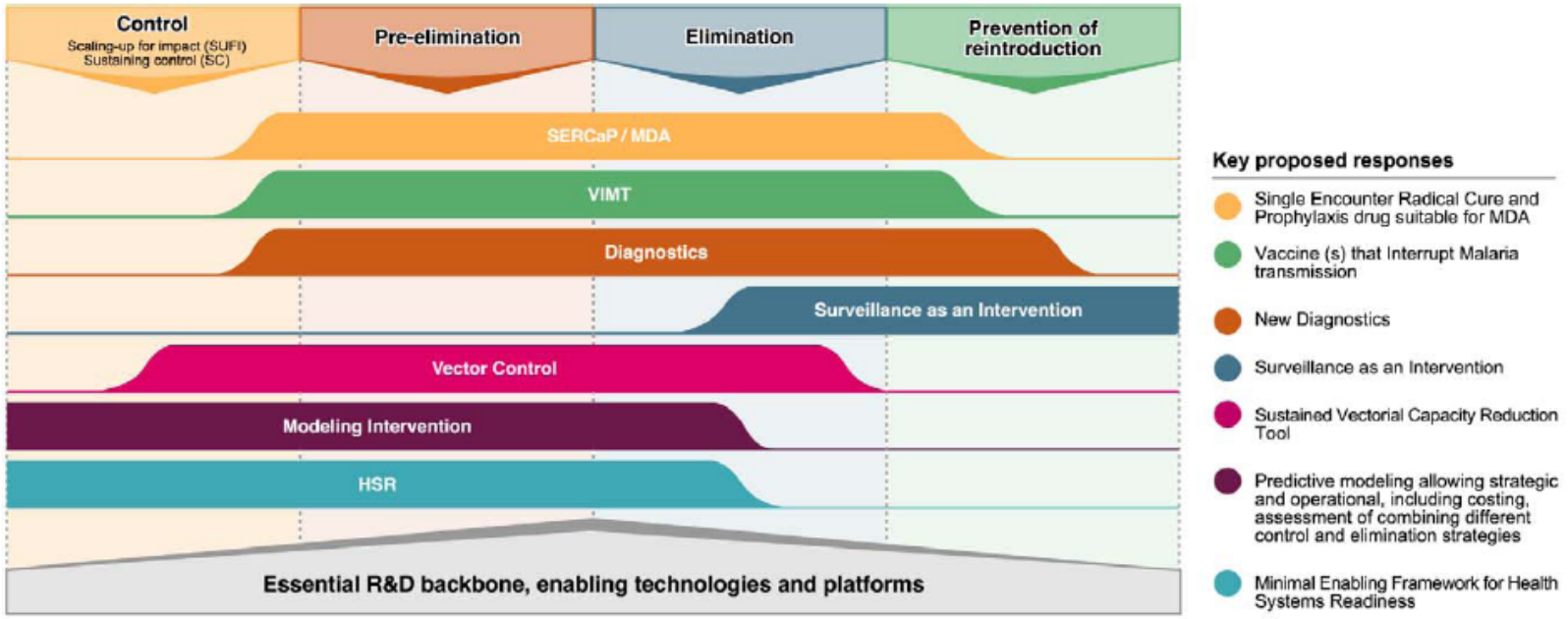


Figure 4. Key research and development issues and their position in relation to the different epidemiological phases towards eradication. Image credit: Fusión Creativa.
doi:10.1371/journal.pmed.1000406.g004

[6] **Source:** PLOS Medicine. malERA: a Research Agenda for Malaria Eradication. Barcelona: The Barcelona Centre for International Health Research; 2011.

Table 1. Indications for antimalarial drugs in the present control era and their relevance in the eradication era.

Indications for Antimalarial Drugs in the Control Era	Relevant to Malaria Eradication?
Prophylaxis	
Causal prophylaxis[a]	Yes, completely blocks infection and thus transmission
Suppressive prophylaxis[b]	No, does not prevent, and may augment, transmission
IPT of pregnant women, infants, or children	Maybe, but only if transmission-blocking drugs are used in a high proportion of the infected reservoir, essentially amounting to intermittent MDA
Treatment of disease	
Uncomplicated malaria	
P. falciparum and *P. malariae*	Maybe, treatment indications for specific clinical syndromes are not directly relevant to the goal of eradication unless treatment drugs have transmission-blocking efficacy; widespread use of treatment drugs with antiliver stage and gametocytocidal activity would contribute to transmission reduction.
P. vivax and *P. ovale*	As above
Severe malaria	As above
Antihypnozoite (liver-stage radical cure)	Yes, high priority
Transmission blocking	Yes, high priority

[a]Causal prophylaxis targets pre-erythrocytic liver stages and, if effective, prevents any parasites from reaching the blood state or being transmitted to mosquitoes.
[b]Suppressive prophylaxis is repeated subcurative dosing that suppresses blood-stage infection and prevents malaria illness but does not eradicate malaria infection or prevent transmission

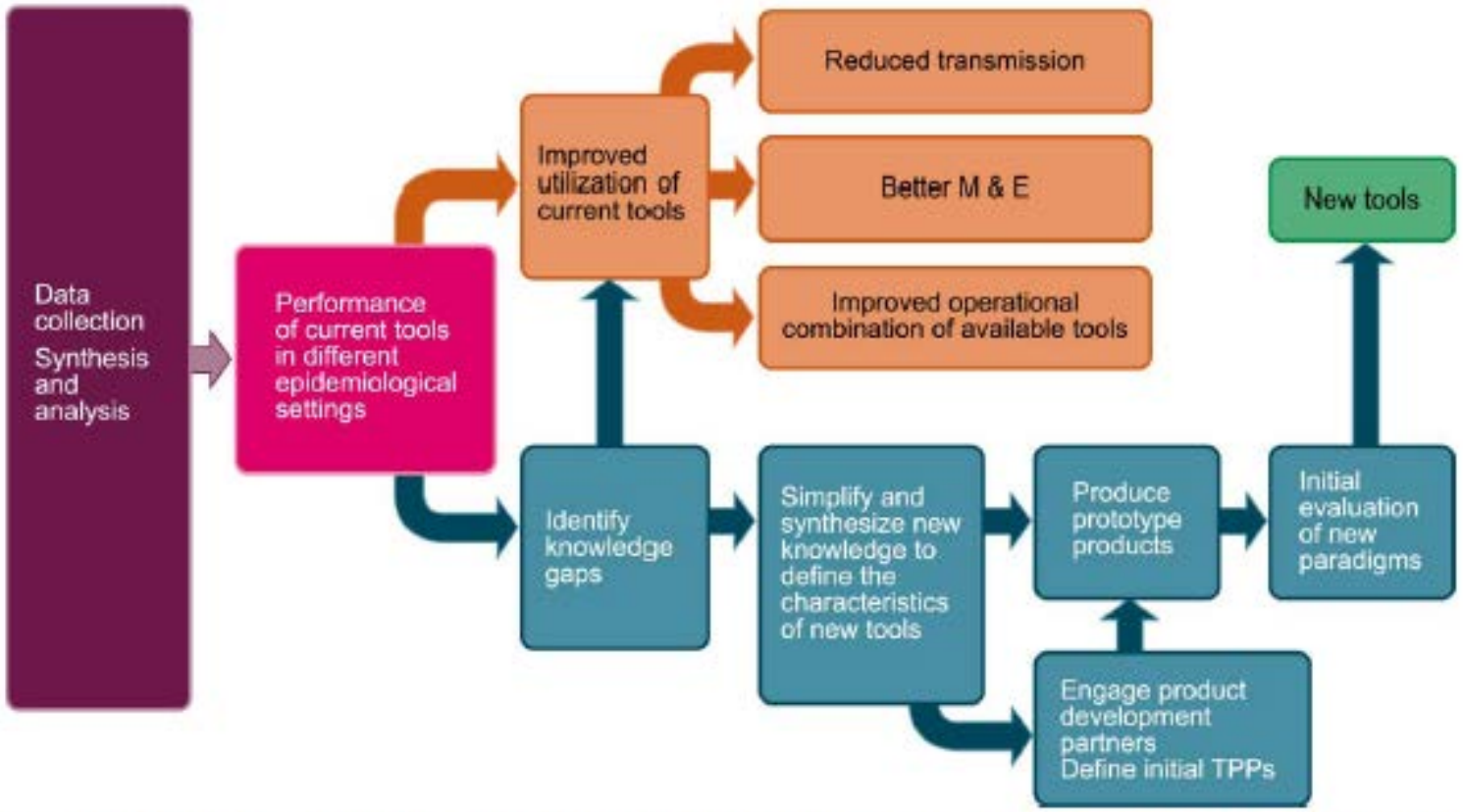


Figure 1. A formalized analytical framework for the collection, analysis, and central presentation of relevant information. M&E, monitoring and evaluation. Image credit: Fusión Creativa.
doi:10.1371/journal.pmed.1000401.g001

Synthesis of Disease-Specific R&D Priorities for Malaria

malERA: A RESEARCH AGENDA FOR MALARIA ERADICATION. 2011.

R&D Areas		MALARIA *R&D Priorities for Achieving Goals*
PLOS Medicine. malERA: a Research Agenda for Malaria Eradication. Barcelona: The Barcelona Centre for International Health Research; 2011.		
FUNDAMENTAL RESEARCH		
	Key Focus Area(s)	• Transition research away from "parasite-first" approaches to an examination of host-parasite-vector population interactions • Better understand the stage-specific biology of the parasite • Define desired target product profiles, incorporating new approaches from different fields • Investigate how basic research can inform future strategies for the development of next-generation interventions and therapeutics • Identify roadblocks that prevent the scale-up of genetic manipulation and functional analysis of essential genes
	Main 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 • Investigate how new technology platforms can permit deep characterization of the metabolome • Design research studies aimed at understanding the epidemiology of the gametocyte • Develop an efficient, inexpensive P. Vivax blood-stage culture system • Create in vitro systems to understand P. Falciparum, P. Vivax and hypnozoite biology as it relates to liver-stage biology • Conduct mechanism of action studies for drugs and vaccines in the current pipeline to inform future strategies • Find ways to improve technologies for the manipulation of Plasmodium • Learn how to implement systems-based approaches in order to incorporate cutting-edge technology (e.g. metabolomics) • Utilize technologies from physical, chemical, and biomedical engineering sciences to improve molecular understanding of parasite development biology • Introduce new technologies to address roadblocks, such as: low frequency of homologous recombination in Plasmodium, difficulties associated with the manipulation of large fragments of AT-rich and repetitive genomic DNA, and the lack of robust and scalable systems for conditional gene expression
	LIVER-STAGE CULTURES	

R&D Areas	MALARIA *R&D Priorities for Achieving Goals*
	Our current understanding of the biology of the parasite's liver stage (the hypnozoite stage) suggests this stage will be an important target in efforts to eradicate malaria [20]. Specifically, hepatic development occupies a critical position in mediating the establishment of blood-stage infection and, consequently, the transmission of malaria. Moreover, in the case of P. vivax, the dormant hypnozoite stages remain in the liver for a variable and protracted period before leading to relapse. Clearly, eradication of P. vivax (and P. ovale) is unlikely to be attained without developing effective hypnozoiticides. The availability of a Plasmodium liver-stage model would allow the investigation of the host factors that are involved in primary and latent intrahepatic development and of the metabolic pathways that regulate development of this parasitic stage. In addition, the existence of such a model would allow the development of much needed drug screens for this stage that could, like the recently available drug screens for asexual bloodstage infections [21–27], take advantage of the unprecedented access to the three chemical compound libraries—GlaxoSmithKline's Tres Cantos Antimalarial TCAMS dataset [24], the Novartis-GNF Malaria Box Dataset, and the St. Jude Children's Hospital Malaria dataset [25]—that are hosted at ChEMBL-NTD (www.ebi.ac.uk/chemblntd), an Open Access repository of primary screening and medicinal chemistry data. Finally, with the resurgence in interest in genetically attenuated or irradiated sporozoite-based, pre-erythrocytic vaccines [28,29], a liver-stage model would permit investigation of the molecular basis of their developmental arrest—an understanding that will be critical in both the licensing of such vaccines and in ensuring that breakthrough infections do not arise. Thus, the development of in vitro systems to understand hypnozoite biology as it relates to liver-stage biology is a clear priority. However, the culture of parasites through the liver stage is likely to be a significant challenge given the intractability of this stage relative to other life stages. Such an endeavour will require a highly collaborative and interdisciplinary approach that includes specialists in the fields of hepatocyte and stem cell biology as well as biomedical engineering. The development of hepatocytes that maintain their polarity and normal trafficking properties is a necessary step towards this kind of model, as is development of primary or immortalized hepatocyte cultures with sufficient life span to allow hypnozoite formation and survival [30–34]. Cell lines that allow high infectivity and that can yield high parasite numbers would be especially valuable for generating more useful quantities of parasite material with which to work. Moreover, a single hepatocyte line may not be amenable or useful to all the different subdisciplines present in the malaria community. Some may be appropriate for immunological studies, while others may be suited to drug studies against primary or relapse infection from hypnozoites [1,2]. Finally, it should be noted that the possibility of using humanized mouse models engrafted with functional human cells and tissues, including human hepatocytes or human hematolymphoid cells, presents a unique in vivo approach that could also facilitate our understanding of Plasmodium liver-stage biology [35].
	DEVELOPMENT OF GENETIC TOOLS FOR P. VIVAX AND APPROACHES FOR SYSTEMATIC MUTAGENESIS IN PLASMODIUM

R&D Areas	MALARIA	
		R&D Priorities for Achieving Goals
	Major advances towards understanding fundamental aspects of model organisms inherently follow technological innovations that move fields in new directions. Thus, the ability to manipulate the genomes of different Plasmodium species has revolutionized malaria research. Nevertheless, we are still a long way from the systematic use of reverse genetics seen in other model systems such as yeast. For example, although the P. falciparum genome was completed more than 5 years ago, as many as half of the annotated genes are still listed as having a hypothetical or unknown function; around 90% of the genes have little biological evidence for function. Furthermore, little is being done currently to coordinate the study of individual genes or gene families, with the exception of recent efforts to systematically define the function of proteins involved in erythrocyte remodeling and export [40]. Despite many recent improvements to genetic technologies in Plasmodium, many roadblocks that prevent scale-up of genetic manipulation and functional analysis of essential genes need to be overcome [41–44]. These roadblocks include the low frequency of homologous recombination in Plasmodium, difficulties associated with the manipulation of large fragments of AT-rich and repetitive genomic DNA, and the lack of robust and scalable systems for conditional gene expression. In addition, there are no practical strategies for achieving saturation mutagenesis. Technologies to tackle some of these roadblocks are available for other organisms [45,46] and need to be introduced to the malaria research agenda. If these technical limitations can be overcome, systematic mutagenesis on a genome-wide scale will allow us to distinguish essential from redundant metabolic pathways and will be critical to obtaining a comprehensive picture of the stage-specific biology of the parasite that could be targeted with drugs or vaccines. Stable, conditional knock-out approaches for genes that are essential in one life stage but not in another would also identify potential drug targets. Improved genetic technologies will also enable the systematic production of large-scale repositories of gene knockout or epitope-tagged versions for every plasmodial gene. Such community resources would avoid duplication and benefit from the economy of scale. More importantly, easy access to large numbers of mutants would inspire new experimental approaches, as they have in the yeast field [47–49], and widen access to genetic technology. Finally, the recent completion of several parasite and mosquito genomes [50–54] and new insights into the contribution of human and mosquito host genotype to transmission have radically changed how researchers approach malaria. This information, together with an internationally accessible repository of transgenic lines for every Plasmodium gene, will change the way that the research community approaches the most basic and relevant questions related to Plasmodium biology (of all species) and interactions of the various Plasmodium species with their hosts.	
	SUMMARY OF THE RESEARCH AND DEVELOPMENT AGENDA FOR BASIC SCIENCE RESEARCH	

R&D Areas	MALARIA	
		R&D Priorities for Achieving Goals
	• A research paradigm shift away from the ‘‘parasite-first’’ approach to an examination of what the human and mosquito host cells provide to the developing parasite is needed to complement on-going approaches • A new approach is needed to support collaborative and truly cross-disciplinary arrangements among scientists to bridge the gap between basic laboratory and clinical/ population-based sciences and to meet the scientific benchmarks outlined by malERA • Desired target product profiles need to be defined without preferred technological approaches being suggested to create opportunities for lateral thinking by experts bringing new approaches from different fields • Careful evaluation and appropriate use of today’s technologies from the physical, chemical, and biomedical engineering sciences is needed to improve the molecular understanding of parasite developmental biology and of the mammalian host-parasite-vector interactions • Mechanism of action studies for drugs and vaccines in the current pipeline are also needed to inform future strategies for the development of the next generation of interventions and therapeutics • The study of human host and vector factors in large-scale, long-term population-based field studies and the use of appropriate technologies in translation applications is also essential	
RESEARCH AND DEVELOPMENT OF NEW DIAGNOSTICS		
	Key Focus Area(s)	• Develop stable tests for case management in low-training, low technology settings with sensitivity sufficient for community level case management • 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 Priorities	• Design antigen-detecting RDTs 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 • Create tests that can detect resistance to artemisinins and ACT partner drugs • Standardize low-cost positive controls for antigen-detecting RDTs suitable for field use • Create sustainable tools for quality control of RDTs at the country level • Investigate non-blood sampling to determine the potential for detecting recoverable antigen in samples. • Develop consistent, reliable staining methods for microscopy • Map and identify G6PD deficiency (if 8-aminoquinolones are to be used) and create tools for field G6PD detection • Develop tools to standardize and improve microscopy interpretation • Create tools for hypnozoite detection and further research hypnozoite biology and biomarkers

R&D Areas	MALARIA	
		R&D Priorities for Achieving Goals
		• Develop field applicable tools for minimally invasive, rapid detection of low-density parasitemia in a high-throughput manner • Identify improved assessment methods (e.g. better serological tests, minimally invasive biomarkers)
	DIAGNOSTICS	
	Methods for measuring transmission are central to an elimination agenda. Current methods for measuring transmission that may be applied in endemic areas are time-consuming, expensive, and too insensitive for use in conditions of low and non-uniform infection [21,22]. Some years after regional elimination, as immunity declines, infection is likely to be symptomatic and may become the best marker of resumed transmission. However, during the early elimination phase in regions previously experiencing high transmission, populations will retain clinical immunity and will not experience symptomatic disease with every infection [23]. Thus, the main challenge identified by the malERA Consultative Group on Diagnoses and Diagnostics and discussed in detail in their article and in the article on Cross-cutting Issues for Eradication [24,25] is to find a robust, sensitive, and specific standardized method for assessment of transmission intensity in the intervening period when transmission continues at low and nonrandom levels. Improved serological tests have been suggested [26], but other minimally invasive biomarkers could be considered. This information will be essential for modeling potential effects of various interventions alone, or in combination, and for assessing efficacy of transmission–reducing vaccines and drugs. Other challenges for diagnostics discussed by the Consultative Group include the need for tools that can rapidly detect and monitor unexpectedly high transmission that leads to outbreaks and that can identify reintroduction of infections that may be asymptomatic [16,24].	
	SUMMARY OF THE R&D AGENDA FOR DIAGNOSIS AND DIAGNOSTICS	
	Overarching questions • What proportion of effort should be directed to screening and surveillance versus early case detection at various time points in elimination? Question to be addressed by modeling and validated in different areas. • Do we need microscopy for elimination, or can other tests replace it? **Programmatic issues** • Further data on thresholds of (i) parasite density likely to cause symptoms in low-transmission settings with variable or waning immunity, and (ii) transmission potential of cases with parasitemia below the threshold of microscopy and RDTs • Diagnostic tests for nonmalarial febrile illness in malariaendemic and malaria-elimination settings • Distribution of severe G6PD variants **Technical issues: case-management tools**	

R&D Areas	MALARIA *R&D Priorities for Achieving Goals*
	High priority Stable tests for case management in low-training, lowtechnology settings with sensitivity sufficient for community-level case management, including: • Antigen-detecting RDTs o Greater consistency in P. falciparum detection, particularly in the case of non-persistent antigens o More sensitive and stable tests to detect non-P. falciparum parasites o Clarification of the programmatic/implementation requirements that will ensure good impact in the field o Standardized low-cost positive controls for antigen-detecting o RDTs suitable for field use o Sustainable tools for quality control of RDTs at a country level. • Further investigation of nonblood sampling to determine the potential for detecting recoverable antigen in these samples. • More consistent, reliable staining methods for microscopy • G6PD deficiency mapping and identification (if 8-aminoquinolones are to be used) *Medium priority* • Multiplexing: Other diseases, markers of severity • Field G6PD detection (may be more important if tafenoquine approved), or raised priorities for P. vivax relapse prevention • Tools to standardize and improve microscopy interpretation *Low priority* • Hypnozoite detection (becomes a high priority if feasibility can be demonstrated through further research on hypnozoite biology, identifying good biomarkers). **Technical issues: surveillance tools** *High priority* • Field-applicable tools for detection of low-density parasitemia in a high-throughput manner, suitable for surveys and active detection of parasite carriage in time to allow management of positive cases • Tools for minimally invasive, very rapid detection of low-density parasite infections suitable for screening of migrants/travelers *Innovation with potential for major operational impact* • Non-invasive, low-density parasite detection

R&D Areas	MALARIA	
		R&D Priorities for Achieving Goals
	Low-hanging fruit with immediate application for elimination • High-throughput field molecular detection, capable of use at district level or below • Positive control methods for RDTs	
RESEARCH AND DEVELOPMENT OF NEW DRUGS		
	Key Focus Area(s)	• Optimize research on currently available malaria drugs • Develop new, innovative drugs for malaria eradication • Produce drugs that can be administered in a single encounter at infrequent intervals, and that result in radical cure of all parasite stages (Single Encounter Radical Cure and Prophylaxis) • Design safer, more efficient drugs for pregnant women • Find ways to address the emergence of artemisinin resistance
	Main Priorities	• Perform pharmacology studies to optimize dosing regimens of 8-aminoquinolines for gametocytocidal and anti-relapse efficacy and safety • Develop rapid and robust point-of-care glucose-6-phosphate dehydrogenase (G6PD) test to improve safety of 8-aminoquinoline use • Determine gametocytocidal and anti-relapse activity of current drugs and those in the pipeline • Develop drugs that prevent transmission by killing or preventing development of gametocytes, or blocking sporozoite development in the mosquito • Design drugs that cure liver stages of vivax (and ovale) malaria • Design sustained or pulsed release formulations and safe schizonticidal drugs for curing asymptomatic falciparum infection • Develop new, safe and effective drugs that block the infectivity of mature sexual forms of P. Falciparum gametocytes and/or dormant hepatic forms of P. Vivax • Create innovative drugs for intermittent preventive treatment during pregnancy • Explore long-acting formulations (e.g. repository formulations, oil-based depot injections cycloguanil pamoate) • Accelerate research into potential new drugs for first-line treatment to address artemisinin resistance
	DRUGS: SINGLE ENCOUNTER RADICAL CURE AND PROPHYLAXIS	
	In the recent past, drug development efforts were guided by the need for first-line drugs to treat P. falciparum infections with an increasing emphasis on drugs with a short half-life that potentially minimize the risk of development of resistance rather than on drugs with a long half-life	

R&D Areas	MALARIA *R&D Priorities for Achieving Goals*
	that have benefits for dosing and post-treatment prophylaxis [13]. Treatment of infected individuals with a variety of drug regiments has been used successfully in combination with intensive vector control to eliminate malaria from areas with relatively strong health systems and stable populations. However, interruption of malaria transmission is likely to require a new set of drugs and formulations. As described in more detail in the article by the malERA Consultative Group on Drugs [14], such drugs will need to be used both in stable transmission areas and in complex urban or remote rural areas, with poorly functioning health systems where concerted campaigns may be the only way of achieving high coverage or preventing reintroduction by migrants or travelers from endemic regions. For such campaigns to impact effectively on inaccessible populations, a single encounter between health providers and target populations is critical. Single Encounter Radical Cure and Prophylaxis (SERCaP) has a target product profile (TPP) that includes radical cure, defined as elimination of all parasites (including the long-lived hypnozoites of P. vivax or P. ovale in the liver), suitability for mass administration (including administration to healthy subjects and the consequent need of a very good safety profile), and prophylaxis for at least 1 month after treatment, to outlast the typical development period of Plasmodia parasites in Anopheline mosquitoes. A drug with this profile would perform in a similar way to a highly efficacious pre-erythrocytic (infection-preventing) vaccine. A drug with this TPP may take a long time to develop, but the development of new drugs that meet some of these essential requirements could dramatically improve chances of eradication. For example, development of new safe and effective drugs that block the infectivity of the mature sexual forms of P. falciparum gametocytes and/or the dormant hepatic forms (hypnozoites) of P. vivax could have a profound impact on transmission rates and would be valuable tools in the efforts to contain and eliminate parasite strains resistant to firstline treatment drugs. Presently, only the 8-aminoquinolines are known to be effective against both P. vivax hypnozoites and P. falciparum stage-five gametocytes. Unfortunately this class of drugs has significant side-effects in some individuals, particularly hemolysis in those withG6PD deficiency, that compromise their widespread use in mass administration for elimination [14].
	LONG-ACTING FORMULATIONS
	Another creative approach from the past that may hold promise for the future is the use of long-acting formulations. ‘‘Repository’’ formulations of malaria drugs to provide prolonged protection were extensively researched in the early 1960s [27], and oil-based depot injections of cycloguanil pamoate provided more than 1 year of protection against experimental challenge with P. falciparum sporozoites [28]. These injections were evaluated in at least 15,000 people, but never deployed as a tool for elimination because of the attendant pain and local abscesses.
	A DRAFT R&D AGENDA FOR DRUGS FOR MALARIA ERADICATION
	KNOWLEDGE GAPS AND RESEARCH PRIORITIES FOR OPTIMIZING CURRENT DRUGS

R&D Areas	MALARIA	
		R&D Priorities for Achieving Goals
	• Pharmacology studies to optimize dosing regimens of 8-aminoquinolines for gametocytocidal and anti-relapse efficacy and safety • Rapid and robust point-of-care glucose-6-phosphate dehydrogenase (G6PD) test to improve safety of 8-aminoquinoline use • Tests that can detect resistance to artemisinins and ACT partner drugs • Determine gametocytocidal and anti-relapse activity of current drugs and those in the pipeline **KNOWLEDGE GAPS AND RESEARCH PRIORITIES FOR DEVELOPING NEW DRUGS FOR MALARIA ERADICATION** *Desired products* • Drugs that prevent transmission by killing or preventing development of gametocytes, or blocking sporozoite development in the mosquito • Drugs that cure liver stages of vivax (and ovale) malaria • Ideally, drugs that can be administered in a single encounter at infrequent intervals, and that result in radical cure of all parasite stages (Single Encounter Radical Cure and Prophylaxis, see Box 1) • Sustained or pulsed release formulations • Exceptionally safe schizonticidal drugs for curing asymptomatic falciparum infection *Fundamental research questions aimed towards developing desired drugs* • Fundamental studies of liver and sexual stage biology (in both host and mosquito) • Mechanisms of resistance and pharmacological strategies to deter resistance • In vitro culture of P. vivax to understand parasite biology *Tools and capacities* • Increased capacity for clinical pharmacology research including pharmacokinetics/pharmacodynamics studies in populations targeted for malaria elimination • Increased capacity for human challenge studies for early go/no go decisions on drug candidates • Assays to measure transmission-blocking activity • Assays to measure activity against liver stages • In vitro culture of P. vivax and other non-falciparum species for drug screening • Genomic and proteomic approaches to identify transmission-blocking and liver-stage activity **KNOWLEDGE GAPS AND RESEARCH PRIORITIES FOR DRUG TREATMENT AND PREVENTION STRATEGIES FOR ERADICATION** • Field studies to evaluate new drugs and approaches in a variety of epidemiological settings	

R&D Areas	MALARIA	
		R&D Priorities for Achieving Goals
	• Robust and highly sensitive malaria diagnostics for malaria infection and especially for carriage of infectious gametocytes • Measures to monitor and improve adherence and safety • How must drug treatment and prevention strategies change as elimination proceeds? • Strategies to deter resistance	

RESEARCH AND DEVELOPMENT OF NEW VACCINES

Vaccines could be a crucial component of efforts to eradicate malaria. Current attempts to develop malaria vaccines are primarily focused on Plasmodium falciparum and are directed towards reducing morbidity and mortality. Continued support for these efforts is essential, but if malaria vaccines are to be used as part of a repertoire of tools for elimination or eradication of malaria, they will need to have an impact on malaria transmission. We introduce the concept of ‘‘vaccines that interrupt malaria transmission’’ (VIMT), which includes not only ‘‘classical’’ transmission-blocking vaccines that target the sexual and mosquito stages but also pre-erythrocytic and asexual stage vaccines that have an effect on transmission. VIMT may also include vaccines that target the vector to disrupt parasite development in the mosquito. Importantly, if eradication is to be achieved, malaria vaccine development efforts will need to target other malaria parasite species, especially Plasmodium vivax, where novel therapeutic vaccines against hypnozoites or preventive vaccines with effect against multiple stages could have enormous impact. A target product profile (TPP) for VIMT is proposed and a research agenda to address current knowledge gaps and develop tools necessary for design and development of VIMT is presented.

	Key Focus Area(s)	• Create a vaccine that targets both the sexual and mosquito stages (transmission-blocking) and the pre-erythrocytic and asexual stages • Develop a vaccine that targets multiple malaria parasite species • Explore novel approaches to elicit longer-lasting protective efficacy • Understand the dynamics between the multiplication of asexual stage parasites, gametocytogenesis, and malaria transmission rates at population level

	Main Priorities	• Expand vaccine development efforts to cover Plasmodium species other than P. Falciparum, especially P. Vivax. • Develop new, innovative vaccine delivery approaches and/or adjuvants • Develop robust assays to study functional immune response at individual level to predict effect on population level transmission • Develop tools to measure malaria transmission rates to facilitate clinical development of vaccines • Explore anti-vector vaccines, highly effective pre-erythrocytic or erythrocytic stage vaccines, and vaccines targeting parasite antigens of sexual and mosquito stages of infection
	RATIONALE OF THE PROPOSED malERA APPROACH TO DEVELOPMENT OF MALARIA VACCINES	
	First, we introduce the broad concept of VIMT (vaccines that interrupt malaria transmission). VIMT may be composed of one or more of the following components: classical TBVs that target sexual and mosquito stage parasite antigens; highly effective pre-erythrocytic vaccines that reduce asexual and sexual stage parasite prevalence rates; highly effective asexual erythrocytic stage vaccines that inhibit multiplication of asexual stage parasites efficiently to reduce blood-stage parasite densities and have an impact on malaria transmission; and vaccines that target vector antigens to disrupt parasite development in the vector. It seems obvious that a highly effective pre-erythrocytic vaccine that prevents erythrocytic stage infection will reduce transmission, but the effect of partially effective pre-erythrocytic or asexual blood-stage vaccines on individual infectivity needs investigation. A successful VIMT must primarily reduce malaria transmission. However, VIMTs that include pre-erythrocytic and/ or asexual blood-stage vaccine components may also provide individuals with protection against malaria. Such VIMT would also protect the population against epidemic spread following reintroduction of malaria after elimination, an important characteristic given that the gains accrued through many years of elimination can be rapidly reversed if malaria is reintroduced to a population with no antimalarial immunity [10]. Second, the observed impact of concerted non-vaccine malaria control efforts on transmission dynamics in several malaria-endemic regions has shown that high-intensity transmission settings (entomological inoculation rate, EIR .50) can be converted to low-to-moderate intensity transmission settings (EIR ,10) [11,12]. Implementation of VIMT together with such control efforts may successfully drive down transmission rates to reduce the effective reproduction rate (Reffective) to below 1.0. Third, the consultative group introduces the concept of a detailed TPP for this class of vaccines and urges that novel clinical development methods and approaches be considered to shorten the time to VIMT registration and implementation. Fourth, the consultative group lays out a detailed research agenda that must be developed, funded, and implemented in parallel with VIMT development efforts. This agenda includes development of critical tools that will be required to register and implement such a vaccine. In particular, we identify the need to develop robust assays to measure biologically relevant transmission- blocking activities at the individual level that are validated as surrogates of reductions in transmission rates at the population level. If this goal is achieved, such assays could become the	

	key tool for measurement of primary vaccine efficacy endpoints in conditional registration trials, thereby simplifying the clinical development program. Finally, the consultative group considers that interested industrial partners should be identified early on in development, because expertise in applied immunology, vaccinology, product development, manufacturing, and regulatory activities is concentrated within industry and will play an essential role in the successful development of VIMT. In addition, it will be important to engage with regulatory agencies to define efficient yet sound regulatory strategies to develop and register new tools that can meet the needs of global malaria elimination and eradication efforts.
	SUMMARY OF THE R&D DEVELOPMENT AGENDA FOR VACCINES
	A prioritized research and development agenda to enable the development of VIMT for use as critical components in malaria elimination efforts includes: • Development and application of novel vaccine delivery approaches and/or adjuvants to elicit long-lasting protective efficacy that makes significant impact on malaria transmission rates under diverse epidemiological settings. • Expansion of vaccine development efforts to cover Plasmodium species other than P. falciparum, especially P. vivax (including hypnozoites). • Understanding the dynamics between multiplication of asexual stage parasites, gametocytogenesis, and malaria transmission rates at the population level. • Development of robust assays to study functional immune responses at the individual level that can predict effect on malaria transmission at the population level and allow decision making in product development. • Development of tools to measure malaria transmission rates, thereby facilitating clinical development of vaccines that reduce malaria transmission.
VECTOR CONTROL	
Key Focus Area(s)	• Understand the ecology, behaviour, and genetic population structure of malaria vectors • Find ways to maintain sustained commitment to the long-term development of novel vector control approaches • Create a coherent research agenda for discovering and developing a broader range of insecticides

	Main Priorities	• Perform large-scale, long-term population-based field studies to understand human host and vector factors • Explore the genetic manipulation of natural vector populations that can reduce high vectorial capacities in high-risk areas • Develop an analytic framework that consolidates existing and new information on malaria transmission. • Research novel modes of action that can circumvent emerging resistance to insecticides, particularly pyrethoid-based insecticides • Create new technologies that address vectors that do not rest or feed indoors that escape current vector control tools • Develop technologies that can simply and rapidly measure transmission • Educate the community effectively and engage the consumer market • Research improved choice of insecticides and methods to reduce the risk of resistance • Design a public portal to facilitate decision-making by the malaria research, control, and tool development communities
	CURRENT TOOLS AND RESOURCE GAPS	
	The key goal of the malERA Consultative Group on Vector Control was to help define the research and development agenda that will be required to sustain and improve the effectiveness of currently available tools like LLINs and IRS and to develop new vector-targeted tools that can be used to interrupt transmission in environments or at intensities that these existing tools cannot reach. It is clear that new technology will be required in very high transmission areas to reduce vectorial capacity and achieve even effective control, let alone elimination. The main aim of this paper is to define a research and development agenda that focuses on those new research questions and knowledge gaps that arise specifically in response to the call for malaria eradication, and that would not otherwise be at the top of the agenda (Table 1). It is particularly important to recognize that this operationally specified goal significantly limits the scope of research and development under consideration, and this document should not be the basis for all vector research related to malaria. Our article does, however, describe the challenges for vector control methodology in the elimination phase, for detecting and monitoring areas of persistent transmission, and for detecting and monitoring nonrandom transmission leading to outbreaks. We also discuss the requirements for rapid and urgent intervention when outbreaks occur (see also [8]). The Consultative Group identified four key components to successful vector control within an eradication agenda. First, the ecology of vectors responsible for malaria transmission in those regions of the world where current tools are insufficient for elimination needs to be understood. Second, sets of synergistic or complementary interventions tools need to be developed and applied through rationally designed programs that can be spatially and temporally combined into effective intervention programs. Third, appropriate monitoring and evaluation tools that can guide the application and evolution of control and elimination programs as malaria endemicity is pushed towards local elimination need to be developed and applied. Finally, there is a critical need for built-in flexibility in programs so that where initial efforts fail, they can adapt to circumstances by incorporating and implementing new approaches. Thus, as malaria programs are scaled up, vector control will have a major role in disease burden reduction but, as programs become increasingly successful in reducing transmission, accurate estimation of the point at which large-scale vector control activities can be relaxed will become critical. Premature removal of mainstream vector control, either through planned reductions in activities or through failure of long-lasting interventions like LLINs or IRS as	

resistance evolves, is likely in many instances to lead to a catastrophic increase in morbidity and mortality because of resurgent malaria in a non-immune population [8,9].

The exact role of vector control as countries enter the elimination phase of activities will be situation specific. However, valuable lessons can be drawn from the WHO Global Malaria Eradication Program (GMEP) of the 1950s and 1960s [10], in which vector control alone was considered to be enough in many situations to eliminate malaria. Although this approach was successful in some cases, success was often short-lived [11,12]. Another valuable lesson can be learned from current efforts to eradicate filariasis. For this vector-borne disease, multiple rounds of mass drug administration in many countries divorced from targeted vector control have not achieved the predicted interruption in transmission [13].

Indeed, there is now a consensus that malaria elimination with current tools is far more likely if the best available tools are used in combinations. In the past two decades, especially in an African context, the combination of drugs and vector control with impregnated nets has been highlighted for its role in the reduction of morbidity and mortality [14]. However as malERA sets out a research and development agenda for elimination/eradication and vector control, other interventions must be considered primarily in terms of their impact on malaria infection and transmission, not instead of, but in addition to, their role in prevention and modification of disease.

We highlight the research and development areas identified as priority areas by the Consultative Group before providing a summary research and development agenda that draws together the various strands of our discussions.

SUMMARY OF THE R&D AGENDA FOR VECTOR CONTROL

- Development of an analytic framework that can bring together existing and new information on all aspects of malaria and malaria transmission through a public portal designed to facilitate decision making by the malaria research, control, and tool development communities.
- An improved choice of insecticides, and formulations coupled with improved methods to reduce the risk of resistance to ensure that the availability of effective insecticides does not become the limiting factor in our ability to reduce transmission to levels where local elimination can be attempted.
- Better understanding of the ecology, behaviour, and genetic population structure of malaria vectors, particularly outdoor biting and resting species that escape current vector control tools.
- Development of innovative new technologies that can:
    - Educate the community effectively and engage the consumer market
    - Control outdoor biting and resting mosquito vectors
    - Simply and rapidly measure transmission
- Sustained commitment to the long-term development of novel approaches like the genetic manipulation of natural vector populations that will permanently reduce the very high vectorial capacities of dominant malaria vectors in sub-Saharan Africa and some parts of Asia.

EPIDEMIOLOGY		
The article by the malERA Consultative Group on Monitoring, Evaluation, and Surveillance considers the need to investigate the performance of surveillance, monitoring, and evaluation by new and old technologies [39,40] and to evaluate optimal strategies for implementation of surveillance as an active responsive intervention to further reduce transmission [41].		
	Key Focus Area(s)	• Create surveillance tools with potential for major operational impact
	Main Priorities	• Investigate the performance of surveillance, monitoring, and evaluation by new and old technologies and to evaluate optimal strategies for implementation of surveillance as an active responsive intervention to further reduce transmission • Conduct research to develop biomarkers such as DNA-based methods or serology as monitoring and evaluation and surveillance tools • Develop information systems to monitor malaria infections, facilitate timely local program decisions and responses to reduce transmission • Develop methods, indicators, and shareable databases for parasite strain information to better track transmission • Develop methods for accessing and tracking population movements and quantifying their contribution and risk of malaria transmission • Explore how maps can be constructed to: o Show the probability of a threshold of transmission being exceeded; o Incorporate a wider range of metrics such as serological and entomological data; and o Assess cost-effectiveness of national stratification initiatives based on remotely sensed satellite data
	TECHNICAL ISSUES: SURVEILLANCE TOOLS	
	Technical issues: surveillance tools *High priority* • Field-applicable tools for detection of low-density parasitemia in a high-throughput manner, suitable for surveys and active detection of parasite carriage in time to allow management of positive cases • Tools for minimally invasive, very rapid detection of low-density parasite infections suitable for screening of migrants/travelers *Innovation with potential for major operational impact* • Non-invasive, low-density parasite detection	

	Low-hanging fruit with immediate application for elimination • High-throughput field molecular detection, capable of use at district level or below • Positive control methods for RDTs
	SUMMARY OF THE R&D AGENDA FOR MONITORING, EVALUATION AND SURVEILLANCE
	• Update the malaria monitoring and evaluation Framework to include transmission reduction, and develop key data elements for a surveillance system from a systematic review of previous elimination attempts • Systematically review lessons learned from experiences with surveillance as an intervention to determine how it can be tailored to various programmatic settings • Identify appropriate program time points for introduction of malaria infection detection in active or passive modes • Develop improved diagnostic tools for use in monitoring and evaluation and surveillance, focusing on practical field-ready tools for detection of asymptomatic infection • Develop information systems to monitor malaria infections, facilitate timely local program decisions and responses to reduce transmission • Develop methods, indicators, and shareable databases for parasite strain information to better track transmission • Develop methods for accessing and tracking population movements and quantifying their contribution and risk of malaria transmission • Explore how maps can be constructed to: show the probability of a threshold of transmission being exceeded; incorporate a wider range of metrics such as serological and entomological data; assess cost-effectiveness of national stratification initiatives based on remotely sensed satellite data • Perform a systematic review to assess and compare metrics of malaria transmission at near zero transmission levels; research the validity of novel metrics to measure transmission at near zero levels, and to measure transmission potential within areas where transmission has been eliminated • Assess the precision, bias, feasibility, and cost-effectiveness of novel sampling methods for routine monitoring of present and past infections in target populations, including mobile populations
OPERATIONAL AND PUBLIC HEALTH RESEARCH	
	Key Focus Area(s) • Develop a toolkit that allows for effectiveness decay analysis for identifying bottlenecks for effective coverage of malaria interventions and decisions on the degree of integration of interventions into existing and strengthened health systems • Integrate new approaches into the planning of elimination, surveillance, monitoring, and evaluation, and to create appropriate interfaces for different user communities. • Develop an essential platform for studying the biology of the liver stages and sexual forms of parasites • Conduct systems analyses of transcription, proteome, and metabolome libraries, rapid screening of drug libraries, high-

		throughput approaches to antigen identification, and the functional definition of gene products • Evaluate health systems' readiness to optimize novel programs, systems, tests, or other interventions, and their continuing performance
	Main Priorities	• Update the malaria monitoring and evaluation framework to include transmission reduction • Develop key data elements for a surveillance system from a systematic review of previous elimination attempts • Identify appropriate program time points for introduction of malaria infection detection in active or passive modes • Perform a systematic review to assess and compare metrics of malaria transmission at near zero transmission levels, research the validity of novel metrics to measure transmission at near zero levels, and to measure transmission potential within areas where transmission has been eliminated • Assess the precision, bias, feasibility, and cost-effectiveness of novel sampling methods for routine monitoring of present and past infections in target populations, including mobile populations
	ENABLING TECHNOLOGIES AND PLATFORMS	
	The development of new tools for elimination is critically dependent on a vibrant and coherent agenda for basic sciences. We believe there are at least two potentially transformative developments that need to be pursued. First, continuous laboratory culture of P. vivax, P. ovale, and P. malariae needs to be developed to provide an essential platform for studying the biology of the liver stages and sexual forms of these parasites. These forms could be important targets of intervention strategies with drugs, vaccines, or other biological or chemical agents aimed at interrupting transmission. Second, systems analyses of transcription, proteome, and metabolome libraries, rapid screening of drug libraries, high-throughput approaches to antigen identification, and the functional definition of gene products are all feasible but not yet fully exploited, but would bring important new tools to the bench scientist and to field operations. These and other aspects of enabling technologies and platforms are considered in detail in the articles prepared by the malERA Consultative Groups on Basic Science and Enabling Technologies and on Cross-cutting Issues for Eradication [25,31].	
	HEALTH SYSTEMS INTEGRATION, OPERATIONAL RESEARCH, AND EFFECTIVENESS-DECAY ANALYSIS	
	The previous formal attempt at global eradication of malaria (1955–1969) depended largely on vertical operations that often bypassed health systems and their health services because it was assumed that eradication operations could be run most efficiently in this way. Many of the elimination efforts failed, because the health systems failed, leading to a pessimistic view that malaria can only be eliminated where economic progress, governance, and efficient health systems are in place to support maintenance of conditions necessary to block transmission [32,33]. It is now clear that the long-term solution to malaria elimination and eradication will require a systems approach in which malariaspecific interventions and actions are integrated into existing health systems [34]. To achieve this, research is needed into health systems, their readiness to optimize novel programs, systems, tests, or other interventions, and their continuing performance [35–37]. During their deliberations, the malERA Consultative Group on Health Systems and Operational Research identified the need for a substantial research approach to establish and	

	validate a tool kit that allows effectiveness-decay analysis of health system impediments to effective and equitable coverage of malaria interventions and that allows decisions to be made on the degree of possible integration of interventions into an existing health system [16,38]. A further critical component of the research agenda identified by this Consultative Group is the development and validation of a decision-making framework to guide the move from control to elimination. Finally, but equally importantly, the article by the malERA Consultative Group on Monitoring, Evaluation, and Surveillance considers the need to investigate the performance of surveillance, monitoring, and evaluation by new and old technologies [39,40] and to evaluate optimal strategies for implementation of surveillance as an active responsive intervention to further reduce transmission [41].	
INNOVATIVE FINANCING		
	Key Focus Area(s)	• None identified
	Main Priorities	• None identified

Disease-specific R&D priority setting

MALARIA

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
1. Program for Appropriate Technology in Health (PATH). Staying the Course? Malaria Research and Development in a Time of Economic Uncertainty. Seattle: PATH; 2011. *The paper provides an overview of the current R&D landscape for products related to malaria treatment and control, including drugs, vaccines, vector control products, and diagnostics. It also presents a detailed breakdown of the types of R&D funding, such as type of research, source of funding, and institution type.*	The status of malaria funding was assessed using investment data for 2004 from the Malaria R&D Alliance report29 and investment data for 2007 to 2009 from the G-FINDER survey. In the sections referring to vector control products, G-FINDER data were supplemented by expert estimates of industry investment (noted in each case). The 2004 data presented in the Malaria R&D Alliance report were collected via an online survey completed by 79 organizations globally in May 2005. Three categories of organisations were surveyed (funders, funding managers and researchers and developers), and funding was captured in six R&D categories: basic research, antimalarial drug discovery and	A. Basic science • None identified B. Diagnostics • Enhance the quality and stability of currently available rapid diagnostic tests (RDTs) C. Drugs • Develop new, shorter-regimen therapies • Explore formulations that are more appropriate for vulnerable populations • Accelerate the development of new drugs to combat resistance D. Preventative vaccines • Identify more effective vaccine candidates E. Therapeutic vaccines • None identified F. Vector control • Determine ways to reduce reliance on pyrethroids for vector control due to the risk of resistance • Develop new active vector control ingredients	A. Basic science • None identified B. Diagnostics • Improve RDTs' ability to detect non-*falciparum* parasites • Develop new and improved tools for field detection of very low-density parasitaemia, including non-*falciparum* parasites • Identify ways to enhance screening for enzymatic deficiency, i.e. G6PD deficiency • Scale up research on future targets that include automated microscopy and non-invasive sampling through analysis of saliva or urine • Develop tests to detect non-malarial febrile disease pathogens or markers of infection requiring specific treatment C. Drugs • Develop a single-dose cure to replace the current three-day drug regimen • Identify ways to enhance the safety and suitability of treatment regimens for children • Develop more treatment options for pregnant women • Focus on a radical cure for *P. vivax* • Create novel compounds to tackle artemisinin resistance and transmission-blocking antimalarials D. Preventative vaccines

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
	development, vaccine development and vaccine trials, vector control research, development of malaria diagnostics and implementation research. R&D categories overlap considerably with the product R&D categories used in G-FINDER and were assumed to be fully comparable. The only exception was implementation research that is not included in the G-FINDER survey and was therefore excluded from analysis. Furthermore, the Malaria R&D Alliance report did not break the six R&D categories into sub-areas (such as discovery and development), which meant authors were unable to include the 2004 data in analysis of which organisations are conducting which types of research and product development.	G. Epidemiology • None identified H. Health systems/public health research • Develop monitoring systems to detect possible resurgence of malaria I. Innovative financing • Identify ways to encourage and secure investment in malarial vaccine development and severely underfunded pools for diagnostic R&D • Determine how investments in malaria R&D can be more evenly distributed across product portfolios	• Develop a more effective second-generation *P. falciparum* vaccine and new vaccine candidates targeting *P. vivax* E. Therapeutic vaccines • None identified F. Vector control • Explore new paradigms in insecticide delivery, including novel active ingredients for bednets and indoor residual spraying (IRS) G. Epidemiology • None identified H. Health systems/public health research • Determine how to adapt screening and monitoring strategies so that a possible resurgence of malaria can be picked up rapidly I. Innovative financing • Investigate ways to make R&D funding, particularly in the public sector, more flexible and responsive to global portfolio developments and goals • Identify ways in which funders can be given improved information and tools to allow them to better coordinate funding and portfolio decisions; this includes the public, philanthropic and private sectors • Find ways to engage more funders in malaria R&D, including more economically advanced countries (G8/G20/Organisation for Economic Co-operation and Development), and research and science and technology agencies in both existing

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
			and new donor countries • Determine how to maintain PDP funding since PDPs account for nearly half of the current product pipeline and virtually all new malaria products delivered in the past five years • Identify ways to ramp up funding to $220–230 million per year from 2016 and beyond to fund late-stage trials of the anticipated second-generation *P. falciparum* vaccine, as well as early preclinical work associated with transmission-blocking vaccines, vaccines for pregnant women and candidate vaccines targeting both *P. vivax* and *P. falciparum*
2. 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. *The report summarizes the findings of a study investigating the clinical development of malaria products and aims to quantify the resources needed for clinical development of the global malaria drug and vaccine portfolio over the five years to 2012,*	Data on vaccine candidates from 1984 to end 2006 was collated through a literature search of major databases; for example, NCBI Entrez-Pubmed, Cochrane review, and ClinicalTrials.gov. Candidates were deemed to be in pre-clinical development if testing in animals was reported (primate or rodent models), or in clinical development if testing in human subjects had commenced. As not all clinical trials are published in the year that they are completed, reviews (from 1997 onwards) and expert interviews relating to historical vaccine development were also assessed.	A. Basic science • Determine the role of antigen diversity for developing vaccine candidates B. Diagnostics • None identified C. Drugs • None identified D. Preventative vaccines • Develop more potent vaccine candidates • Promote research into new technology platforms that could increase vaccine potency • Find ways to ensure that vaccines meet batch-to-batch reproducibility E. Therapeutic vaccines • None identified	A. Basic science • None identified B. Diagnostics • None identified C. Drugs • None identified D. Preventative vaccines • Create and standardize assays, reagents and protocols used at each stage of malaria vaccine product development • Develop a shared set of vaccine ranking criteria based on safety, type of immune response induced, ability to generate a functional antigen, potential formulations and manufacturability • Integrate new technologies or technologies not previously used for malaria vaccines into the research process e.g. adenovirus vectors, prime boost approaches and synthetic peptides • Evaluate technical feasibility during preclinical

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
including funding for clinical trials and associated manufacturing and toxicology, and demand for malaria licensure trial sites.	For the historical vaccine snapshots, data was collated using the NCBI Entrez-Pubmed search engine with the keywords MALARIA AND VACCINE for the years 1984-1986 for the 1985 candidates, and 1994-1996 for 1995 candidates. To be included in the snapshot, the vaccine candidates had to be active (either in or between trials) in the years examined. Data relating to malaria clinical trials was collected by conducting desk research on all published clinical trials, with enrolment start and finish dates recorded. Clinical trial registries (e.g. ClinicalTrials.gov) were also sourced to determine actual or expected start and finish dates for past, current, and future trials. This data was cross-referenced with Clinical Development Plans and other trial data collected via on-site visits with product developers and through telephone interviews.	F. Vector control • None identified G. Epidemiology • None identified H. Health systems/public health research • Determine how to ensure that trials, including phase IV trials, are allocated to avoid site competition and to maximise site progress along the development trajectory • Identify ways to build on the Malaria Vaccine Technology Roadmap • Determine how to improve the coordination of global R&D and reach agreement on a challenge model for blood-stage vaccine candidates • Clarify and codify a streamlined regulatory pathway to allow the global portfolio to move forward more quickly I. Innovative financing • Provide a clearer picture of the malaria funding gap • Find ways to increase funding for basic malaria vaccine research to avoid shrinkage of the clinical portfolio over time • Identify ways to direct investments	development to successfully scale-up a candidate to a stable, reproducible product E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology • None identified H. Health systems/public health research • Identify ways to ensure that all product development sites have an on-site staff training programme • Explore a formal mentoring system and a linked proposal of formal training attachments between younger sites and experienced African licensure sites, Western clinical trial institutions and/or Western pharmaceutical firms • Identify appropriate means to set up/build on a centralised information source on all upcoming licensure and phase IV trials • Determine ways to develop an agreed minimum site audit template and/or develop a shared Trial Site Audit service • Develop an African-based CRO to provide contract staff for clinical trials, including experienced staff and a pool of more junior staff, to mitigate large employment swings at sites I. Innovative financing • Design a donor coordination exercise to collate

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
		towards novel malaria technology platforms • Investigate how immunogenic adjuvants can be made more accessible to all malaria vaccine developers	information on their collective forward funding commitments and assess against likely costs • Determine ways to encourage greater pairing of industry innovators with public malaria researchers to develop joint projects • Research incentives or policies to encourage relationships between public and academic vaccine developers and industrial facilities to cut learning curve times, ensure expertise is maintained and facilitate technology transfer • Investigate biotech-relevant policy and incentive options for groups trying high-risk, high-innovation approaches • Design incentives to encourage biotechs wishing to test out novel technologies or constructs to collaborate with well-established product-developers who have the technical skills and experience to make the technology feasible • Explore ways to enhance public-private collaborations to improve manufacturers' access to potent adjuvants • Investigate possible funding streams for contracted industry input to public candidates, e.g. by leveraging the existing manufacturing expenditures through the proposed Industry R&D Facilitation Fund
3. World Health Organization. World Malaria Report 2012. Geneva: World Health Organization; 2012. *The World Report*	Standard reporting forms were sent in March 2012 to the 99 countries with ongoing malaria transmission and two countries that recently entered the prevention of reintroduction phase.	A. Basic science • Improve understanding of artemisinin resistance and how to best manage it • Curtail the transmission of malaria by reducing the human parasite reservoir	A. Basic science • Prioritize in vitro studies to measure the intrinsic sensitivity of parasites to antimalarial drugs • Conduct molecular marker studies to identify genetic mutations and subsequently confirm the presence of mutations in blood parasites • Perform pharmacokinetic studies to characterize

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
summarizes the current status of malaria control in all affected countries; it provides a critical analysis and interpretation of data provided by national malaria control programs, and also reviews progress towards internationally agreed targets and goals, describes trends in funding, intervention coverage and malaria cases and deaths on a region and country-specific basis.	Information was requested on (i) populations at risk (ii) vector species (iii) number of cases, admissions and deaths for each parasite species (iv) completeness of outpatient reporting (v) policy implementation (vi) commodities distributed and interventions undertaken (vii) results of household surveys, and (viii) malaria financing. Surveys provide information on the percentage of the population that sleeps under a mosquito net, and of children with fever who are treated and the medication they receive. Information on malaria financing was obtained from the Organisation for Economic Co-operation and Development (OECD) database on foreign aid flows and directly from the Global Fund and the US President's Malaria Initiative (PMI).	B. Diagnostics • None identified C. Drugs • Routinely conduct therapeutic drug efficacy studies • Confirm and better characterize drug resistance • Prioritize research products that reduce morbidity and mortality by ensuring rapid, complete cure of *Plasmodium* infection, thus preventing the progression of uncomplicated malaria to severe and potentially fatal disease, as well as preventing chronic infection that leads to malaria-related anaemia D. Preventative vaccines • Prioritize the development and distribution of a licensed malarial vaccine E. Therapeutic vaccines • None identified F. Vector control • Identify ways to reduce the intensity of local malaria transmission at the community level by reducing vector longevity, human-vector contact and density of the local vector mosquito population • Consolidate all available data on	drug absorption and drug action in the body B. Diagnostics • None identified C. Drugs • Measure the clinical and parasitological efficacy of medicines and the detection of small changes in treatment outcome over time D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • Find means to ensure that decisions regarding the choice of insecticide are supported by adequate and up-to-date information on resistance among local anopheline vectors • Determine the extent to which chloroquine-resistant *P. vivax* has spread • Develop new insecticides appropriate for use on insecticide-treated nets G. Epidemiology • None identified H. Health systems/public health research • Determine how to develop resistance monitoring using both bioassay (susceptibility) tests and genetic methods • Determine why discrepancies between urban and rural areas, and between wealth quintiles,

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
		vector resistance • Develop new insecticidal agents and other interventions that do not rely on insecticides G. Epidemiology • Investigate how to improve malaria surveillance systems for better case detection, particularly in high-burden settings H. Health systems/public health research • Investigate how to intensify resistance monitoring • Investigate why there are discrepancies in access to treatment for vulnerable groups such as infants and pregnant women • Investigate how diagnosis and treatment can be provided at the community level through a programme of community case management in under-resourced settings • Find ways to scale-up intermittent preventative treatment (IPT) for pregnant women (IPTp) and infants (IPTi) • Learn how to expand universal diagnostic testing in the public and private sectors • Investigate how to scale up universal access to long-lasting insecticidal nets (LLINs)	exist in the uptake of intermittent preventative treatment (IPTp) among pregnant women in some countries, and how the approach for a more equitable scale-up of IPTp can be replicated in other countries • Determine how to expand the new strategy targeting the diagnosis and treatment of malaria, pneumonia and diarrhoea at community levels termed integrated community case management (iCCM) of childhood illness • Develop information systems that link diagnostic testing and treatment data I. Innovative financing • None identified

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
		I. Innovative financing • Examine new ways to make existing funds stretch further by increasing the value for money of malaria commodities and the efficiency of service delivery	
4. World Health Organization Global Malaria Programme. Global Plan for Insecticide Resistance Management in Malaria Vectors. Geneva: World Health Organization; 2012. *The WHO's Global Plan for Insecticide Resistance Management in Malaria Vectors provides an overview of the threat of insecticide resistance, its impact on malaria control, and available / future strategies for managing resistance. The report also presents an overview of the results of the WHO Malaria Rapid Diagnostic Test (RDT) Product Testing.*	The RDT evaluations summarized in the report were performed as a collaboration between WHO, TDR, FIND, the US Centers for Disease Control and Prevention (CDC) and other partners. All companies manufacturing under Quality System Standard were invited to submit a limited number of products (2–3) for evaluation under the programme. Of these 168 total products, 164 progressed to testing against panels of patient-derived P. falciparum and P. vivax parasites, and a parasite-negative panel. Thermal stability was assessed after two months of storage at elevated temperature and humidity, and a descriptive ease of-use assessment was recorded. The evaluation is designed to	A. Basic science • Investigate how to fill existing gaps in knowledge about insecticide resistance mechanisms • Better understand the fundamental genetic processes of the spread of resistance • Develop new methods to assess the impact of resistance on malaria transmission B. Diagnostics • None identified C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • Identify new active ingredients for insecticides with different modes of action	A. Basic science • Identify clear genetic markers for important oxidase-mediated forms of resistance to pyrethoids • Discover genetic mutations responsible for metabolic resistance to pyrethoids in different geographical settings • Utilize high-throughput DNA-based methods to identify resistant genes • Find ways to colonize a range of vector strains resistant to different insecticides in different locations • Better understand genetic dominance, fitness cost, cross-resistance, linkage, disequilibrium, drivers of selection pressure and behavioural resistance B. Diagnostics • None identified C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
	provide comparative data on the performance of the submitted production lots of each product. Such data will be used to guide procurement decisions of WHO and other UN agencies and national governments. Product testing is part of a continuing programme of work to improve the quality of RDTs that are used, and to support broad implementation of reliable malaria diagnosis in areas where malaria is prevalent. A fifth round of product testing will begin in January 2013.	• Find ways to reduce reliance on insecticides in controlling malaria transmission G. Epidemiology • Gather epidemiological evidence that supports the development of new, innovative vector control paradigms • Assess current epidemiological methods to inform decision-making globally and nationally H. Health systems/public health research • Investigate how to effectively manage insecticide resistance • Create a defined system for evaluating the evidence for new forms of vector control I. Innovative financing • None identified	• None identified F. Vector control • Develop innovative, non-insecticide-based vector control tools (e.g. spatial repellents, area-wide treatments, traps and targets, and animal treatments) G. Epidemiology • Conduct epidemiological testing for durable wall lining to complement IRS for wide-scale implementation • Revise epidemiological malaria models to include insecticide resistance • Create an aggregated global database to provide global direction on insecticide resistance monitoring H. Health systems/public health research • Investigate how to measure the impact of resistance on the effectiveness of vector control • Conduct small-scale trials to assess the relative effectiveness of resistance management strategies in delaying the emergence of resistance and killing resistance vectors • Explore the formation of the WHO's proposed "vector control advisory group" for making recommendations on new vector control tools for public health purposes I. Innovative financing • None identified

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
5. PLOS Medicine. malERA: a Research Agenda for Malaria Eradication. Barcelona: The Barcelona Centre for International Health Research; 2011. *The PLOS Research Agenda for Malaria Eradication Report is a compilation of publications that address the research agenda to eradicate malaria globally. This report is sponsored by The Malaria Education Research Agenda (malERA), an initiative that complements the current research agenda by identifying key knowledge gaps and defining the strategies and tools that will result in malaria eradication.*	Funded by the Bill and Melinda Gates Foundation, malERA aims to define the critical knowledge base, strategies, and tools required to reduce the basic reproduction rate (R0 or the number of secondary cases arising from a single case) to less than one. Scientists involved in malaria research were challenged to develop a multidisciplinary, global research and development agenda that would be actionable by research and public health agencies and funders/sponsors and available for discussion and debate through publication in a readily accessible format. The process engaged more than 250 scientists in a series of 20 consultations around the world (Figure 2) and was managed by a three-tier governance structure (Figure 3). This report briefly introduces the work undertaken by the various malERA Consultative Groups.	A. Basic science • Transition research away from "parasite-first" approaches to an examination of host-parasite-vector population interactions • Better understand the stage-specific biology of the parasite. • Define desired target product profiles, incorporating new approaches from different fields • Investigate how basic research can inform future strategies for the development of next-generation interventions and therapeutics • Identify roadblocks that prevent the scale-up of genetic manipulation and functional analysis of essential genes B. Diagnostics • Develop stable tests for case management in low-training, low technology settings with sensitivity sufficient for community level case management • 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 C. Drugs • Optimize research on currently available malaria drugs	A. Basic science • 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 • Investigate how new technology platforms can permit deep characterization of the metabolome • Design research studies aimed at understanding the epidemiology of the gametocyte • Develop an efficient, inexpensive P. Vivax blood-stage culture system • Create in vitro systems to understand P. Falciparum, P. Vivax and hypnozoite biology as it relates to liver-stage biology • Conduct mechanism of action studies for drugs and vaccines in the current pipeline to inform future strategies • Find ways to improve technologies for the manipulation of Plasmodium • Learn how to implement systems-based approaches in order to incorporate cutting-edge technology (e.g. metabolomics) • Utilize technologies from physical, chemical, and biomedical engineering sciences to improve molecular understanding of parasite development biology • Introduce new technologies to address roadblocks, such as: low frequency of homologous recombination in Plasmodium, difficulties associated with the manipulation of large fragments of AT-rich and repetitive genomic DNA, and the lack of robust and scalable systems for conditional gene expression

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
		• Develop new, innovative drugs for malaria eradication • Produce drugs that can be administered in a single encounter at infrequent intervals, and that result in radical cure of all parasite stages (Single Encounter Radical Cure and Prophylaxis) • Design safer, more efficient drugs for pregnant women • Find ways to address the emergence of artemisinin resistance D. Preventative vaccines • Create a vaccine that targets both the sexual and mosquito stages (transmission-blocking) and the pre-erythrocytic and asexual stages • Develop a vaccine that targets multiple malaria parasite species • Explore novel approaches to elicit longer-lasting protective efficacy • Understand the dynamics between the multiplication of asexual stage parasites, gametocytogenesis, and malaria transmission rates at population level E. Therapeutic vaccines • None identified F. Vector control • Understand the ecology, behaviour, and genetic population structure of malaria vectors	B. Diagnostics • Design antigen-detecting RDTs 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 • Create tests that can detect resistance to artemisinins and ACT partner drugs • Standardize low-cost positive controls for antigen-detecting RDTs suitable for field use • Create sustainable tools for quality control of RDTs at the country level • Investigate non-blood sampling to determine the potential for detecting recoverable antigen in samples. • Develop consistent, reliable staining methods for microscopy • Map and identify G6PD deficiency (if 8-aminoquinolones are to be used) and create tools for field G6PD detection • Develop tools to standardize and improve microscopy interpretation • Create tools for hypnozoite detection and further research hypnozoite biology and biomarkers • Develop field applicable tools for minimally invasive, rapid detection of low-density parasitemia in a high-throughput manner • Identify improved assessment methods (e.g. better serological tests, minimally invasive biomarkers)

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
		• Find ways to maintain sustained commitment to the long-term development of novel vector control approaches • Create a coherent research agenda for discovering and developing a broader range of insecticides G. Epidemiology • Create surveillance tools with potential for major operational impact H. Health systems/public health research • Develop a toolkit that allows for effectiveness decay analysis for identifying bottlenecks for effective coverage of malaria interventions and decisions on the degree of integration of interventions into existing and strengthened health systems • Integrate new approaches into the planning of elimination, surveillance, monitoring, and evaluation, and to create appropriate interfaces for different user communities. • Develop an essential platform for studying the biology of the liver stages and sexual forms of parasites • Conduct systems analyses of transcription, proteome, and metabolome libraries, rapid screening of drug libraries, high-	C. Drugs • Perform pharmacology studies to optimize dosing regimens of 8-aminoquinolines for gametocytocidal and anti-relapse efficacy and safety • Develop rapid and robust point-of-care glucose-6-phosphate dehydrogenase (G6PD) test to improve safety of 8-aminoquinoline use • Determine gametocytocidal and anti-relapse activity of current drugs and those in the pipeline • Develop drugs that prevent transmission by killing or preventing development of gametocytes, or blocking sporozoite development in the mosquito • Design drugs that cure liver stages of vivax (and ovale) malaria • Design sustained or pulsed release formulations and safe schizonticidal drugs for curing asymptomatic falciparum infection • Develop new, safe and effective drugs that block the infectivity of mature sexual forms of P. Falciparum gametocytes and/or dormant hepatic forms of P. Vivax • Create innovative drugs for intermittent preventive treatment during pregnancy • Explore long-acting formulations (e.g. repository formulations, oil-based depot injections cycloguanil pamoate) • Accelerate research into potential new drugs for first-line treatment to address artemisinin resistance D. Preventative vaccines • Expand vaccine development efforts to cover Plasmodium species other than P. Falciparum,

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
		throughput approaches to antigen identification, and the functional definition of gene products • Evaluate health systems' readiness to optimize novel programs, systems, tests, or other interventions, and their continuing performance • Develop a decision-making framework to guide the move from control to elimination I. Innovative financing • None identified	especially P. Vivax. • Develop new, innovative vaccine delivery approaches and/or adjuvants • Create robust assays to study functional immune response at individual level to predict effect on population level transmission • Develop tools to measure malaria transmission rates to facilitate clinical development of vaccines • Explore anti-vector vaccines, highly effective pre-erythrocytic or erythrocytic stage vaccines, and vaccines targeting parasite antigens of sexual and mosquito stages of infection E. Therapeutic vaccines • None identified F. Vector control • Perform large-scale, long-term population-based field studies to understand human host and vector factors • Explore the genetic manipulation of natural vector populations that can reduce high vectorial capacities in high-risk areas • Develop an analytic framework that consolidates existing and new information on malaria transmission. • Research novel modes of action that can circumvent emerging resistance to insecticides, particularly pyrethoid-based insecticides • Create new technologies that address vectors that do not rest or feed indoors that escape current vector control tools • Develop technologies that can simply and rapidly measure transmission

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
			• Educate the community effectively and engage the consumer market • Research improved choice of insecticides and methods to reduce the risk of resistance • Design a public portal to facilitate decision-making by the malaria research, control, and tool development communities G. Epidemiology • Investigate the performance of surveillance, monitoring, and evaluation by new and old technologies and to evaluate optimal strategies for implementation of surveillance as an active responsive intervention to further reduce transmission • Conduct research to develop biomarkers such as DNA-based methods or serology as monitoring and evaluation and surveillance tools • Develop information systems to monitor malaria infections, facilitate timely local program decisions and responses to reduce transmission • Develop methods, indicators, and shareable databases for parasite strain information to better track transmission • Develop methods for accessing and tracking population movements and quantifying their contribution and risk of malaria transmission • Explore how maps can be constructed to: o Show the probability of a threshold of transmission being exceeded; o Incorporate a wider range of metrics such as serological and entomological data; and o Assess cost-effectiveness of national stratification initiatives based on remotely sensed satellite data

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
			H. Health systems/public health research • Update the malaria monitoring and evaluation framework to include transmission reduction • Develop key data elements for a surveillance system from a systematic review of previous elimination attempts • Identify appropriate program time points for introduction of malaria infection detection in active or passive modes • Perform a systematic review to assess and compare metrics of malaria transmission at near zero transmission levels, research the validity of novel metrics to measure transmission at near zero levels, and to measure transmission potential within areas where transmission has been eliminated • Assess the precision, bias, feasibility, and cost-effectiveness of novel sampling methods for routine monitoring of present and past infections in target populations, including mobile populations I. Innovative financing • None identified
6. European Commission. Final Report: Challenges for the Future Research on HIV/AIDS, Malaria, and Tuberculosis. Luxembourg: European Communities; 2009. *The European Commission's Final*	On 13 and 14 November 2008, the European Commission (DG Research) brought together a large number of stakeholders in an International Conference on Poverty-Related Diseases (PRDs) with the aim of increasing the impact of EU-funded research on controlling PRDs. Leading scientists,	A. Basic science • Identify reliable markers for immune protection against malaria. • Address major knowledge gaps in biology and pathogenesis of P. vivax. • Identify new potential targets for drug and/or vaccine development. • Improve understanding of the mechanisms of transmission-blocking immunity.	A. Basic science • Research the respective roles of innate and acquired immune response, antigen-presentation pathways, receptor binding, longevity of immune response, etc. • Conduct studies on transmission-blocking immunity through high-throughput antibody assays. • Perform immunogenicity testing of malaria vaccine candidates in outbred or humanized

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
Report on the Challenges for the Future Research on HIV/AIDS, Malaria and Tuberculosis provides a summary of the 2008 European Commission Conference for research priorities on HIV/AIDS, Malaria, and Tuberculosis. Providing an update on the progress that has been achieved, the panel of speakers also provide detailed insight into current gaps and future research priorities.	research managers, decision-makers, funding agencies and relevant international NGOs attended (over 350 representatives from 63 countries), with significant participation from disease-endemic countries. The goals of the conference were to: i) regain political momentum for continuing and intensifying research addressing the "big three" global killer diseases; ii) set the scene by reporting on research efforts supported by the EC since 2002, when HIV/AIDS, malaria and TB first became a separate research focus under the EU's 6th Framework Programme (FP6); iii) gather input from relevant stakeholders (scientists from Europe and disease-endemic countries, industry, funding agencies, global partners, etc.) in order to set research priorities on PRDs for the remainder of the 7th Framework Programme (FP7) and beyond. After a plenary session on day 1, separate breakout sessions	B. Diagnostics • None identified C. Drugs • Design new drugs for the treatment and control of malaria. • Identify new molecular targets for antimalarial drugs D. Preventative vaccines • Develop an effective vaccine that combines antigens expressed during the different stages of the parasite's lifecycle. • Create a malaria vaccine, specifically for women in child-bearing age. • Enhance immunogenicity through vectored vaccines or new adjuvants that trigger immunity. E. Therapeutic vaccines • None identified F. Vector control • Develop novel vector control interventions and tactics. • Improve surveillance and management of insecticide resistance. • Create new insecticides and tools for resistance diagnosis and management. G. Epidemiology	rodent systems. • Use genomics, systems biology, and targeted molecular approaches to identify new drug candidates. • Utilize traditional or natural resources, in addition to synthetic compounds, for drug discovery. • Conduct long-lasting immuno-epidemiological studies to develop assays or surrogate markers to assess protection. • Create functional assay platforms for the identification of drug candidates. • Develop a convenient laboratory animal model for routine evaluation of P. falciparum and P. vivax. B. Diagnostics • None identified C. Drugs • Develop antimalarials that simultaneously target multiple development stages of the parasite and possibly the early insect stage. • Research potential drugs suitable for pregnancy and P. vivax. • Explore drugs that can block sexual or fertilized stages of the parasite in the mosquito. • Develop new drug delivery systems (e.g. slow release) • Explore alternative drug regimes (e.g. population-wide IPT). D. Preventative vaccines • Identify new functional antigens with immunogenic potential using systems-biology

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
	for the three diseases were organized. On day 2 conclusions of the breakout sessions were presented and discussed. This report summarises deliberations and recommendations of the HIV/AIDS, Malaria and TB working groups.	• None identified H. Health systems/public health research • Build research capacity in endemic countries. • Conduct focused research effort on methods, technologies and associated platforms. • Leverage resources from different industries for drug development purposes. • Develop bio-informatic tools and databases for vectors and transmission. • Develop relevant platforms for functional annotation and validation of vector gene sequences. • Aim research at novel applications of currently available tools. • Improve monitoring and surveillance systems. • Scale up interventions for large-scale impact, accommodating for regional / local considerations. • Monitor cost-effectiveness of interventions. I. Innovative financing • None identified	approach. • Explore use of attenuated whole parasites for a natural multi-antigen vaccine. • Research antigenic variation and immune evasion of the parasite to identify potential targets for vaccine development. • Understand variable antigens with extensive polymorphism for vaccine development consideration. • Assess the potential of specific antigens for inclusion in a multi-component vaccine candidate, particularly P. vivax. E. Therapeutic vaccines • None identified F. Vector control • Understand the range of ecological parametics, including species biology and behaviour, ecological adaptation to climate and environment, and underlying genetic factors. • Research the metabolic pathways and immune responses that affect insecticide resistance. • Fill knowledge gaps for non-An. gambiae mosquitoes for the development of new vector control tools. • Conduct research to better understand host seeking, biting, resting, mating, egg-laying behaviour. G. Epidemiology • None identified H. Health systems/public health research

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
			• Expand research capacity through training, research and laboratory infrastructure, GCP standards, general institutional capacities, and strong national regulatory environments. • Create an open access library of compounds with known parasitic activity for academic research purposes. • Develop systems for recombinant expression of malarial proteins for structural and functional analysis. • Promote infrastructures or centres of excellence, accessible to academic bodies, with state-of the art facilities • Promoting interdisciplinary research including academia, industry and Public Private Partnerships • Promote collaboration between regulatory agencies to bring antimalarial drugs to market quicker. • Create natural product depositories, recombinant protein and production facilities, and processing facilities for support of molecular target specific screening programs. • Perform studies to address operational issues (e.g. detection of asymptomatic malaria carriers; the effective and timely elimination of the parasites by ACT; ensuring access to ACTs to all community members; optimal combination of ITNs and IRS; social and economic developments needed to improve crucial sanitation and housing conditions; the development of leadership for malaria control, building on trust, values and local empowerment. • Determine how to integrate strategies into regular health services or other public health

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
			programs. • Perform studies to address the impact of malaria interventions on the performance and sustainability of community-based health care systems to be recruited for scale-up for all age groups. I. Innovative financing • None identified
7. 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. *The Evidence to Policy Initiative's Maintaining the Gains in Global Malaria Control report provides an update on the global effort to control malaria recently. Focusing on the need for long-term, sustainable financing for malaria control efforts, the report provides a number of recommendations to donors and countries to maintain continued*	A number of methods were used to model the health impacts of sustained malaria control, including the Lives Saved Tool and Okiro and Snow's Method. Data on malaria morbidity and mortality in focus regions were analyzed to estimate the number of clinical cases and deaths that could be averted each year through the continued implementation of current control programs. Data from 2000-2010 on the annual number of suspected malaria cases and deaths from the WHO 2010 World Malaria Report and data reported by health facilities to the national malaria control program. The trends apparent in this data over time were useful for	A. Basic science • None identified B. Diagnostics • None identified C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology • None identified H. Health systems/public health research • Better understand the link between malaria and other industries	A. Basic science • None identified B. Diagnostics • None identified C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology • None identified H. Health systems/public health research • Conduct research to better understand timing for scaling back of prevention efforts. • Determine the economic benefits of sustaining malaria control to the agricultural sector and

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
progress in malaria control.	evaluating impact, but adjustments were required to account for underreporting and healthcare-seeking behaviours and results were compared with other published resources where possible.	I. Innovative financing • Explore Identify ways to ensure sustained, predictable financing for malaria Identify alternatives to donor financing and diversify the funding pool by broadening the number of donors	tourism. I. Innovative financing • Determine ways to foster novel domestic resource streams for malaria control, e.g. tourist taxes, community health insurance schemes, prize-linked savings, modifications to national tax codes, endowment funds, and National Health Solidarity Funds. • Create new mechanisms to improve the predictability and quality of financial resources, e.g. trust funds • Evaluate and consider widely adopting the Cash on Delivery (COD) aid approach wherein donors reward countries by tying continued financing to the maintenance of low malaria prevalence • Define the most cost-effective mix of interventions between surveillance and targeted prevention (ITNs and IRS) • Examine ways to reduce the prices of ITNs and insecticides through more effective procurement and negotiation
8. Policy Cures. Saving Lives and Creating Impact: EU Investment in Poverty-Related Disease. London: Policy Cures London; October 2012. *Policy Cures' Saving Lives and Creating Impact report assesses the impact of EU funding for poverty-related and neglected diseases*	The scope for PRND R&D and primary financial investment data in this report was extracted from the G-FINDER databases. Financial data was reported in 2007 euros to make the data comparable across the four years and to avoid conflating real year-on-year changes with changes due to inflation. Other specific datapoints were	A. Basic science • Conduct high quality basic research to contribute to the development of products targeted at malaria. B. Diagnostics • Develop new tools to accurately, rapidly diagnose malaria in developing countries. C. Drugs • Create new, innovative antimalarial drugs to combat resistance	A. Basic science • None identified B. Diagnostics • None identified C. Drugs • Explore combination therapies to address emerging antimalarial drug resistance. • Conduct research on sufadoxine-pyrimethamine for intermittent preventative treatment for pregnant women.

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
(PRND) R&D, highlighting the return on investment for both developing countries and the EU. Focusing on the EU's role in funding PRND R&D, the report highlights the gains made by various EU research institutions, partnerships, and private industry.	provided by the EC, the European and Developing Countries Clinical Trials Partnership (EDCTP), European Vaccine Initiative (EVI), Tuberculosis Vaccine Initiative (TBVI), the Bill & Melinda Gates Foundation and Thomson Reuters, including: Member State and 3rd-party contributions to EDCTP, number of publications on neglected tropical diseases in 2011, and government funding commitments to EVI and TBVI. Qualitative policy data was obtained through desk-based research, and supplemented by communications with specific institutes or organisations mentioned in the report.	• Develop fixed-dose paediatric formulations for antimalarial drugs. • Develop antimalarial drugs for pregnant women. D. Preventative vaccines • Develop an effective vaccine for the prevention of malaria. E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology • None identified H. Health systems/public health research • Integrate the private sector into the poverty-related neglected disease R&D landscape. • Improve coordination efforts funders and researchers. • Identify the right balance of funding between product development and basic science. • Encourage collaboration amongst researchers to jointly develop product development portfolios. • Align efforts of aid organizations and science and technology agencies. I. Innovative financing	D. Preventative vaccines • Estimate the potential epidemiological benefit of an effective vaccine. E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology • None identified H. Health systems/public health research • Identify key product development partnerships (PDPs) to engage talented researchers in private industry. I. Innovative financing • Reduce restrictions on funding requirements to ensure that the best research candidates are prioritized (under the EU 7th Framework Programme). • Streamline administrative processes to expedite funding flows to reach researchers. • Explore pooled funding mechanisms to encourage collaboration.

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
		• Improve financing coordination efforts amongst various stakeholders.	
9. 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. *COHRED's Strengthening Pharmaceutical Innovation in Africa report focuses on the agenda to promote pharmaceutical innovation in Africa by African countries. This report suggests different mechanisms and tools to support African countries moving forward, specifically advocating for a systems and evidence-based approach.*	The geographical scope of the study is Africa. It focuses on diseases that disproportionately affect Africa, including neglected tropical diseases. The method used was keyword internet searches, key informant interviews and discussions review of literature and documentation3, participation and consultation in a number of international meetings and consultations on pharmaceutical in several low income countries. The data obtained was analyzed manually along main emerging themes. The draft report was externally peer reviewed. Step 1: Identifying and categorising projects and programmes contributing to the improvement of access to medical products in Africa. Global, regional and national examples were considered. Step 2: examination of a minimum set of conditions, policies; human, structural and	A. Basic science • None identified B. Diagnostics • None identified C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology • None identified H. Health systems/public health research • Leverage African strengths in pharmaceutical innovation (e.g. African Ministerial Council on Science and Technology). I. Innovative financing • Utilize innovative financing mechanisms across industries and stakeholders.	A. Basic science • None identified B. Diagnostics • None identified C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology • None identified H. Health systems/public health research • Create policies to encourage local production of medicines to treat neglected diseases. • Utilize technology transfer and licensing agreements to promote local drug production. I. Innovative financing • Create new product development public-private partnerships (PDPPPs). • Engage companies in using preferential pricing arrangements.

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
	financial resources to identify initiatives most likely to be successfully implemented in any African country.		• Leverage philanthropic donations to strengthen national pharmaceutical innovation systems. • Expand access to treatment through intergovernmental organization-sponsored buyer co-payments. • Raise funds through solidarity taxes on airlines. • Engage venture capital to invest in neglected disease R&D.
10. The George Institute for International Health. Registering New Drugs: The African Context. London; The George Institute for International Health, January 2010. *The Registering New Drugs report reviews the various mechanisms and strategies available to support the registration of new drugs for neglected tropical diseases (NTDs) in developing countries. It addresses the development and strengthening of the capacity of national regulatory authorities to monitor quality, safety, and efficacy of health products, since regulatory issues are often obstacles*	A select group of experts from various organizations (including: World Health Organization, US Food and Drug Administration, European Medicines Agency, etc.) were consulted for the purposes of this analysis. The International Expert Advisory Group (EAG) played a substantial role in reviewing this report and shaping the final analysis and recommendations. The draft report was also work-shopped at a regional meeting in Nairobi, attended by many African regulators, including representatives from Angola, Democratic Republic of Congo, Ethiopia, Uganda, Tanzania and members of the HAT (human African trypanosomiasis) and LEAP (leishmaniasis) platforms.	A. Basic science • None identified B. Diagnostics • None identified C. Drugs • Assess the safe interaction of malaria drugs in patients with TB coinfection. D. Preventative vaccines • Identify promising candidates for a new preventative malaria vaccine. E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology • None identified H. Health systems/public health research • Develop new mechanisms and	A. Basic science • None identified B. Diagnostics • None identified C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology • None identified H. Health systems/public health research • Create centers of regulatory excellence in African subregions. • Provide automatic WHO prequalification for novel neglected disease products. • Include regulators from endemic countries in

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
to access.		pathways to ensure the urgent approval of neglected tropical disease drugs in developing countries. I. Innovative financing • None identified	regulatory reviews of neglected disease products. • Select Western medicines regulatory agencies to review prequalification decisions. I. Innovative financing • None identified
11. Moran, Mary; Ropars, Anne-Laure; Guzman, Javier; Diaz, Jose; Garrison, Christopher. The New Landscape of Neglected Disease Drug Development. London: The London School of Economics and Political Science; 2005. *The New Landscape of Neglected Disease Drug Development report provides an overview of health outcomes for developing country neglected disease patients and presents recommendations to increase the quality and number of drugs available. It also presents policies and incentives that Western governments could implement to achieve this*	An empirical approach was used for this report, covering known neglected disease drug R&D from 1975 to end 2004. All findings and conclusions are based on a review of existing knowledge, supported by original research and interviews with stakeholders involved in the development and use of new drugs. Using a multidisciplinary approach, this report consults groups from various fields (government, public health, industry. Etc.) Analysis and conclusions relate only to neglected disease drug R&D and cannot be automatically translated across to vaccines and diagnostics. Drug development activity was included only as it relates to the ten neglected diseases listed by the World Health Organization Special Programme for Research and Training in Tropical Diseases	A. Basic science • None identified B. Diagnostics • None identified C. Drugs • Develop new, innovative antimalarial drugs suitable for developing country use. • Identify new classes of malaria products that can "outwit" parasites to avoid drug resistance. • Develop drug adaptations that make treatment compliance easier (e.g. paediatric syrups, simpler formulations, etc.). D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology	A. Basic science • None identified B. Diagnostics • None identified C. Drugs • Conduct research on synthetic peroxides in the development of new antimalarials. • Explore ease-of-use considerations for patients and health care workers (e.g. dosing intervals, total length of treatment, oral formulations, etc.). • Consider appropriateness of product to country health systems (e.g. cold chain issues, hospital-based admin, etc.). • Create products targeted at various populations (e.g. children, adults, pregnant women, severely ill patients, etc.). D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • None identified

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
objective.	(WHO/TDR). A number of areas of activity were excluded from the scope of this report. Developing country drug development was not considered as it is unlikely to be amenable to Western government incentives. Additionally, basic exploratory research that is not compound-based and country infrastructure, implementation, and human resource considerations were also not included in this report.	• None identified H. Health systems/public health research • Create a central clearinghouse for information regarding: targets or compounds related to neglected disease research, funding sources, and services and skills offered. I. Innovative financing • Identify new, innovative public-private partnerships (PPPs) for drug development, and create policies to encourage PPPs. • Provide shared platform services to PPPs (e.g. legal, human resources, etc.) • Offer support to PPPs in negotiating industry deals. • Create an industry R&D fund (IRFF) to underwrite industry participation in PPPs. • Provide PPP-sponsored start-up funds to new small companies. • Sell "fast-track" regulatory review of commercial drugs to finance neglected disease R&D. • Award prizes to multinationals who invest in neglected disease drug development. • Reduce financial obligations on patent and maintenance fees.	G. Epidemiology • None identified H. Health systems/public health research • Generate neglected disease data that can be cross-applied to core commercial compounds. • Upgrade clinical trial sites in developing countries I. Innovative financing • Identify PPPs that are willing to commit to a long-term funding mechanism (entirety of R&D process). • Collaborate with industry partners that will contract with PPPs to develop drugs for neglected diseases. • Garner funds from G8 countries to create the IRFF.

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
12. UNITAID. Malaria Diagnostic Technology Landscape. World Health Organization; Dec 2011. *This report describes the role of malaria diagnostic tests, unmet needs in malaria diagnosis, and factors considered in diagnostic test selection, followed by a review of existing malaria diagnostic tests and new technologies in the development pipeline. The technologies described include those for patient management, as well as those that may be more suitable for surveillance, especially in the context of elimination.*	In general, the material in this landscape was gathered by the author from publicly available information, published and unpublished reports and prospectuses, and interviews with developers and manufacturers. With regards to the technology review, significant prior work (reports, literature etc.) has been done to describe existing malaria diagnostic technologies and this is summarized below. For existing technologies, the methodology largely involved review of existing reports supplemented by expert interviews and targeted literature searches. In contrast to existing technologies, very little in-depth work has been done previously on the malaria diagnostic pipeline. Key informant interviews, along with literature and internet searches were used to identify new technologies actively being developed and commercialized. (Due to the nature of this work and the timeframe for the report, a totally exhaustive search was not possible.)	A. Basic science • None identified B. Diagnostics • Develop screening tests for detection of malaria in pregnancy, tests that measure low-level transmission, and tests that detect asymptomatic malaria infections for use in elimination campaigns • Develop tests that assist with the differential diagnosis of fever and management of non-malaria fever • Develop tests related to the diagnosis and treatment of the liver stage of P. vivax malaria • Enhance the robustness of tests to withstand extreme heat and humidity • Develop tests that are affordable, widely deployable, easy to use, rapid and accurate C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • None identified	A. Basic science • None identified B. Diagnostics • Create a test sensitive enough to detect all cases of placental malaria as today's case management tests (microscopy and RDTs) are not sensitive enough • Develop a low-cost, high-throughput screening test is to conduct large population surveys that are used to monitor progress over time and to identify hot-spots (i.e. foci) of continued transmission • Develop test for these situations a test that has a low limit of detection, and that is highly sensitive, rapid, and portable, to screen high-risk populations, e.g. migrant workers • Design a multiplex point-of-care (POC) test that detects several common causes of fever at one time (e.g. malaria, dengue, and influenza) • Develop a POC test that serves as a triaging tool providing information on management of the patient rather than pinpointing the exact cause of fever, e.g. it would include a malaria test and biomarkers for severity of disease, information that helps differentiate broadly between bacterial versus viral infections C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
	Once products were identified, detailed information on these new technologies was obtained primarily through conversations with technology developers, as well as through publications, where they exist. In some instances, technologies were identified but the developers were not available to provide additional information. Because these products are in the development phase, the ultimate performance and operational characteristics may change by the time the product is launched. Similarly, projections of market launch will shift as time goes by, as will price estimates.	G. Epidemiology • None identified H. Health systems/public health research • Learn how to increase access to malaria diagnostics • Investigate how to strengthen the management of fever more broadly to maximize the public health impact of tests • Develop strategies for rapidly interpreting malarial surveillance data and translating it into public health action I. Innovative financing • None identified	• None identified F. Vector control • None identified G. Epidemiology • None identified H. Health systems/public health research • Determine ways to overcome factors that obstruct access to testing, e.g. unaffordable prices, limited awareness, little incentive for the private sector to offer testing, local regulatory and policy issues, and a need for extremely user-friendly test formats and packaging appropriate for the private sector • Revisit existing protocols for fever management, commence studies to investigate the common causes of fever, review treatment options for non-malaria fever, and possibly demand new diagnostic technologies that assist with the differential diagnosis of fever • Develop and refine new technologies that incorporate data storage and remote transmission capability, e.g. those that focus on surveillance data capture and analysis I. Innovative financing • None identified
13. UNITAID. Malaria Diagnostics Market Landscape. World Health Organization; Dec 2012. *This Landscape Report*	This report is based upon: • Desk review of literature and published and unpublished reports • Review of existing market data and reports	A. Basic science • None identified B. Diagnostics • None identified	• Basic science • None identified • Diagnostics • None identified

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
reflects an initiative within UNITAID to describe and monitor the malaria diagnostics landscape, including disease trends, technologies, and market characteristics. This report focuses on the market for malaria diagnostic tests, and on rapid diagnostics tests (RDTs) in particular.	• Identification of existing sources of aggregate data on the market, and analysis of data when it was available • Key informant and expert interviews, including representatives from industry, programs, donors, and academia. Research for this report was conducted from February-April 2012, and information is up to date as of April 2012.	C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology • None identified H. Health systems/public health research • None identified I. Innovative financing • Develop means to increase the availability of information on the quality of malaria diagnostics (including development of technologies to simplify quality control testing), reinforce competition around quality, ensure consistency during manufacturer scale up, and assure the integrity of tests in the field • Identify strategies to stabilize prices of RDTs and improve predictability of demand • Find ways to draw funding for interventions that support RDT	• Drugs • None identified • Preventative vaccines • None identified • Therapeutic vaccines • None identified • Vector control • None identified • Epidemiology • None identified • Health systems/public health research • None identified • Innovative financing • Develop quality control technologies for use at all levels of the supply chain from manufacturer to point of service • Find ways to support the WHO Product and Lot Testing program and their transition to a less costly and more sustainable business model • Develop stronger incentives for upstream quality assurance, e.g. site visits, stepped-up lot testing, or changes to the WHO Product Testing program • Find ways to encourage buyers to focus on quality and product characteristics, as opposed to price alone • Strategize how interventions can be structured with frequent evaluations and flexibility to incorporate new learning • Reinforce the data on the availability of testing

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
		implementation, e.g. health worker training, supervision • Develop the private sector market for malaria RDTs and determine how to expand access to testing and improve targeting of ACTs in the private sector • Identify ways to increase funding for product development for underserved populations, including pregnant women, populations living in low transmission settings, and populations affected by *P. vivax* • Develop mechanisms to strengthen market knowledge	and use of results • Improve the completeness of data on RDT procurement • Determine how to enhance efforts to collect and synthesize information on the private sector markets
14. UNITAID. Malaria Diagnostics Technology Landscape: Semi-Annual Update. World Health Organization: Dec 2012. *The Malaria Diagnostics Technology Landscape is published annually and is prepared as part of a broad and on-going effort at UNITAID to understand the technology landscape for malaria diagnostics. This document is a semi-annual update, focused on updates to the diagnostic pipeline first described in the Malaria Diagnostics Technologies*	The Malaria Diagnostics Technology Landscape Update is compiled by Jennifer A. Daily with support from UNITAID. The updates in this document were provided by the developers of these diagnostic technologies. If technologies that appear in the Malaria Diagnostics Technologies Landscape do not appear in this update, it is either because the developer did not provide an update or indicated that there were none at this time.	A. Basic science • None identified B. Diagnostics • None identified C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology • None identified	A. Basic science • None identified B. Diagnostics • None identified C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology • None identified

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
Landscape.		H. Health systems/public health research • None identified I. Innovative financing • None identified	H. Health systems/public health research • None identified I. Innovative financing • None identified
15. 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. *This report's goal is to discuss the results of WHO's tests on the efficacy and usefulness of various Malaria Rapid Diagnostic Test Performance. The report is fourth in an ongoing series and overall found improvements/upward trends in all areas among RDTs that were resubmitted for testing. It*	Product Testing Is part of the WHO-FIND Malaria RDT Evaluation Programme. This Programme develops methods for evaluation and provides relevant data on antigen-detecting malaria rapid diagnostic tests. The programme is a collaboration of many institutions in malaria-endemic and non-endemic countries, with the global specimen bank maintained, and the testing performed, at CDC. The results provide comparative data on two lots of products against a panel of parasite samples diluted to a low parasite density (200 parasites/µl), considered close to the threshold that tests must detect to reliably identify clinical malaria in many settings (6), and a higher parasite density (2000 (or 5000) parasites/µl).	A. Basic science • None identified B. Diagnostics • Develop screening tests for detection of malaria in pregnancy, tests that measure low-level transmission, and tests that detect asymptomatic malaria infections for use in elimination campaigns • Develop new tests with a high rate of antigen detection combined with a low false-positive rate, good heat (thermal) stability and robustness against humidity for use in endemic countries C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • None identified	A. Basic science • None identified B. Diagnostics • Find ways to enhance tests' sensitivity to detect infection among vulnerable individuals who may develop illness at low parasite densities, e.g. young children, pregnant women, immigrants, those well protected by bed nets) • Develop storage and shipping products to ensure test stability and sensitivity in high temperatures with high humidity C. Drugs • None identified D. Preventative vaccines • None identified E. Therapeutic vaccines • None identified F. Vector control • None identified G. Epidemiology • None identified

Source	Approach, Methodology, Criteria, People Involved	Identified Important Questions/Goals Needing Research	Key Findings/Priorities for Addressing these Questions/Goals
provides guidelines on how to approach parasite based diagnostics– recommending national programs use results from these reports to select the most appropriate RDTs based on local climate and characteristics of the malaria endemic to the area.		G. Epidemiology • None identified H. Health systems/public health research • Develop strategies to ensure quality preparation and interpretation of RDT results in field settings I. Innovative financing • None identified	H. Health systems/public health research • Design training programs for health workers with limited training and supervision in endemic countries • Investigate how to plan beyond rational procurement to ensure consistent supplies of all necessary materials (including gloves, sharps disposal containers, and supplies required for further case management), training of end-users, community sensitization, and monitoring of diagnostic quality and results • Identify ways to improve the management of other febrile diseases and health service delivery systems with an integrated approach with other health programmes impacting on the management of febrile illness I. Innovative financing • None identified

Synthesis of Disease-Specific R&D Priorities for Malaria

R&D Areas	MALARIA	
	Goal	***R&D Priorities for Achieving Goals***
BASIC SCIENCE	• Determine the role of antigen diversity for developing vaccine candidates[{B}] • Better understand artemisinin resistance, its fundamental genetic processes, and how to best manage it[{B},{C},{D}] • Develop new methods to assess the impact of resistance on malaria transmission.[{D}] • Explore how to reduce the human parasite reservoir to curtail transmission[{C}] • Determine how to obtain a comprehensive understanding of the stage-specific biology of the parasite. [{E}] • Define desired target product profiles, incorporating new approaches from different fields. [{E}] • Assess and determine ways to overcome roadblocks that prevent scale-up of genetic manipulation and functional analysis of essential genes. [{E}] • Identify reliable markers for immune protection against malaria. [{F}] • Identify and find ways to address major knowledge gaps in biology and pathogenesis of P. vivax. [{F}] • Understand the ecology, behaviour, and genetic population structure of malaria vectors.[{E}] • Find ways to improve understanding of the mechanisms of transmission-blocking immunity. [{F}]	• Conduct *in vitro* studies that measure the intrinsic sensitivity of parasites to antimalarial drugs[{C}] • Conduct molecular marker studies to identify genetic mutations and subsequently confirm the presence of mutations in blood parasites[{C}] • Perform pharmacokinetic studies to characterize drug absorption and drug action in the body[{C}] • Identify clear genetic markers for important oxidase-mediated forms of resistance to pyrethroids.[{D}] • Discover genetic mutations responsible for metabolic resistance to pyrethroids in different geographical settings.[{D}] • Utilize high-throughput DNA-based methods to identify resistant genes.[{D}] • Conduct research to better understand genetic dominance, fitness cost, cross-resistance, linkage, disequilibrium, drivers of selection pressure and behavioural resistance.[{D}] • Examine entire parasitic life-cycle based approach to understand transitions from one host to another.[{E}] • Find ways to distinguish essential metabolic pathways through systematic mutagenesis on a genome-wide scale. [{E}] • Explore the use of new technology platforms to permit deep characterization of the metabolome. [{E}] • Develop an efficient, inexpensive P. vivax blood-stage culture system. [{E}] • Create in vitro systems to understand P. Falciparum, P. vivax, and hypnozoite biology as it relates to liver-stage biology. [{E}] • Conduct mechanism of action studies for drugs and vaccines in current pipeline to inform future strategies. [{E}] • Determine how to improve technologies for the manipulation of Plasmodium. [{E}] • Develop methods to implement systems-based approaches to incorporate cutting-edge technology into basic malaria research (e.g. metabolomics). [{E}] • Utilize technologies from physical, chemical, and biomedical engineering sciences to improve molecular understanding of parasite development biology. [{E}] • Utilize and explore the potential for new technologies to address roadblocks, such as: low frequency of homologous recombination in Plasmodium, difficulties

R&D Areas	MALARIA	
	Goal	***R&D Priorities for Achieving Goals***
		associated with the manipulation of large fragments of AT-rich and repetitive genomic DNA, and the lack of robust and scalable systems for conditional gene expression.{E} • Further elucidate the respective roles of innate and acquired immune response, antigen-presentation pathways, receptor binding, longevity of immune response, etc.{F} • Conduct studies on transmission-blocking immunity through high-throughput antibody assays. {F} • Perform immunogenicity testing of malaria vaccine candidates in outbred or humanized rodent systems. {F} • Use genomics, systems biology, and targeted molecular approaches to identify new drug candidates. {F} • Utilize traditional or natural resources, in addition to synthetic compounds, for drug discovery. {F} • Conduct long-lasting immuno-epidemiological studies to develop assays or surrogate markers to assess protection. {F} • Create functional assay platforms for the identification of drug candidates. {F} • Develop a convenient laboratory animal model for routine evaluation of P. falciparum and P. vivax. {F} • Perform pharmacology studies to optimize dosing regimens of 8-aminoquinolines for gametocytocidal and anti-relapse efficacy and safety{E}
DIAGNOSTICS	• Determine methods to enhance the quality and stability of currently available rapid diagnostic tests (RDTs)for low resource settings{A},{E} • 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.{E} • Develop screening tests for detection of malaria in pregnancy, tests that measure low-level transmission, and tests that detect asymptomatic malaria infections	• Develop new and improved tools for consistent field detection of very low-density parasitaemia, including non-*falciparum* parasites {A},{E} • Create tests that can detect resistance to artemisinins and ACT partner drugs{E} • Identify ways to enhance screening for enzymatic deficiency, i.e. G6PD deficiency{A} • Investigate future product targets that include automated microscopy and non-invasive, non-blood sampling through analysis of saliva or urine{A},{E} • Develop tests to detect non-malarial febrile disease pathogens or markers of infection requiring specific treatment{A} • Develop technologies that can simply and rapidly measure transmission. {E} • Discover a robust, sensitive, and specific standardized method for assessment of transmission intensity in the intervening period when transmission continues at

R&D Areas	MALARIA	
	Goal	***R&D Priorities for Achieving Goals***
	for use in elimination campaigns[{L},{N}] • Develop tests that assist with the differential diagnosis of fever and management of non-malaria fever[{L}] • Develop tests related to the diagnosis and treatment of the liver stage of P. vivax malaria[{L}] • Develop tests that are affordable, widely deployable, easy to use, rapid and accurate[{L}] • Develop new tests with a high rate of antigen detection combined with a low false-positive rate, good heat (thermal) stability and robustness against humidity for use in endemic countries[{N},{L}]	low levels.[{E}] • Determine how to standardize low-cost positive controls for antigen-detecting RDTs suitable for field use. [{E}] • Create sustainable tools for quality control of RDTs at the country level. [{E}] • Develop consistent, reliable staining methods for microscopy. [{E}] • Develop tools to standardize and improve microscopy interpretation. [{E}] • Map and identify G6PD deficiency (if 8-aminoquinolones are to be used) and create tools for field G6PD detection. [{E}] • Create tools for hypnozoite detection and further research hypnozoite biology and biomarkers. [{E}] • Develop field applicable tools for minimally invasive, rapid detection of low-density parasitemia in a high-throughput manner. [{E}] • Identify improved assessment methods (e.g. better serological tests, minimally invasive biomarkers). [{E}] • Develop rapid and robust point-of-care glucose-6-phosphate dehydrogenase (G6PD) test to improve safety of 8-aminoquinoline use[{E}] • Create a test sensitive enough to detect all cases of placental malaria as today's case management tests (microscopy and RDTs) are not sensitive enough[{L}] • Develop a low-cost, high-throughput screening test is to conduct large population surveys that are used to monitor progress over time and to identify hot-spots (i.e. foci) of continued transmission[{L}] • Develop a test that has a low limit of detection, and that is highly sensitive, rapid, and portable, to screen high-risk populations, e.g. migrant workers[{L}] • 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}] • Develop a POC test that serves as a triaging tool providing information on management of the patient rather than pinpointing the exact cause of fever, e.g. it would include a malaria test and biomarkers for severity of disease, information that helps differentiate broadly between bacterial versus viral infections[{L}] • Find ways to enhance tests' sensitivity to detect infection among vulnerable individuals who may develop illness at low parasite densities, e.g. young children, pregnant women, immigrants, those well protected by bed nets)[{N}] • Develop storage and shipping products to ensure test stability and sensitivity in high temperatures with high humidity[{N}]

R&D Areas	MALARIA	
	Goal	***R&D Priorities for Achieving Goals***
DRUGS	• Develop new, shorter-regimen drug therapies[{A}] • Explore drug formulations that are more appropriate for vulnerable populations[{A}] • Find ways to accelerate the development of new drugs to combat artemisinin resistance[{A},{E}] • Conduct routine therapeutic drug efficacy studies[{C}] • Find ways to optimize and accelerate research for currently available malaria drugs[{E}] • Produce drugs that can be administered in a single encounter at infrequent intervals[{E}] • Develop drug adaptations that make treatment compliance easier (e.g. paediatric syrups, simpler formulations, etc.)[{F}] • Identify new molecular targets for antimalarial drugs[{F}]	• Develop a single-dose cure to replace the current three-day drug regimen[{A}] • Identify fixed dose paediatric formulations and ways to enhance the safety and suitability of treatment regimens for children[{A},{H}] • Develop more treatment options for pregnant women[{A},{F}] • Investigate a radical cure option for *P. vivax* [{A},{F}] • Create novel compounds to tackle artemisinin resistance and transmission-blocking antimalarials[{A},{E}] • Develop antimalarials that simultaneously target multiple development stages of the parasite and possibly the early insect stage.[{F}] • Explore drugs that can block sexual or fertilized stages of the parasite in the mosquito[{F}] • Assess the safe interaction of malaria drugs in patients with TB coinfection[{J}] • Conduct research on synthetic peroxides in the development of new antimalarials[{K}] • Explore ease-of-use considerations for patients and health care workers (e.g. dosing intervals, total length of treatment, oral formulations, etc.).[{K}] • Consider appropriateness of product to country health systems (e.g. cold chain issues, hospital-based admin, etc.)[{K}] • Develop new drug delivery systems (e.g. slow release)[{F}] • Explore alternative drug regimes (e.g. population-wide IPT)[{F}] • Explore the potential for combination therapies to address emerging antimalarial drug resistance.[{H}] • Determine ways to measure the clinical and parasitological efficacy of medicines and the detection of small changes in treatment outcome over time[{C}] • Determine the gametocytocidal and anti-relapse activity of current drugs and those in the pipeline[{E}] • Develop drugs that prevent transmission by killing or preventing development of gametocytes, or blocking sporozoite development in the mosquito[{E}] • Design drugs that cure liver stages of vivax (and ovale) malaria[{E}] • Develop sustained or pulsed release formulations and safe schizonticidal drugs for curing asymptomatic falciparum infection[{E}] • Develop new, safe and effective drugs that block the infectivity of mature sexual forms of P. Falciparum gametocytes and/or dormant hepatic forms of P. vivax. [{E}] • Create innovative drugs for intermittent preventive treatment during

R&D Areas	MALARIA	
	Goal	***R&D Priorities for Achieving Goals***
		pregnancy. {E} • Evaluate the efficacy of long-acting formulations (e.g. repository formulations, oil-based depot injections cycloguanil pamoate) {E}
VACCINES	• Identify more effective and potent vaccine candidates{A},{B},{C} • Develop an effective vaccine that combines antigens expressed during the different stages of the parasite's lifecycle{F} • Determine how to enhance immunogenicity through vectored vaccines or new adjuvants that trigger immunity{F} • Prioritize research into new technology platforms that could increase vaccine potency{B} • Find ways to ensure that vaccines meet batch-to-batch reproducibility{B} • Create a vaccine that targets both the sexual and mosquito stages (transmission-blocking) and the pre-erythrocytic and asexual stages{E} • Develop vaccine that targets multiple malaria parasite species{E} • Explore novel vaccine approaches to elicit longer-lasting protective efficacy{E}	• Develop a more effective second-generation *P. falciparum* vaccine and new vaccine candidates targeting *P. vivax*{A} • Create and standardize assays, reagents and protocols used at each stage of malaria vaccine product development{B} • Develop a shared set of vaccine ranking criteria based on safety, type of immune response induced, ability to generate a functional antigen, potential formulations and manufacturability{B} • Determine how to integrate new technologies or technologies not previously used for malaria vaccines into the research process e.g. adenovirus vectors, prime boost approaches and synthetic peptides{B} • Find ways to evaluate technical feasibility during preclinical development to successfully scale-up a candidate to a stable, reproducible product{B} • Develop new, innovative vaccine delivery approaches and/or adjuvants {E} • Create robust assays to study functional immune response at individual level to predict effect on population level transmission {E} • Develop tools to measure malaria transmission rates to facilitate clinical development of vaccines {E} • Determine how to expand vaccine development efforts to cover Plasmodium species other than P. Falciparum{E} • Explore anti-vector vaccines, highly effective pre-erythrocytic or erythrocytic stage vaccines, and vaccines targeting parasite antigens of sexual and mosquito stages of infection{E} • Identify new functional antigens with immunogenic potential using systems-biology approach{F} • Explore the use of attenuated whole parasites to develop a natural multi-antigen vaccine{F} • Investigate antigenic variation and immune evasion of the parasite to identify potential targets for vaccine development. {F} • Better understand variable antigens with extensive polymorphism for vaccine development consideration. {F} • Assess the potential of specific antigens for inclusion in a multi-component

R&D Areas	MALARIA	
	Goal	***R&D Priorities for Achieving Goals***
		vaccine candidate, particularly P. vivax. {F}
VECTOR CONTROL	• Determine how to maintain sustained commitment to long-term development of novel vector control ingredients and approaches{A},{C},{E},{F} • Create a coherent research agenda for discovering and developing a broader range of insecticides{E} • Develop strategies to improve surveillance and management of insecticide resistance{F} • Find ways to reduce the reliance on insecticides in controlling malaria transmission{D} • Determine ways to reduce reliance on pyrethroids for vector control due to the risk of resistance{A},{C} • Identify ways to reduce the intensity of local malaria transmission at the community level by reducing vector longevity, human-vector contact and density of the local vector mosquito population{C} • Consolidate all available data on vector resistance{C}	• Explore new paradigms in insecticide delivery, including novel active ingredients for bednets and indoor residual spraying (IRS) {A},{B} • Find means to ensure that decisions regarding the choice of insecticide are supported by adequate and up-to-date information on resistance among local anopheline vectors{C} • Determine the extent to which chloroquine-resistant *P. vivax* has spread{C} • Develop new insecticides with different modes of action appropriate for use on insecticide-treated nets{C},{D} • Develop innovative, non-insecticide-based vector control tools (e.g. spatial repellents, area-wide treatments, traps and targets, and animal treatments){D} • Explore the genetic manipulation of natural vector populations that can reduce high vectorial capacities in high-risk areas{E} • Research the metabolic pathways and immune responses that affect insecticide resistance{F} • Determine how to fill knowledge gaps for non-An. gambiae mosquitoes for the development of new vector control tools {F} • Better understand host seeking, biting, resting, mating, egg-laying behaviour{F} • Understand the range of ecological parametics, including species biology and behaviour, ecological adaptation to climate and environment, and underlying genetic factors. {F} • Develop an analytic framework that consolidates existing and new information on malaria transmission. {E} • Investigate and assess novel modes of action that can circumvent emerging resistance to insecticides, particularly pyrethoid-based insecticides. {E} • Create new technologies that address vectors that do not rest or feed indoors that escape current vector control tools. {E} • Develop methods to reduce the risk of resistance{E}

R&D Areas	MALARIA	
	Goal	***R&D Priorities for Achieving Goals***
EPIDEMIOLOGY	• Find ways to gather epidemiological evidence to support the development of new, innovative vector control paradigms[{D}] • Assess current epidemiological methods to inform decision-making globally / nationally[{D}] • Determine how to collectively shift away from "parasite-first" approach to an examination of host-parasite-vector population interactions[{E}]	• Perform large-scale, long-term population-based field studies to understand human host and vector factors[{E}] • Design research efforts to understand the epidemiology of the gametocyte[{E}] • Conduct epidemiological testing for durable wall lining to complement IRS for wide-scale implementation[{D}] • Revise epidemiological malaria models to include insecticide resistance[{D}] • Understand dynamics between multiplication of asexual stage parasites, gametocytogenesis, and malaria transmission rates at population level[{E}] • Develop and refine new technologies that incorporate data storage and remote transmission capability, e.g. those that focus on surveillance data capture and analysis[{L}]
PUBLIC HEALTH AND OPERATIONAL RESEARCH	• Develop monitoring systems to detect possible resurgence of malaria[{A},{F}] • Determine how to ensure that trials, including phase IV trials, are allocated to avoid site competition and to maximise site progress along the development trajectory[{B}] • Identify ways to build on the Malaria Vaccine Technology Roadmap[{B}] • Determine how to improve the coordination of global R&D and reach agreement on a challenge model for blood-stage vaccine candidates[{B}] • Clarify and codify a streamlined regulatory pathway to allow the global portfolio to move forward more quickly[{B}] • Determine why there are discrepancies in access to treatment for vulnerable groups such as infants and pregnant women[{C}] • Investigate how diagnosis and treatment can be provided at the community level through a programme of community case management in under-resourced	• Determine how to adapt screening and monitoring strategies so that a possible resurgence of malaria can be picked up rapidly[{A}] • Identify ways to ensure that all product development sites have an on-site staff training programme[{B}] • Develop a formal mentoring system and a linked proposal of formal training attachments between younger sites and experienced African licensure sites, Western clinical trial institutions and/or Western pharmaceutical firms[{B}] • Identify appropriate means to set up/build on a centralised information source on all upcoming licensure and phase IV trials[{B}] • Develop an agreed minimum site audit template and/or develop a shared Trial Site Audit service[{B}] • Determine ways to develop an African-based CRO to provide contract staff for clinical trials, including experienced staff and a pool of more junior staff, to mitigate large employment swings at sites[{B}] • Determine how to develop resistance monitoring using both bioassay (susceptibility) tests and genetic methods[{C}] • Determine why discrepancies between urban and rural areas, and between wealth quintiles, exist in the uptake of intermittent preventative treatment (IPTp) among pregnant women in some countries, and how the approach for a more equitable scale-up of IPTp can be replicated in other countries[{C}] • Determine how to expand the new strategy targeting the diagnosis and treatment of malaria, pneumonia and diarrhoea at community levels termed integrated community case management (iCCM) of childhood illness[{C}]

R&D Areas	MALARIA	
	Goal	***R&D Priorities for Achieving Goals***
	settings[C] • Determine how to address gaps in knowledge regarding effective insecticide resistance management methods[D] • Create a defined system for evaluating the evidence for new forms of vector control[D] • Develop a toolkit that allows for effectiveness decay analysis for identifying bottlenecks for effective coverage of malaria interventions and decisions on the degree of integration of interventions into existing and strengthened health systems[E] • Determine how to integrate new approaches into the planning of elimination, surveillance, monitoring, and evaluation, and to create appropriate interfaces for different user communities[E] • Develop an essential platform for studying the biology of the liver stages and sexual forms of these parasites[E] • Perform systems analyses of transcription, proteome, and metabolome libraries, rapid screening of drug libraries, high-throughput approaches to antigen identification, and the functional definition of gene products[E] • Research health systems' readiness to optimize novel programs, systems, tests, or other interventions, and their continuing performance[E] • Develop a decision-making framework to guide the move from control to	• Conduct research to measure the impact of resistance on the effectiveness of vector control [D] • Perform small-scale trials to assess the relative effectiveness of resistance management strategies in delaying the emergence of resistance and killing resistance vectors[D] • Explore the formation of the WHO's proposed "vector control advisory group" for making recommendations on new vector control tools for public health purposes. [D] • Find ways to update the malaria monitoring and evaluation framework to include transmission reduction[E] • Develop key data elements for a surveillance system from a systematic review of previous elimination attempts[E] • Identify appropriate program time points for introduction of malaria infection detection in active or passive modes[E] • Develop information systems to monitor malaria infections, facilitate timely local program decisions and responses to reduce transmission[E] • Develop methods, indicators, and shareable databases for parasite strain information to better track transmission[E] • Develop methods for accessing and tracking population movements and quantifying their contribution and risk of malaria transmission[E] • Explore how maps can be constructed to:[E] o Show the probability of a threshold of transmission being exceeded; o Incorporate a wider range of metrics such as serological and entomological data; and o Assess cost-effectiveness of national stratification initiatives based on remotely sensed satellite data[E] • Perform a systematic review to assess and compare metrics of malaria transmission at near zero transmission levels, research the validity of novel metrics to measure transmission at near zero levels, and to measure transmission potential within areas where transmission has been eliminated[E] • Assess the precision, bias, feasibility, and cost-effectiveness of novel sampling methods for routine monitoring of present and past infections in target populations, including mobile populations[E] • Develop and assess the utility of biomarkers such as DNA-based methods or

R&D Areas	MALARIA	
	Goal	***R&D Priorities for Achieving Goals***
	elimination [E] • Investigate the performance of surveillance, monitoring, and evaluation by new and old technologies and to evaluate optimal strategies for implementation of surveillance as an active responsive intervention to further reduce transmission[E] • Determine how to build research capacity in endemic countries[F] • Conduct focused research effort on methods, technologies and associated platforms[F] • Develop bio-informatic tools and databases for vectors and transmission.[F] • Develop relevant platforms for functional annotation and validation of vector gene sequences[F] • Develop novel applications for currently available tools[F] • Determine how to scale up interventions for large-scale impact, accommodating for regional / local considerations[F] • Better understand the link between malaria and activities in other industries[G] • Develop new mechanisms and pathways to ensure the urgent approval of neglected tropical disease drugs in developing countries[J] • Determine how to increase access to malaria diagnostics[L] • Investigate how to strengthen the management of fever more broadly to maximize the public health impact of	serology as monitoring and evaluation and surveillance tools[E] • Determine how to expand research capacity through training, research and laboratory infrastructure, GCP standards, general institutional capacities, and strong national regulatory environments[F] • Design an open access library of compounds with known parasitic activity for academic research purposes[F] • Develop systems for recombinant expression of malarial proteins for structural and functional analysis[F] • Determine how to create natural product depositories, recombinant protein and production facilities, and processing facilities for support of molecular target specific screening programs[F] • Perform studies to address operational issues (e.g. detection of asymptomatic malaria carriers; the effective and timely elimination of the parasites by ACT; ensuring access to ACTs to all community members; optimal combination of ITNs and IRS; social and economic developments needed to improve crucial sanitation and housing conditions; the development of leadership for malaria control, building on trust, values and local empowerment[F] • Assess the impact of malaria interventions on the performance and sustainability of community-based health care systems to be recruited for scale-up for all age groups[F] • Design a public portal to facilitate decision-making by the malaria research, control, and tool development communities[E] • Conduct research to better understand timing for scaling back of prevention efforts[G] • Determine the economic benefits of sustaining malaria control to the agricultural sector and tourism[G] • Determine how to create centers of regulatory excellence in African subregions[J] • Determine methods to provide automatic WHO prequalification for novel neglected disease products[J] • Find ways to include regulators from endemic countries in regulatory reviews of neglected disease products[J] • Determine how to select Western medicines regulatory agencies to review prequalification decisions[J] • Determine ways to overcome factors that obstruct access to testing, e.g.

R&D Areas	MALARIA	
	Goal	***R&D Priorities for Achieving Goals***
	tests[L] • Develop strategies for rapidly interpreting malarial surveillance data and translating it into public health action[L] • Develop strategies to ensure quality preparation and interpretation of RDT results in field settings[N]	unaffordable prices, limited awareness, little incentive for the private sector to offer testing, local regulatory and policy issues, and a need for extremely user-friendly test formats and packaging appropriate for the private sector[L] • Evaluate existing protocols for fever management, commence studies to investigate the common causes of fever, review treatment options for non-malaria fever, and possibly demand new diagnostic technologies that assist with the differential diagnosis of fever[L] • Design training programs for health workers with limited training and supervision in endemic countries[N] • Investigate how to plan beyond rational procurement to ensure consistent supplies of all necessary materials (including gloves, sharps disposal containers, and supplies required for further case management), training of end-users, community sensitization, and monitoring of diagnostic quality and results[N] • Identify ways to improve the management of other febrile diseases and health service delivery systems with an integrated approach with other health programmes impacting on the management of febrile illness[N]
INNOVATIVE FINANCING	• Identify ways to encourage and secure investment in malarial vaccine development and severely underfunded pools for diagnostic R&D[A],[B] • Determine how to provide a clearer picture of the malaria funding gap[B] • Find ways to increase and sustain funding for basic malaria control and vaccine research to avoid shrinkage of the clinical portfolio over time[B],[G] • Identify ways to direct investments towards novel malaria technology platforms[B] • Investigate how immunogenic adjuvants can be made more accessible to all malaria vaccine developers[B] • Examine new ways to make existing funds stretch further by increasing the value for	• Identify ways to ramp up funding to $220–230 million per year from 2016 and beyond to fund late-stage trials of the anticipated second-generation *P. falciparum* vaccine, as well as early preclinical work associated with transmission-blocking vaccines, vaccines for pregnant women and candidate vaccines targeting both *P. vivax* and *P. falciparum*[A] • Design a donor coordination exercise to collate information on their collective forward funding commitments and assess against likely costs[B] • Determine ways to encourage greater pairing of industry innovators with public malaria researchers to develop joint projects[B] • Evaluate incentives or policies that could encourage relationships between public and academic vaccine developers and industrial facilities to cut learning curve times, ensure expertise is maintained and facilitate technology transfer[B] • Investigate biotech-relevant policy and incentive options for groups trying high-risk, high-innovation approaches[B] • Design incentives to encourage biotechs wishing to test out novel technologies or constructs to collaborate with well-established product-developers who have the technical skills and experience to make the technology feasible[B] • Explore ways to enhance public-private collaborations to improve manufacturers’

R&D Areas	MALARIA	
	Goal	***R&D Priorities for Achieving Goals***
	money of malaria commodities and the efficiency of service delivery[C] • Determine how to leverage resources from different industries for drug development purposes[F],[G] • Develop methods to monitor cost-effectiveness of interventions[F] • Identify ways to ensure sustained, predictable financing for malaria[G] • Identify alternatives to donor financing and diversify the funding pool by broadening the number of donors[G] • Find ways to reduce reliance on increased financing for malaria control by identifying and capitalizing on programmatic efficiencies[G] • Explore innovative financing and fund management mechanisms and improve coordination for sustaining malaria control[G],[H] • Determine how to integrate the private sector into the poverty-related neglected disease R&D landscape[H] • Determine how to improve coordination efforts between funders and researchers to jointly develop product development portfolios[H] • Identify the right balance of funding between product development and basic science[H] • Determine how to align efforts of aid organizations and science and technology agencies[H] • Develop means to increase the availability	access to potent adjuvants[B] • Investigate possible funding streams for contracted industry input to public candidates, e.g. by leveraging the existing manufacturing expenditures through the proposed Industry R&D Facilitation Fund[B] • Find way to incentivize investments in infrastructures or centres of excellence that are accessible to academic bodies and possess state-of the art facilities[F] • Find ways to promote interdisciplinary research including academia, industry and Public Private Partnerships[F] • Determine how to promote collaboration between regulatory agencies to bring antimalarial drugs to market quicker[F] • Determine ways to foster novel domestic resource streams for malaria control, e.g. assess the potential funds generated from tourist taxes, community health insurance schemes, prize-linked savings, modifications to national tax codes, endowment funds, and National Health Solidarity Funds[G] • Create new mechanisms to improve the predictability and quality of financial resources, e.g. trust funds[G] • Evaluate and consider widely adopting the Cash on Delivery (COD) aid approach wherein donors reward countries by tying continued financing to the maintenance of low malaria prevalence[G] • Define the most cost-effective mix of interventions between surveillance and targeted prevention (ITNs and IRS) [G] • Examine ways to reduce the prices of ITNs and insecticides through more effective procurement and negotiation[G] • Identify key product development partnerships (PDPs) to engage talented researchers in private industry[H] • Determine how to reduce restrictions on funding requirements to ensure that the best research candidates are prioritized (under the EU 7th Framework Programme) [H] • Determine how to streamline administrative processes to expedite funding flows to reach researchers[H] • Evaluate the potential for pooled funding mechanisms to encourage collaboration[H] • Evaluate how changes to policies could encourage local production of medicines to treat neglected diseases[I]

R&D Areas	MALARIA	
	Goal	***R&D Priorities for Achieving Goals***
	of information on the quality of malaria diagnostics (including development of technologies to simplify quality control testing), reinforce competition around quality, ensure consistency during manufacturer scale up, and assure the integrity of tests in the field[{M}] • Identify strategies to stabilize prices of RDTs and improve predictability of demand[{M}] • Find ways to draw funding for interventions that support RDT implementation, e.g. health worker training, supervision[{M}] • Develop the private sector market for malaria RDTs and determine how to expand access to testing and improve targeting of ACTs in the private sector[{M}] • Identify ways to increase funding for product development for underserved populations, including pregnant women, populations living in low transmission settings, and populations affected by *P. vivax*[{M}] • Develop mechanisms to strengthen market knowledge[{M}]	• Utilize technology transfer and licensing agreements to promote local drug production[{I}] • Determine how to create new product development public-private partnerships (PDPPPs) [{I}] • Determine how to engage companies in using preferential pricing arrangements[{I}] • Determine how to leverage philanthropic donations to strengthen national pharmaceutical innovation systems[{I}] • Determine how to expand access to treatment through intergovernmental organization-sponsored buyer co-payments[{I}] • Determine how to engage venture capitalists to invest in neglected disease R&D[{I}] • Generate neglected disease data that can be cross-applied to core commercial compounds[{K}] • Identify PPPs that are willing to commit to a long-term funding mechanism (entirety of R&D process) [{K}] • Determine how to collaborate with industry partners that will contract with PPPs to develop drugs for neglected diseases[{K}] • Find ways to incentivize greater funds from G8 countries to create the IRFF[{K}] • Determine how to provide shared platform services to PPPs (e.g. legal, human resources, etc.)[{K}] • Determine how to create a central clearinghouse for information regarding: targets or compounds related to neglected disease research, funding sources, and services and skills offered[{K}] • Identify new, innovative public-private partnerships (PPPs) for drug development, and create policies to encourage PPPs[{K}] • Determine how to offer support to PPPs in negotiating industry deals[{K}] • Create and assess how an industry R&D fund (IRFF) might underwrite industry participation in PPPs[{K}] • Evaluate how the provision of PPP-sponsored start-up funds to new small companies might influence their investments in neglected disease R&D [{K}] • Identify strategies to sell “fast-track” regulatory review of commercial drugs to finance neglected disease R&D[{K}] • Investigate options to award prizes to multinationals who invest in neglected disease drug development, and how such incentives affect total industry investment in R&D [{K}]

R&D Areas	MALARIA	
	Goal	***R&D Priorities for Achieving Goals***
		• Find ways to reduce financial obligations on patent and maintenance fees{K} • Develop quality control technologies for use at all levels of the supply chain from manufacturer to point of service{M} • Determine how the WHO Product and Lot Testing program can be transitioned into a less costly and more sustainable business model{M} • Develop stronger incentives for upstream quality assurance, e.g. site visits, stepped-up lot testing, or changes to the WHO Product Testing program{M} • Find ways to encourage buyers to focus on quality and product characteristics, as opposed to price alone{M} • Strategize how interventions can be structured with frequent evaluations and flexibility to incorporate new learning{M} • Determine how to reinforce the data on the availability of testing and use of results{M} • Find ways to improve the completeness of data on RDT procurement {M} • Determine how to enhance efforts to collect and synthesize information on the private sector markets{M}

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.

Synthesis of Disease-Specific R&D Priorities for Tuberculosis

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
BASIC SCIENCE	• Intensify TB-specific biomarker research, and validate TB-specific biomarkers for active TB disease in children and adults to assist in the production of diagnostic tests for clinical use[{A},{B},{F},{G},{H},{J}] • Identify biomarkers that can predict cure, treatment efficacy and failure, and relapse[{F},{H}] • Identify specific single biomarkers or combinations of biomarkers that can distinguish latent tuberculosis infection versus subclinical versus active tuberculosis disease; identify those who are at highest risk for progression to disease; and predict protective immunity[{H},{J}] • Better understand the interaction between the bacillus and the human host[{B},{C},{H}] • Delineate the specific mechanisms of protective immune networks between people (host) and *M. tuberculosis* (pathogen)[{H}] • Better characterize *M. tuberculosis* to refine understanding about the transition from latent to active TB and identify the biomarkers of disease progression[{B},{C},{H}] • Understand why prolonged antibiotic treatment is needed[{B}] • Develop new molecules with novel ways of inhibiting or killing the TB bacteria[{F}] • Better define the profile of desired characteristics (ie, target product profile) for key biomarker research areas[{H}]	• Identify a group of biomarkers that could be used for a simple diagnostic test within five years[{A},{B},{G}] • Pursue proteomics research to identify a set of proteins or biomarkers specific for TB that could lead to a serum-based antigen detection assay for the diagnosis of TB metabolomics,[{A}] treatment response and sterilizing activity[{B}] • Determine why certain individuals infected with *M. tuberculosis* are resistant to TB disease[{B},{J}] • Identify new targets for anti-TB drugs and early indicators of protective immunity for vaccine efficacy[{B},{J}] • Learn what constitutes protective immunity in different age groups and populations against TB[{J}] • Identify the respective components of the host's immune system and of the pathogen that are responsible for elimination of *M. tuberculosis* or for preventing reactivation of latent TB infection[{C},{J}] • Understand mechanisms leading to persistence or elimination of bacilli in various conditions (e.g. according to age or HIV infection) for the identification of drug targets[{C}] • Better characterize the interaction of *M. tuberculosis* with the immune system during the phases of progression from infection to disease[{C}] • Investigate role of mucosal lung immunity in addition to systemic immunity[{C}] • Identify bacterial and/or host biomarkers (or combinations of biomarkers) that will help distinguish the stages of TB and allow accurate identification of patients at various levels of the disease spectrum between latent and active TB[{C},{D},{E}] • Elucidate the design of systems biology models of *M. tuberculosis* metabolism and physiology to facilitate modern cell and target-based drug discovery[{C}] • Identify biomarker(s) that measures medicine activity in real time or can predict whether a medicine or regimen will result in a stable cure for a patient[{F}] • For biomarkers that are non-culture-based, find ways to increase the availability of well characterised biobanks containing bio-specimens from patients who have had adequate follow-up to establish long-term treatment outcome and better qualify biomarkers as a surrogate for a clinical endpoint[{H},{J}] • Identify correlate or surrogate endpoints of protective immunity[{J}]

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
	• Strategize how to maximise and optimise biomarker research through coordination and increased collaborations between basic scientists, clinical triallists, pharmaceutical industry and end users[{H}] • Determine how to validate new biomarker discoveries and translate new biomarker discoveries into functional point-of-care use[{H}] • Find ways to obtain better data about the molecular immune mechanisms of resistance —and the correlation of those mutations with clinical outcomes—for the development of drug susceptibility testing (DST) assays and vaccines[{I},{J}]	• Conduct full synthesis studies on the role of month 2 culture status as a biomarker predictor of required duration of treatment[{H}] • Determine the optimum methods for specimen collection (pooled over 12–16 h *vs* spot) and processing (decontamination with sodium hydroxide variably decreases mycobacterial viability) for automated liquid culture systems used in biomarker development[{H}] • Conduct studies on the ability to resuscitate or recognise live but dormant non-replicating bacilli and mechanisms behind relapse to improve existing culture-based detection systems[{H}] • Conduct further studies of lipoarabinomannan as a candidate biomarker[{H}] • Explore changes in tuberculosis-specific gene and protein expression profiles (transcriptomics) as potentially viable in assessing of the early response to tuberculosis treatment[{H}] • Investigate the prognostic significance of resuscitation-promoting factors in the detection of otherwise non-culturable mycobacteria in sputum[{H}] • Explore the measurement of host gene expression profiles as biomarkers of treatment efficacy, and if this method could provide more information about clinical outcome than would quantitative sputum microbiology[{H}] • Conduct prospective longitudinal studies of MicroRNA and metabolomic patient profiles as potential indicators of TB cure and reactiviation[{H}] • Conduct further studies of bactericidal or viral neutralisation assays after vaccination in people in tuberculosis-endemic regions to assess the potential correlation with clinical outcomes[{H}] • Pursue cross-sectional studies of close tuberculosis contacts without HIV with minimally symptomatic subclinical disease that could provide important information about candidate biomarkers[{H}] • Determine how to scale up the translational science needed to provide the basis for molecular diagnostics development[{I}] • Find ways to link gene mutations to phenotypic resistance (ie, the amount of drug needed to inhibit bacterial growth) using translational sciences research[{I}] • Develop strain collections (preferably sequenced) that will assist with the testing of new diagnostic assays and the development of genomic databases that would predict drug susceptibility phenotypes[{I}] • Gain a more thorough understanding of the very earliest events of infection with

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
		Mtb and their consequences[J] • Better understand and characterize the antigens involved in Mtb host immune evasion mechanisms[J] • Conduct genome-wide host gene expression profiling studies that can point to novel host biomarker signatures of both protective immunity and disease activity, identify potential correlates of protection, and also unravel cellular pathways involved in the pathogenesis of and resistance to Mtb[J] • Explore novel (high risk) approaches using immunological, transcriptional and other biological state-of-the-art technologies to identify correlates of immunity for tuberculosis[J]
DIAGNOSTICS	• Develop a rapid low-cost, accurate, user-friendly, specific and highly sensitive point-of-care (POC) diagnostic test[A],[B],[C],[E],[F],[G] • Simplify and improve detection of TB cases using rapid, non-sputum based POC test for the diagnosis of extra-pulmonary TB (EPTB), smear-negative and childhood/pediatric TB [A],[C],[E] • Determine ways to reliably identify latent TB infection and determine the risk of progression to active disease to enable the rational use of preventative therapy[A],[C],[E] • Develop a simple-to-perform, improved rapid molecular DST assays for first- and second-line drug resistance [A],[B],[E],[G] • Design tests that can be performed at the point-of-care level of the health care system and that produce quick results on the same day[A],[B],[C],[E] • Develop cost-effective, patient-centred applications on common technology platforms appropriate to different tiers of developing country health systems[A] • Design tools to improve the diagnosis of	• Identify ways to improve specificity of tuberculin skin tests for use in endemic countries[A] • Develop IFN-gamma release assays that can distinguish between latent and active TB[A] • Determine how to improve sputum sample treatment procedures for all new methods of direct assay microscopy[A] • Design an improved sputum preparation process for Antigen detection, point-of-care tests and 16S rRNA testing[A] • Determine how to adapt liquid chromatography methods for use in TB diagnostics[A] • Determine how to simplify nucleic acid amplification tests to reduce technicians' workloads[A] • Design tools that utilize molecular assays to detect gene mutations[A] • Identify ways to extend line probe assays towards the detection of quinolone resistance and made more user-friendly[A] • Develop a simple and inexpensive test with at least as good a detection limit as direct microscopy 1x 104 bacteria/ml for Antigen detection, point-of-care tests and 16S rRNA testing to reduce the workload of laboratory personnel[A] • Develop successful "E-nose," urinalysis and breath analysis technologies for use in detecting TB[A] • Explore a low-cost, accurate, rapid and non-invasive technique (e.g. analysis of breath or exhaled breath condensate) to greatly assist in the TB diagnosis among children[A],[C] • Develop an indirect assay antibody detection point-of-care test that uses a simple

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
	drug-susceptible and drug-resistant TB[{B}] • Identify ways to improve diagnostics to predict disease progression and rapidly screen and diagnose MDR- and XDR-TB, and HIV-associated TB[{C}] • Develop urgently needed POC TB diagnostic tools that can be used in peripheral health-care settings[{C,},{D},{E}] • Develop tools that can diagnose TB in children[{D},{F}] • Develop a rapid 'rule-out' or triage test, especially for TB-HIV co-infection in high burden settings[{E}] • Find ways to gain consensus on which target product profile (TPP) attributes will have the biggest impact on reducing the incidence of TB in disease-endemic countries, and which meet clinical and practical needs[{E},{I}] • Investigate the clinical and programmatic effects and cost-effectiveness of the Xpert MTB/RIF assay[{G}]	ELISA or lateral flow format as an ideal test[{A}] • Develop second- generation Xpert assays and possible alternative molecular technologies[{B}] • Investigate ways to combine existing and new diagnostics to optimize the detection of various forms of TB, including drug-sensitive, drug-resistant and latent TB infection, in diverse population settings[{C},{D}] • Identify combinations of methods for collecting useful specimens from children[{C},{D}] • Identify a systemic marker of bacterial load in TB[{C},{D}] • Investigate the performance of all fast follower NAATs to better understand the potential application of these tools for TB diagnosis in low-resource settings[{E}] • Develop methods to ensure that the performance of highly-sensitive NAATs is not compromised by manufacturing, transport, storage, the environment, or the user[{E}] • Develop urgently needed standardized external quality assurance (EQA) devoted to the Xpert® MTB/RIF and fast-follower NAATs to ensure adequate performance of equipment and users via uniform standards[{E}] • Find ways to ensure that EQA panels for Xpert® MTB/RIF assay seek fulfillment of the following elements: o (i) testing material must contain whole *M. tuberculosis*; o (ii) transportation of EQA material must be safe; o (iii) testing procedures must be compatible with the current Xpert® MTB/ RIF testing protocol; o (iv) health care workers who do not have laboratory skills must be able to perform the EQA testing in non-laboratory settings; and o (v) the EQA program must be cost-effective and sustainable[{E}] • Determine whether new fast follower NAAT tests fit with current TB diagnostic algorithms and if they can be successfully implemented in peripheral microscopy laboratories in high burden countries[{E},{I}] • Identify which types of sample preparation/processing methods allow for truly decentralized implementation at the microscopy center level[{E}] • Determine the acceptable trade-off between higher throughput and lower cost NAATs vs. more manual involvement on the other as compared to partially integrated assays with higher cost per test but reduced needs for user input[{E}]

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
		• Determine how appropriate quality control procedures for test integrity can be developed for and maintained in peripheral facilities with minimal oversight from National Tuberculosis Programs (NTPs)[{E}] • Determine the tolerance of test hardware to excessive heat, humidity, and dust[{E}] • Identify if the fast-follower NAATs can be made more affordable and cost-effective compared to the Xpert® MTB/RIF assay given the recent price reduction of the GeneXpert® technology[{E}] • Conduct case studies of successfully scaled-up tests and pragmatic trial results, incorporating their features into new test TPPs[{E}] • Utilize patient, clinical and user assessments to identify tests that meet perceived needs[{E}] • Investigate mathematical modeling to explore the likely impact of various TPPs on reducing TB incidence[{E}] • Find ways to ensure that the most critical elements evaluated in POC testing are rapid turn-around and communication of results to guide clinical decisions and completion of testing and follow-up action in the same clinical encounter (or at least on the same day)[{E}] • Determine how POC testing can fit within real-world workflow patterns and economic/incentive structures to ensure use and sustainability[{E}] • Determine whether Xpert® MTB/RIF implemented in centralized/reference laboratories will have an impact on reducing diagnostic and treatment delays[{E}] • If Xpert® MTB/RIF is mostly used for drug-resistance screening or for smear-negative TB, determine if it will have an impact on TB transmission and incidence[{E}] • Investigate whether implementation of Xpert® MTB/RIF and newer NAATs in a passive case detection approach reduce patient delays in seeking care, and the role of these technologies in intensified and active case finding[{E}] • Determine whether NAATs be successfully implemented at the point-of-care to enable same-day TB diagnosis and treatment (i.e. a “test and treat” approach[{E}] • Develop a protocol whereby sputum samples are pretreated to prevent the DNA in non-viable organisms being amplified during PCR[{G}] • Assess the ability of the Xpert MTB/RIF assay to diagnose HIV-associated tuberculosis through urine sample testing on different populations[{G}] • Investigate whether the Xpert MTB/RIF assay might enable active tuberculosis

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
		screening to be done within antenatal clinics in high tuberculosis burden settings{G} • Investigate whether Xpert MTB/RIF assay's new software and cartridge combination, G4, improves line-probe assays concordance with rifampicin resistance{G} • Explore the potential for fully automated NAAT systems that use isothermal amplification and operate at lower temperatures to be used outside the laboratory environment{G} • 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} • Test the viability of the rifampicin DST to diagnose MDR tuberculosis{I} • Investigate isoniazid DST as a means to detect isoniazid-resistant, rifampicin-susceptible strains, whose patients have reduced treatment success{I} • Study DST to detect susceptibility to rifampicin and fluoroquinolones for implementation of 4-month regimens, especially in countries that already do DST for rifampicin{I} • For the PaMZ regimen, develop a rapid test for moxifloxacin and pyrazinamide because clinically significant resistance to PA-824 has not yet been shown{I} • Develop DST for PA-824 and other new drugs for use in surveillance as resistance to them develops and their use becomes more widespread{I} • Better characterize silent mutations by standardised and validated culture-based pyrazinamide resistance assays and incorporate findings into a molecular testing algorithm{I}
DRUGS	• Develop shorter TB regimens to cure all forms of TB that are safe, compatible with ART, effective against latent tuberculosis infection, affordable, easily managed in the field and that remain effective by limiting the development of drug resistance{B},{C},{F} • Develop pediatric medicine formulations for children of all ages{B},{C},{F},{I} • Find ways to obtain better data on how best to use current medicines, especially in	• Determine how to improve the efficacy and tolerability of treatment for MDR-TB{B} • Identify optimal treatment regimens for all TB patient types, including TB-HIV co-infection and infected children{B},{C},{I} • Investigate how to treat latent TB infection in people without active TB disease{B} • Determine optimal dosage, safety and efficacy of new drugs and their interaction with other TB and non-TB drugs{C},{I} • Identify new anti-TB drugs that are fully compatible with ART for the treatment of HIV–TB co-infection{C} • Investigate the interaction between first- and second-line drugs and antiretroviral

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
	patients co-infected with HIV and in children[F] • Investigate the drug-drug interactions of TB medications with treatments for other diseases or conditions, particularly with ART and opioid substitution therapy (OST) for drug-resistant TB (DRTB)[F] • Find ways tp enhance treatment cure rates for MDR-TB and XDR-TB[F] • Conduct urgently needed research into whether delamanid and bedaquiline can be safely and effectively co-administered, as they are the two novel TB medicines furthest in development to treat people with MDR- or XDR-TB[F] • Find ways to ensure joint development and implementation of new tuberculosis regimens and new DST assays for enhanced clinical performance[I]	agents[C] • Determine the best methods to test and identify optimal combinations of drugs early enough in overall drug development[C] • Investigate how to reduce side effects and pill burden for patients co-infected with HIV[F] • Conduct more randomized, controlled clinical studies to explore options that enhance cure rates for MDR-TB and XDR-TB[F] • Determine how to obtain research evidence that can guide clinicians in determining appropriate TB treatment for children under five, especially for those with DR-TB[F] • Tailor pediatric fixed-dose combination (FDC) formulations to deliver the dosages suitable to treat DS-TB in children[F] • Determine how to include children in studies of second-line medicines (SLMs) so clinical trial data are able to inform the use of these medicines in children[F] • Determine whether self-administered once-weekly rifapentine and isoniazid regimens with shortened duration actually improve adherence and cut costs by reducing patient visits, staff time, and number of pills in practice, particularly in high-burden countries[F] • Develop second-generation compounds with better activity and better safety profiles than their predecessors[F] • Develop child-friendly treatment formulations so pharmacokinetics (PK) studies of new compounds and SLMs can be initiated[F] • Conduct pediatric PK studies to identify the therapeutic dose needed based on the absorption, metabolism, distribution, and excretion of the medicine based on child age and stage of development[F] • Clarify the data and regulatory pathway on how best to combine more than one new compound to come up with a new regimen in a clinical trial[F] • Conduct post-marketing studies to identify treatment failures and resistance mechanisms of new TB drugs[I]
VACCINES	• Develop a more effective vaccine to supersede the BCG vaccine[B],[J] • Develop a safe, effective, affordable vaccine to prevent all forms of TB in all age groups and that is safe for people with HIV	• Determine the immune-dominant antigens associated with different metabolic states of *M. tuberculosis* to be added to vaccines to increase protection[C] • Identify much-needed markers and correlates of immune protection to assist in the selection of next generation vaccine candidates[B] • Determine whether TB vaccines can effectively reduce the transmission of *M.*

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
	and other forms of immunosuppression[C],[J] • Identify correlates of immunity and biomarkers for TB vaccine development[J] • Design a vaccine that elicits a response that is superior to natural immunity induced by infection with Mtb[J] • Explore the potential for developing a transmission-blocking TB vaccine[J] • Determine how to build and engage in collaborative efforts to advance the use of novel adjuvants for TB vaccines[J] • Determine how to establish comprehensive, measurable and globally acceptable criteria for selecting, assessing and advancing the best vaccine candidates in human clinical studies[J] • Find ways to increase the profile of TB vaccine research at global, national and community levels in order to generate support and political will, to increase investment in TB vaccine research, to create an enabling and supportive environment for clinical trials, and to lay the groundwork for acceptance and adoption of new TB vaccines once licensed[J] • Determine if vaccines can prevent infection and provide sterilizing immunity[J]	*tuberculosis*[B] • Identify novel model systems for preclinical and clinical testing of TB vaccines, including pre- and post-exposure models and models that mimic reactivation[C] • Determine the respective roles of innate and adaptive immunity in preventing *M. tuberculosis* infection and reactivation of latent disease and better understand immune responses against different metabolic stages of the pathogen in different populations[C] • Develop improved vaccines for prime–boost vaccination strategies and determine their optimal conditions of use, e.g. duration of intervals, boosting dose and number of boosts[C] • Better understand the immune response to BCG and new vaccines[C] • Identify and standardize assays to assess vaccine-induced immunogenicity to allow better comparison of candidate vaccines[C] • Develop new animal and human challenge models and objective criteria for down selecting vaccines for the various target profiles, especially vaccines preventing reactivation of latent *Mycobacterium tuberculosis* (Mtb) infection[J] • Utilize innovative research approaches to gain a better understanding of TB immunology, microbiology, pathology, molecular biology and vaccinology[J] • Integrate creativity in R&D via the following strategies:[J] o Use out-of-the-box approaches and advanced technologies to identify mechanisms of protective immunity for tuberculosis[J] o Expand the antigenic vaccine repertoire and introduce new antigen combinations to prevent infection and provide sterilizing immunity[J] o Facilitate translational research, comparative preclinical studies and animal models that mimic human TB disease[J] • Explore antibody-mediated mechanisms for transmission blocking vaccines development[J] • Explore and expand the glycolipid and polysaccharide repertoire of Mtb vaccine development[J] • Investigate the use of non-conserved, sequence variable antigens of Mtb which could prove to be conformationally conserved in the design of vaccines, particularly live whole cell vaccines[J] • Investigate the use of stage specific, less dominant, and more sequence variable antigens recruiting novel populations of immune cells for use in adjuvant

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
		development{J} • Identify new or better animal models that enable assessment of protective responses for specific human target populations (including natural infection) and for defining correlates of protection, e.g. promising cattle and pig transmission models{J} • Determine how to standardize existing animal models {J} • Explore applications of new technologies for measuring vaccine responses in animal models such as modern imaging technologies{J} • Identify ways to utilize circulating human clinical isolates as challenge strains in preclinical models {J} • Develop and adapt models for vaccine submissions to regulatory agencies to address issues of safety, immunogenicity and effectiveness required for regulatory approvals {J} • Find ways to learn from experimental failures by publishing data or making it available through information sharing mechanisms {J} • Develop methods to learn from the successes and failures of others, especially those researching malaria, HIV and cancer vaccines{J} • Discover biomarkers that predict vaccine efficacy, that serve as useful markers of vaccine success, that correlate with natural protection and susceptibility, as well as markers that correlate with disease risk following infection{J} • Further investigative and identify biomarkers that are associated with disease progression or remission, e.g. longitudinal assessment of a range of clinical markers can provide a sensitive and specific indicator of vaccine effects through modulation of the disease state{J} • Find ways to introduce novel assays into vaccine trials to establish a surrogate of protective immunity{J} • Identify signatures of efficacy that can be used as readouts for induction of protective responses in TB vaccine studies{J} • Find ways to improve clinical capabilities for testing novel TB vaccines in all age groups, in individuals infected with Mtb and/or HIV and in BCG vaccinated persons in a cost effective manner in difficult environments in endemic countries{J} • Find ways to develop innovative partnerships, sharing of sites, harmonization of endpoints and other clinical trial parameters and mechanisms for acquiring

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
		efficient regulatory review of trials[{J}] • Determine TB prevalence and incidence, select trial sites and choose target populations for TB vaccines that result in the greatest reduction in disease[{J}] • Design clinical trials with appropriate endpoints for determining an acceptable efficacy for TB vaccines in different target populations[{J}] • Determine ways to address regulatory and ethics issues and plan for post-licensure sustainability in developing countries[{J}] • Conduct efficacy trials that target HIV negative adolescents/adults given that they have higher rates of TB, they are important targets for mass vaccination campaigns and clinical endpoint definitions will likely be much clearer [{J}] • Define large, global networks that would aim to conduct specific types of trials for promising vaccine candidates to overcome barriers of testing in a single location[{J}] • Determine how organizations performing clinical studies in areas endemic for infectious diseases can best share trial site infrastructure to expedite clinical trials of vaccines[{J}] • Target infants for replacement and prime-boost vaccine development, and conduct accurate assessments of efficacy in this group[{J}] • Explore adaptive trial designs that can drop ineffective or reactogenic candidates, or modify group sizes based on predefined criteria to accelerate the clinical development of a vaccine[{J}] • Develop creative strategies for obtaining timely regulatory approvals while assuring the quality of the review and protecting clinical subjects[{J}] • Identify how to engage regulatory authorities early in the development process so that sponsors can receive advice from regulators on clinical trial design, endpoints and ethical issues[{J}] • Conduct post-marketing surveillance to assess the potential for rare adverse events [{J}] • Determine ways to establish mechanisms for assuring the sustained quality of TB vaccines following marketing authorization and distribution[{J}] • Determine how to perform head to head candidate comparisons within agreed upon model systems to help decision making in the candidate selection process[{J}] • Develop robust critical assessment of vaccine product characteristics [{J}] • Explore standardizing assays among laboratories evaluating clinical specimens or use of a centralized laboratory to enable comparison among different

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
		candidates[J] • Find ways to obtain consensus within the TB community on stage-specific criteria for moving new candidates through various stages of development from research to preclinical and through subsequent phases of clinical trial testing[J] • Determine can investigators can cooperate to combine new Mtb antigens with novel adjuvants to develop the best TB vaccines[J] • Determine if antibody responses to TB vaccines are relevant to protection[J] • Identify the best clinical strategies for showing that vaccines can effectively prevent the reactivation of latent TB disease[J] • Identify the best strategies for studying therapeutic TB vaccines[J]
EPIDEMIOLOGY	• Utilize epidemiological research to close the gap between notified cases and estimated TB incidence[B] • Investigate ways to improve the measurement and estimation of TB incidence and mortality among children[B] • Determine which sources of data should be used to establish TB incidence rates[J] • Determine whether the number of MDR-TB cases is increasing, decreasing or stable[B] • Find ways to expand current knowledge of the distribution and natural history of TB, especially the roles of its various determinants, to improve control activities, influence policy-making and ensure more efficient and effective methods of service delivery[C]	• Conduct systematic literature reviews of existing data on incident childhood TB, under-reporting of TB in children and misdiagnosis[B] • Determine how to expand case-based electronic recording and reporting systems that would facilitate compilation and analysis of aged is aggregated data[B] • Design nationwide inventory surveys to measure under-reporting of childhood TB[B] • Develop strategies to collect age-specific data from sample VR systems and mortality surveys in high-burden countries including China, India and Indonesia[B] • Determine how to provide a definitive assessment of trends in MDR-TB globally and/or regionally[B] • Conduct measurements of the burden of disease and of variations in the dynamics of TB according in specific settings[C] • Identify the causes of low case detection and treatment, especially in certain high-risk groups and settings[C] • Study variations in the dynamics of TB according to setting, and identify the effect of the germ, the host and the environment on *M. tuberculosis* transmission[C] • Understand the relative contributions of different foci of TB transmission (e.g. household, community, nosocomial transmission) at population level[C] • Identify various biological, environmental, population-based and social drivers of *M. tuberculosis* transmission[C] • Better understand the interaction between the pathogen, the host and social determinants on *M. tuberculosis* transmission in specific settings and in high-risk populations (including TB–HIV co-infected and MDR- and XDR-TB patients)[C]

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
		• Determine how to gather good quality data through epidemiological studies that can serve as a guide for planning vaccine efficacy trials, and determine how to fund such work[{J}]
PUBLIC HEALTH AND OPERATIONAL RESEARCH	• Identify ways to perform crucial needs assessments to measure the extent and nature of the problems faced by the people on whom the tests will be performed[{A}] • Determine how to ensure technology is adaptable to local laboratory infrastructure[{A}] • Determine how to best treat people with latent TB infection on a massive scale, especially in high-risk populations[{B}] • Ascertain how to best achieve mass vaccination[{B}] • Identify ways to transform sophisticated laboratory technologies into robust yet accurate point-of-care platforms[{B}] • Determine how to improve TB control programme performance and design interventions that result in improved policy-making, better implementation in health systems and more efficient and effective methods of service delivery[{C},{F}] • Identify ways to improve TB case-finding and screening, access to diagnostics, treatment access and delivery, TB-HIV programme interactions and infection control in both the general context of health services and for specific high-risk groups[{C},{D},{E}] • Determine how to decentralize and scale-up use of the automated nucleic acid amplification test (NAAT) for TB	• Determine how to integrate regular needs assessments early in the diagnostic R&D process [{A}] • Identify ways to produce *user requirements documents* as part of the needs assessments that capture detailed information on the expected performance in real-life conditions, time to results (and preferably time to treatment initiation), technical requirements, users' skills, medical algorithms within which the test is to be used and a clear description of the setting where the test is to be implemented[{A}] • Define and evaluate the performance of new diagnostic tests in terms of feasibility, cost-effectiveness, reduced diagnostic delay and impact on clinical decision-making and patient benefit[{C},{D},{F}] • Investigate methods and means to optimize TB case-finding and measure impact of intensive case-finding on mortality and other outcomes, particularly among HIV-infected populations, infants and children[{C}] • Identify the most effective TB screening algorithms[{C}] • Develop means to scale up isoniazid preventive therapy under field conditions and in HIV clinics delivering ART[{C},{F}] • Develop strategies to strengthen the links between TB and HIV control programmes at all levels of health care, with optimal integration of interventions[{C},{F}] • Identify strategies to scale-up access to MDR- and XDR-TB treatment in resource-limited settings and improve treatment outcomes, whether or not associated with ART[{C},{G}] • Study how to best integrate TB care with that of chronic diseases, with particular emphasis on diabetes[{C}] • Develop methods to expand access to treatment for vulnerable and marginalized groups by making use of private or alternative health care providers[{C}] • Determine the efficacy of individual TB infection control measures in resource-limited settings and strategies to implement, monitor and evaluate TB infection control in health facilities, communities and households[{C}] • Find ways to integrate Ministries of Health and the public and private health-care

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
	diagnosis[{D},{E}] • Develop mechanisms to ensure that product development efforts meet the real needs of TB control programs[{D}] • Find ways to ensure that TB programs adequately address preventing and treating the disease among high-risk populations, e.g. drug users and persons suffering from malnutrition, marginal housing, and poor housing conditions like overcrowding and bad ventilation [{F}] • Examine how to expand the integration of IPT with ART and place responsibility for IPT on national AIDS programs (NAPs) so TB treatment is essential to HIV management and services become more integrated[{F}] • Identify ways to increase global capacity for drug susceptibility testing (DST)[{G}] • Identify ways to support the paradigm shift towards drug regimen development, as opposed to individual medicine development, that will require regulatory agencies, research institutions, funders, policy makers, and advocates to work more collaboratively to ensure that the efficient testing and approval of new regimens is safe and maximizes resources[{F}] • Identify ways to harmonize regulatory requirements for TB treatment approval across agencies to expedite the review process[{F}] • Identify ways to increase the effectiveness of procurement mechanisms for the uptake of quality assured medicines[{F}]	sectors in informing developers as to the appropriate specifications that a product must meet to warrant effective and widespread sustained use[{D}] • Identify ways to support the implementation of GeneXpert instruments and Xpert cartridges[{E}] • Investigate how to accelerate access to Xpert® MTB/RIF in countries with a high prevalence of TB/HIV co-infection[{E}] • Consider how to train staff in peripheral microscopy centres to implement and use viable new fast follower NAATs[{E},{G}] • Develop processes to ensure quality assurance (QA) of NAAT performance is conducted before testing begins to demonstrate appropriate functionality[{E}] • Identify how the performance of minimally-supervised NAAT users can be monitored via routine proficiency testing[{E}] • Determine the appropriate regulatory and policy pathway for country-level adoption and scale-up of fast follower NAAT technologies[{E}] • Conduct clinical and public health impact evaluations of Xpert MTB/RIF at different health care levels[{E}] • Conduct operational research and cost-effectiveness evaluations of MTB/RIF[{E}] • Determine the optimal positioning of MTB/RIF in diagnostic algorithms[{E}] • Conduct qualitative and quantitative research to better understand patient health-seeking and provider behaviors in the community and elsewhere to design diagnostic technologies where early diagnosis is likely to succeed[{E}] • Find ways to scale-up operational research to map out where individuals in the population seek health care, where health care services are available, what resources (including lab capacity) exist at each level of health care, what fraction of patients with suspected TB access each level of health care (patient volumes), where TB treatment services are available, and where technology deployment is likely to capture the largest fraction of patients with TB early in the infectious period[{E}] • Utilize implementation science to understand the most important barriers to POC testing to use such data to design TPPs that can overcome delivery obstacles and health system limitations[{E}] • Determine how to best design systems for rapid reporting of diagnostic test results to care providers, and a mechanism to link test results to appropriate counseling and treatment[{E}]

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
	• Explore ways to engage civil society in greater advocacy around TB medicines to potentially positively impact forecasting efforts, the regulatory environment and procurement and distribution{F} • Explore ways to scale-up central biobanks for the provision well-characterised samples for the validation of biomarkers research{H} • Determine how to best utilize surveillance data and mathematical modelling to help country stakeholders design appropriate DST algorithms and decide whether to change drug regimens{I} • Determine how to establish existing or emerging resistance levels via surveillance data{I} • Investigate how to expand uponefforts to raise awareness of the role of new TB vaccines as part of a comprehensive response to the global TB epidemic, and build support at all levels{J}	• Determine the best strategy for deploying new diagnostics at the first point of contact among informal and private sector health providers{E} • Determine ways to scale up the implementation of isoniazid prevention therapy to treat latent TB infection (LTBI), and to get persons with LTBI to seek care{F} • Identify ways to strengthen laboratory infrastructure and mentor new investigators for TB research in mid- to high-burden countries, e.g. by developing detailed manuals translated into local languages, training, and standardization exercises to qualify the laboratories in accordance with international guidelines{F},{G} • Determine how to develop capacity for regulatory authorities to ensure that they are able to respond to trial sponsors and provide timely feedback on protocols and medicine applications, e.g. by streamlining the process for submitting dossiers to health authorities {F} • Find ways to reduce administrative delays in the application process that hinder implementation, raise the cost of studies, and may deter companies from investing in developing treatments for TB{F} • Determine how to achieve better national planning for medicines stockouts in the public sector{F} • Conduct urgently needed operational research on the clinical outcomes and effects of programmatic implementation efforts for Xpert MTB/RIF{G} • Determine the potential benefits from reduced morbidity, mortality, and disease transmission associated with appropriate delivery of TB treatment and lower rates of inappropriate therapy {G} • Strategize how national ministries of health can take a step-wise approach to introduction and scale-up of Xpert MTB/RIF, beginning with the establishment of an in-country coordination mechanism, e.g. an Xpert MTB/RIF assay technical working group or advisory team{G} • Develop Xpert MTB/RIF implementation plans that consider the local epidemiology, available diagnostic services and laboratory systems, first-line and second-line drug treatment capacity and align with relevant strategic plans (eg, national tuberculosis and AIDS control programmes and national laboratory strategic plans){G} • Conduct embedded research studies and enhance monitoring and assessment of the South African success with Xpert MTB/RIF assay implementation{G}

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
		• Find ways to match increased diagnosis of drug-sensitive tuberculosis and MDR tuberculosis with expanded capacity to effectively treat these cases, including a scale-up in quality MDR tuberculosis treatment facilities and trained staff{G} • Design rigorous quality assessment programmes for TB treatment and diagnosis to ensure results are accurate, e.g. following the South African model that used dried culture spots of inactivated *M tuberculosis* on filter paper {G} • Find ways to obtain nationally representative data on moxifloxacin and pyrazinamide resistance{I} • Identify how to scale up surveillance to monitor the development of resistance to bedaquiline, delamanid and others{I} • Find ways to inspire research collaboration within a country undertaking a drug resistance survey to pilot new DSTs and develop monitoring systems linked with treatment outcomes and patient care; such a study could provide the proof of principle and the data to validate new integrated monitoring system{I} • Determine where DST should be placed in treatment algorithms for various epidemiological and economic contexts{I} • Determine what different DST assays—with different speed, accuracy, price, and technical specifications (ie, which drugs, how many mutations)—would achieve in terms of a population-level effect and cost-effectiveness, and what the trade-offs are between these various specifications{I} • Determine the population-level effect and cost-effectiveness of different DST algorithms (eg, DST for all, DST for only patients who are being re-treated or in whom previous treatment had failed, or use of new regimens without DST) as a function of baseline drug resistance and rate of emerging resistance{I} • Determine whether DST is better bundled into case-detection assays (as with the Xpert MTB/RIF assay), or if should it be a reflex test that is done only after tuberculosis is diagnosed{I} • Determine how to simplify the patient protocol for DST to improve follow-up should non-centralised DST remain the leading public health strategy{I} • Gain a greater understanding of the complexities of global control of TB, as well as the shortcomings of the currently available BCG vaccine to stimulate demand for new TB vaccines from communities, national level policymakers, decision makers and international leaders who set global health priorities and action{J} • Find ways to broadly communicate and disseminate the findings of recent public

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
		health impact modeling and expand cost-effectiveness modeling for TB vaccines[{J}] • Fully investigate linkages between TB and other global health and development issues, such as HIV/AIDS and maternal and child health, the threat of MDR and XDR-TB and the contributions that new TB vaccines could make to advance the global health and development agenda[{J}] • Identify ways to inform and engage the media, government officials, NGOs, affected communities and other key stakeholders at the community, regional and country level about the value of TB vaccine development efforts and clinical trials in order to ensure transparency, generate a supportive environment and reduce the probability of misinformation or negative public response to clinical trials[{J}] • Find ways to link to organizations developing similar products for neglected global diseases other than TB so that lessons learned and solutions to common problems can be effectively communicated to the TB community[{J}] • The organizations developing new diagnostics and drugs for TB should work closely together with the vaccine community to effectively reduce TB disease in at risk communities[{J}] • Determine the best criteria for measuring the public health impact of vaccines[{J}]
INNOVATIVE FINANCING	• Determine ways to increase funding levels to adequately support TB R&D, particularly for investments in diagnostics development and quality clinical trials[{A},{B},{F},{G},{J}] • Find ways to reduce the cost and time taken for sufficient evidence to be gathered on diagnostic tools prior to their review and endorsement by WHO's STAG-TB, particularly for smaller companies[{D},{G}] • Determine market potential and market barriers for new TB diagnostic tests, after accounting for the roll-out of Xpert® MTB/RIF[{E},{F},{I}] • Conduct market analyses to support new product development that will: o (i) convince industries and investors that investments in new TB tools are	• Identify ways to expand financing approaches beyond market incentive mechanisms that rely on high prices to fund R&D as they do not result in creating advanced diagnostics in the areas of highest need[{A}] • Strategize how to ensure competition for market share is tempered with collaboration for product development, especially between academic and commercial groups[{D}] • Determine how to engage biotech start-ups from emerging economies in developing diagnostic tools to meet target product profiles[{D}] • Identify how to increase developers' access to well-characterized specimen panels with which to guide their product development and provide initial evaluation data[{D}] • Determine how to create harmonized study protocols and permit accurate comparison in multiple settings in order to facilitate more rapid diagnostic uptake by country programs once a WHO STAG-TB endorsement is made[{D}] • Identify how fast follower NAAT scan receive sufficient donor or investor support to undergo validation and demonstration studies that are required for WHO review and endorsement[{E}]

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
	needed, o (ii) inform target product profiles (TPPs) that can guide product development and scale-up, and o (iii) guide donor/funder decisions[{E},{F},{I}] • Improve poor market forecasting for TB medicines to better anticipate demand, reduce risk and incentivize more manufacturers to enter the field of TB medicines development [{F}] • Develop consistent and coordinated procurement practices to achieve the lowest sustainable price for quality assured TB medicines[{F}] • Learn how to accurately size the market for TB medicines [{F}] • Find ways to expand financing to provide sufficient resources to advance and sustain research on TB vaccines[{J}] • Identify new funders and determine how to establish new partnerships and collaborations for TB R&D[{J}] • Identify opportunities for cost-sharing across sectors and better utilization of existing resources[{J}] • Explore new innovative financing models[{J}] • Identify ways to broaden the base of advocates, allies and champions for TB and vaccine R&D[{J}] • Find ways to establish and fund trusted global organizations or consortia that can broker partnerships, coordinate meetings, establish useful websites and offer venues that solve problems in a timely manner[{J}]	• Determine how much of the diagnostic TB market is addressed with Xpert® MTB/RIF, and problems/needs that have yet to be addressed[{E}] • Create detailed TPPs necessary for product-specific needs in order to guide investments and engage industries and donors in meeting unmet needs[{E}] • Determine how to improve coordination between the leading funders of TB medicine procurement[{F}] • Find ways to consolidate the fragmented public sector market for TB medicines[{F}] • Determine how to obtain better data on the quality of medicines and their appropriate use in the private sector to allow a more accurate assessment of the total global market[{F}] • Determine how to fully roll out the public-private mix to ensure rational use of medicines in line with global treatment standards and to harness the private-sector demand to further strengthen the market for QA TB medicines[{F}] • Develop strategies that can further efforts 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 TB treatment[{F}] • Investigate ways to coordinate external donor funding and country-based public-sector funding to demonstrate actual demand and strengthen market forecasting of QA products[{F}] • Determine how the donor assistance that has heavily subsidised the implementation of Xpert MTB/RIF in resource-limited settings will affect the development and entry of newer diagnostic assays to the marketplace[{G}] • Develop a mechanism to ensure that private laboratories pass along any savings from assays purchased at concessionary prices toward private sector procurement of new DST assays[{I}] • Find ways to provide diagnostic companies with greater information to predict user needs (where the user is often a national tuberculosis programme) and market demand to reduce the risk associated with DST investments[{I}] • Find ways to engage emerging economies, and particularly the “BRICS” countries (Brazil, Russia, India, China and South Africa), as important partners in global efforts to develop new TB vaccines[{J}] • Determine ways to provide donors, policymakers, health care providers, civil society and other key stakeholders with information and evidence to support

R&D Areas	TUBERCULOSIS	
	Goals	***R&D Priorities for Achieving Goals***
		investment in TB vaccines[J] • Determine how to engage with the broader global health community, emphasizing the alignment between TB research and global health and development[J] • Find ways to link the TB advocacy and research communities that operate independently of one another to promote the need for continued and expanded investment in global health research[J]

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.
D. UNITAID. Tuberculosis Diagnostic Technology Landscape. Geneva: World Health Organization; 2012.
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.
J. Brennan P, Robertson B. Tuberculosis vaccines: a strategic blueprint for the next decade. Elsevier. 2012. 92(1):S1-S35.

Synthesis of Disease-Specific R&D Priorities for HIV/AIDS

R&D Areas	HIV/AIDS	
	Goals	***R&D Priorities for Achieving Goals***
BASIC SCIENCE	• Conduct research on approaches to eliminate viral latency and associated reservoirs of persistent infection{C} • Explore how to induce broadly reactive neutralising antibodies, as well as how to induce and maintain mucosal immunity{C} • Determine methods to exploit innate immunity and how to control infection with cell-mediated responses {C} • Explore the interactions between effective microbicides (or oral PREP) and potential prophylactic vaccines{C} • Identify new broadly neutralizing antibodies for vaccine development{D} • Determine methods to address the management of long-term toxicity in treated patients{C} • Understand correlates or surrogates of HIV protection and/or viral containment{C} • Continue the ability to perform para-clinical studies in non-human primates and small human clinical trials for safety and immunogenicity{C} • Determine the optimal time to initiate clinical antiretroviral therapy{C} • Perform research to facilitate diagnosing the infection early in its course and reduce infectiousness {C} • Develop new anti-microbicidal agents to prevent transmission beyond the use of	• Explore the utilization of immune modulation, gene therapy, and therapeutic vaccines to address viral latency{C} • Conduct basic research into B-cell biology as it relates to the induction and maintenance of effective antibodies, and better understand the mechanisms of B cell impairment{C} • Determine how innate immunity can be engaged to enhance immunity of vaccines as applied to the rational development of novel adjuvant strategies{C} • Explore how innate immunity might be utilized to accelerate amnestic vaccine responses following viral exposure{C} • Determine whether microbicide-vaccine interactions could boost or modify vaccine responses{C} • Explore whether microbicides (or PREP) could be used during immunization to cover any period of potential enhanced susceptibility induced by potent immunogens, adjuvants or vectors {C} • Investigate whether a combination of vaccines and microbicides can prevent viral breakthrough that might be seen with either intervention strategy if used alone {C} • Conduct studies to understand the risk of resistance for next generation microbicides{C} • Research the structures of antibodies, how they evolve, and how they are produced by the immune system{D} • Investigate mutations in the CCR5 gene or removal of the CCR5 protein for cure research {D} • Perform trials to assess the safety and effectiveness of new microbicides and rectal microbicides (e.g. tenofovir gel 1%){D} • Conduct research for dapirivine-based vaginal rings that combine antiretrovirals with contraceptive hormones{D} • Continue research into pre-exposure prophylaxis and treatment as prevention using different dosing strategies amongst various populations{D} • Research HSV-2 prevention in HIV-negative individuals using various therapeutic and prophylactic methods (e.g. acyclovir) {D} • Increase molecular understanding of the HIV envelope spike structure and its interaction with broadly neutralizing antibodies (bNAbs) that may support NAbs induction{C} • Explore additional functional antibody activities (including ADCC, ADCI, macrophage

R&D Areas	HIV/AIDS	
	Goals	***R&D Priorities for Achieving Goals***
	antiretroviral microbicides[{A}] • Develop microbicides that are combination products that reduce the potential for resistance[{C}] • Develop better biomarkers of safety and efficacy for microbicides[{C}]	inhibition, transcytosis inhibition and viral aggregation) to determine their potential contribution to protection[{C}] • Conduct research related to inducing antibodies to the chemokine coreceptors and/or providing broadly neutralizing antibodies passively via a viral vector or stem cell transformation[{C}] • Define the antigens and appropriate vectors that elicit the most potent inhibition of virus replication [{C}] • Examine insert and vector design in order to maximize breadth and magnitude of CD8 responses[{C}] • Develop novel CD8 inhibition assays[{C}] • Define the role of virus-specific CD4 T helper cell responses (both positive and negative attributes) in durable HIV containment[{C}] • Conduct follow-up studies to RV144 results to better understand immunoglobulin IgG antibodies that bind to V1/V2 variable loops and plasm IgA antibodies that bind to the HIV envelope[{D}] • Study individuals who appear to be protected from HIV despite high-risk behavior in order to facilitate the design of immunogens able to elicit the corresponding protective responses in non-infected individuals[{C}] • Identify ways to maintain non-human primate facilities for clinical trials[{C}] • Develop new insights into clinical markers identifying when a patient has a biological failure, and how to combine the (new) available drugs accordingly[{C}] • Investigate methods to determine antriretroviral levels in blood to assess resistance and adherence [{E}] • Develop rectal microbicides to prevent sexual transmission of HIV among men who have sex with men (MSM)[{A}] • Create microbicide formulations that maximize subject adherence and give sustained release to reduce compliance burden[{C}] • Elucidate the molecular events leading to infection to support rational targeting of microbicide strategies [{C}] • Conduct parallel studies in human and nonhuman primates to determine whether ex-vivo viral challenge of mucosal biopsies following in vivo application of microbicides may provide a surrogate marker of protection [{C}] • Develop and utilize scientific criteria to determine the potential window of protection for microbicides (time from application to intercourse)[{C}]

R&D Areas	HIV/AIDS	
	Goals	***R&D Priorities for Achieving Goals***
DIAGNOSTICS	• Further develop a broad range of new testing strategies and services that are simple to use and easy to access[{A},{J},{L}] • Develop new, innovative diagnostic tools for resource-poor settings.[{E},{J},{L}] • Find ways to improve efficiency of CD4, viral load, and early infant diagnosis (EID) RDTs[{J}] • Focus on quality improvements at all levels of diagnostic testing for HIV/AIDS[{J},{L}]	• Focus on enhancing provider-initiated testing and counselling and developing rapid testing technologies and home-based testing methods[{A}] • Develop diagnostic tools capable of detecting early stages of infection[{E}] • Research tools that will simplify and accelerate HIV testing (rapid point-of-care tests)[{E}] • Develop high-quality, cost-effective point of care (POC) CD4 testing options to reduce loss to follow-up for rural patients[{J}] • 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}] • Explore disposable CD4 testing models to replace device-based systems in resource-limited settings[{J},{L}] • Develop more tests that can be used at POC and that deliver same-day results, e.g. using mobile technologies[{J},{L}] • Develop more viral load assays that can detect and quantify all known HIV-1 subtypes (like the Cavidi ExaVir assay), as well as inter-subtype recombinants and emerging variations[{J}] • Design more viral load tests with the ability to use dried blood samples (DBS) to greatly simplify the transport of samples and ease of use for health workers[{J}] • Explore applications of DBS used in laboratory-based viral load platforms for use in EID testing[{J}] • Investigate ways to accelerate the launch of POC testing platforms dedicated to EID and viral load technologies[{K},{M}]
DRUGS	• Find ways to improve results at each stage of the treatment continuum[{A}] • Determine how to improve the efficiency and effectiveness of treatment programmes for high-risk groups[{A}] • Identify drug leads directed against known targets but also against novel viral (i.e. structural and regulatory proteins) or cellular targets[{C}] • Design new drugs that target highly	• Determine whether to maintain lifelong triple antiretroviral therapy for pregnant women living with HIV who initiate treatment at CD4 counts above 350 per ml, whether to include efavirenz in combination regimens for pregnant women and the type and duration of recommended infant-feeding practices to maximize prevention benefits for the child[{A}] • Evaluate and refine joint treatment drug regimens for co-infection of TB and HIV[{A}] • Investigate treatment options that reduce the risk of HIV transmission among children[{A}] • Determine whether antiretrovirals acting later in the viral cycle (integrase, protease inhibitors etc) have a role to play in prevention. [{C}]

R&D Areas	HIV/AIDS	
	Goals	***R&D Priorities for Achieving Goals***
	conserved molecular and functional areas or epitopes on their target and that show minimal, if any, cross-resistance to other classes of existing antivirals{C} • Create new drugs with less long-term side effects{C} • Explore pharmacological and mechanistic insights in drug-action and drug/drug interaction to define and select the most optimal drug combinations{C} • Find ways to build upon the successful outcomes of oral pre-exposure prophylaxis results{C} • • Identify potential TB drugs that can be safely administered to HIV-positive TB patients{H}	• Understand how new technology (multi-plex cytokine analysis, proteomics, transcriptomics, etc.) can be best applied to safety monitoring{C} • Assess vaginal and penile drug safety{C} • Develop markers of drug pharmacokinetics and pharmacodynamics as potential predictors of efficacy {C} • Evaluate competing concepts and candidates using standardized methodologies{C} • Investigate the potential of two approaches in cure research: (1) a sterilizing cure that would eradicate HIV from the body (2) a functional cure that would keep the patient healthy without drugs but not eliminate the virus from the body{D} • Explore complementary strategies that target CD4 cells and other locations that are resistant to antriretrovirals and can attack latent HIV once it becomes active {D} • Create more efficient, less toxic antiretroviral medications{E} • Develop simpler, longer lasting formulations{E} • Investigate and confirm the safety and efficacy of various TB drugs for HIV-positive TB patients{H} • Explore ease-of-use considerations for patients and health care workers (e.g. dosing intervals, total length of treatment, oral formulations, etc.) {I} • Assess the appropriateness of product to country health systems (e.g. cold chain issues, hospital-based admin, etc.){I} • Create products targeted at various populations (e.g. children, adults, pregnant women, severely ill patients, etc.){I} • Develop adaptations that make treatment compliance easier (e.g. paediatric syrups, simpler formulations, etc.){I} • Identify drugs that are endowed with a high genetic barrier (i.e. multiple mutations in the target are required to afford significant phenotypic resistance) from the very beginning in the drug development process{C} • Utilize pharmacokinetics and genetics during drug treatment to predict the emergence of potential side-effects{C} • Investigate the optimal use old as well as new drugs, particularly in rational combinations{C} • Identify and address potential viral reservoirs during novel drug development using various approaches (i.e. immunotherapy){C} • Assess the efficacy of intermittent dosing for oral pre-exposure prophylaxis{C} • Refine current strategies and develop new strategies for preventing vertical

R&D Areas	HIV/AIDS	
	Goals	***R&D Priorities for Achieving Goals***
		transmission to infants at birth and during breastfeeding{D} • Explore immunotherapeutic approaches, particularly in combination with chemotherapy{C} • Determine how to best utilize relevant ADMET models (Absorption-Distribution-Metabolism-Excretion- Toxicity) during the drug discovery/ development process to increase safety{C}
VACCINES	• Develop a neutralizing antibody-based vaccine that prevents HIV infection{C},{D},{O} • Explore non-classical routes to antibody-mediated protection for vaccine development{C} • Create a T-cell based disease-modifying vaccine{C} • Understand the role of mucosal immunity in the development of a preventive HIV vaccine{C} • Find ways to build upon the progress of multiple potential vaccine candidates currently in the pipeline{D} • Determine why the STEP vaccine trial failed and its implications for the T-cell concept and future vaccine development{O} • Develop better immune-monitoring assessment tools{O} • Pursue new avenues and explore cross-fertilization from genetics, structural biology, systems biology, cell biology, and peptide chemistry (among others) to generate knowledge useful in vaccine design and evaluation{O}	• Investigate novel target identification, engagement of innate immunity, and the possible use of gene therapy to express protective factors{C} • Perform studies to evaluate and develop effective heterologous prime-boost strategies{C},{D} • Design mucosal delivery strategies for DNA, proteins, and vectors {C} • Utilize non-classical combinations such as NRTI-sparing regimens, and including a role for new agents like IN or entry inhibitors{C} • Find ways to increase the availability of mucosal adjuvants{C} • Develop technologies to better assess mucosal responses {C} • Develop an HSV-2-specific vaccine{D} • Develop therapeutic vaccines that can exhibit substantial viral-load reduction. {E} • Develop immunogens that induce antibodies to neutralize a broad array of primary isolates of HIV{O} • Develop a vaccine that successfully contains both antibodies and T-cells that recognize diverse strains of HIV and that reach the site of infection very quickly before infection becomes irreversibly established{O} • Design and conduct more studies that test the T-cell vaccine concept{O} • Determine how and whether insufficient T-cell response or other qualities of the cellular immune response (such as the balance between HIV-specific CD4+ T cell and CD8+ T cell responses, or the polyfunctionality, proliferative capacity, specificity, avidity, and the location or kinetics) played a role in the failure of the STEP vaccine{O} • Examine the genomic sequences of infecting HIV strains to demonstrate whether immunization resulted in early immunologic pressure on the incoming HIV virus in the STEP trial, and potentially suggest which HIV genes or epitopes should be included in subsequent vaccines{O} • Conduct studies with mucosal and biopsy specimens to explore whether activation of cells at the mucosal sites were different between vaccine and placebo recipients

R&D Areas	HIV/AIDS	
	Goals	***R&D Priorities for Achieving Goals***
		in the STEP trial{O} • Determine whether the Ad5 vaccine elicited T-cell or antibody-mediated responses that could have enhanced HIV acquisition in the STEP trial{O} • Design whole-genome studies that may reveal associations between host genetic background, baseline Ad5 titer, and HIV acquisition{O} • Evaluate immunity to vectors, including at the tissue level{O} • Develop better NHP models, and more closely link them to clinical research, e.g. via parallel studies, and the exchange of researchers, including young investigators, between the clinic and NHP facilities so that common questions in HIV vaccine discovery can be identified and addressed using common tools {O} • Investigate whether a specific vaccine such as Ad5 induces the same immune responses and degree of cell activation at mucosal sites in non-human primates (NHPs) as in humans{O} • Determine whether the use of heterologous gene inserts increases the breadth of immune responses{O} • Investigate whether electroporation of DNA alters the qualitative or quantitative nature of induced immune responses{O} • Develop and validate additional assays that measure proliferative capacity, mucosal recruitment, cytotoxic capacity, or other immune functions that may provide a more robust indication of functional antiviral activity{O} • Further define the first events leading to HIV and SIV's entering the gut-associated lymphoid tissue{O} • Determine the rate and mechanisms by which immune cells are mobilized to the site of infection and whether innate responses can alter the course of infection{O} • Characterize the cellular and humoral immune responses needed to control viral replication through modulation and/or elimination of specific cell subsets in the SIV model and studies of HIV-infected populations{O} • Determine the 3D structure of the HIV envelope trimer{O} • Determine why broadly neutralizing antibodies are uncommon and how they can be elicited{O} • Define the specificities of antibodies that neutralize diverse primary HIV isolates{O} • Develop more relevant animal models (and challenge viruses) to explore protection or enhancement of infection or disease, especially heterologous challenge models{O} • Determine why SIV is apathogenic in some NHP studies{O}

R&D Areas	HIV/AIDS	
	Goals	***R&D Priorities for Achieving Goals***
		• Identify correlates of vaccine-induced immune protection, especially the mechanisms whereby non-pathogenic (e.g. attenuated) SIV's prevent infection by pathogenic virus[{O}]
EPIDEMIOLOGY	• Develop methods to ensure that testing programmes are reaching the age and population cohorts at highest risk, particularly those co-infected with TB and HIV[{A}]	• Determine how to strengthen health reporting systems to monitor treatment retention by age and sex[{A}] • Find ways to strengthen case reporting and the tracking of progress of the collaborative HIV and TB activities by HIV stakeholders through harmonized indicators and globally recommended patient monitoring systems[{A}] • Identify how to improve the reporting of sex-aggregated epidemiological and HIV service coverage data for injection drug users[{A}] • Produce reliable national estimates of the total number of people who inject drugs[{A}] • Investigate how to reach out to, and monitor, a higher proportion of MSM[{A}] • Estimate service needs and coverage among women at highest risk of HIV in countries with concentrated epidemics[{B}] • Develop methods to monitor incidence rates rigorously (e.g. type of virus and recent infections)[{C}]
PUBLIC HEALTH AND OPERATIONAL RESEARCH	• Investigate ways to improve retention rates for people enrolled in HIV care and treatment[{A}] • Find ways to consult and engage communities in planning how to best scale up access to treatment[{A}] • Identify ways to make health systems more responsive to the needs of vulnerable populations[{A},{B}] • Accelerate the next phase of HIV treatment by prioritizing implementation research on existing interventions[{A}] • Identify ways to expand joint treatment programmes for co-infection of TB and HIV[{A}] • Determine how to increase population-based HIV testing to reach persons at	• For MSM, investigate how combining prevention efforts on HIV-related behaviour, access to antiretroviral therapy for MSM who are HIV-positive, and the potential use of pre-exposure prophylaxis in a coordinated and accelerated programme can reduce the sexual transmission of HIV[{A}] • Strategize how to link HIV-positive persons to easily accessible care that where they can be swiftly evaluated[{A}] • Find new ways to improve treatment coverage among children, especially those who are youngest and most vulnerable[{A}] • Develop methods to reach more men earlier with HIV testing and treatment services in high-prevalence settings[{A}] • Design methods to involve people living with HIV and affected communities in planning, implementing and evaluating high-quality, rights-based care and treatment programmes to improve retention rates[{A},{B}] • Produce consistent nationwide data that permit retention rates to be tracked over time, and continue reporting for people who transfer to new treatment centers[{A}] • Research how to scale-up the three I's for HIV and TB (intensified TB case- finding, isoniazid preventive therapy and infection control for TB)[{A}]

R&D Areas	HIV/AIDS	
	Goals	***R&D Priorities for Achieving Goals***
	highest risk, particularly sex workers, MSM and people who inject drugs {B} • Determine how to increase access to antiretroviral therapies for all eligible persons{B} • Assess the effectiveness of new prevention technologies and tools.{D} • Assess the public health implications of antiretroviral utilization in HIV-positive patients.{E} • Determine how to improve access to robust, high-quality CD4, viral load, and early infant diagnosis (EID) RDTs at the point of patient care, particularly in hard-to-reach places, to enhance ART staging and monitoring{J},{L},{N} • Determine the appropriate country-specific mix of high-volume laboratories and POC testing{J} • Develop ways to improve systems for sample referral and results distribution for central labs{J} • Map barriers to, and foster the acceleration of, new technology introduction, especially for POC technologies{J},{L} • Better understand the testing continuum required for the HIV patient{L}	• Identify means to provide HIV discordant couples with greater access to antiretroviral therapies, and use antiretroviral therapy as a prophylaxis for people at high risk of HIV infection{B} • Investigate ways to overcome human resource constraints on service delivery{B} • Determine why despite improving access to health care, pregnant women are not starting, or being reported to start, antiretroviral therapy{B} • Develop combined behavioural, biomedical and structural strategies, both intensively in specific populations in concentrated epidemics and across the whole population in generalized epidemics{B} • Understand and resolve the gender gap in services for drug users whereby women who inject drugs have even poorer access to HIV services{B} • Create accurate monitoring and interpretation systems to identify drug resistance selection and virus tropism{C} • Develop a database that contains information, including: patient HIV samples (i.e. genetics, mutations), treatment history, and immunological parameters{C} • Identify social and cultural factors that deter at-risk people from being tested. {C} • Better understand the pathogenesis and possible excess risk of HIV-infected populations contracting age-related comorbidities{C} • Quantify the benefits and risks from using (and not providing access to) antiretroviral therapy and other biomedical interventions{C} • Assess the impact of TB co-infection and how it is most optimally managed{C} • Better understand HIV transmission from theoretical, qualitative and quantitative behavioural and social research perspectives{D} • Assess the impact of the implementation of male circumcision and non-surgical circumcision on HIV prevention {D} • Find ways to improve research and development efforts for female condoms, as well as community education and advocacy efforts for their use{D} • Evaluate the effectiveness of early treatment of antiretrovirals on HIV-positive individuals{E} • Investigate ways to reduce costs, improve training of laboratory technicians, enhance the quality of laboratory instruments and well-functioning sample transport systems for CD4, viral load and EID RDTs{J},{L} • Identify ways sample transport networks can enable access to testing for patients in peri-urban and rural settings{J},{L}

R&D Areas	HIV/AIDS	
	Goals	***R&D Priorities for Achieving Goals***
		• Determine how cost effectiveness and access can be enhanced via the consolidation of centralized testing facilities in high volume centers (e.g., super-labs)[{J},{L}] • Examine how factors like urban/rural split of the country, the expected volume of each category of testing, the comparative all-in cost of centralized versus decentralized testing and the ability to effectively transport samples between collection sites and laboratories affects the high-volume laboratory and POC testing mix[{J},{L}] • Determine how to upgrade patient management algorithms to accommodate the effective use of viral load information[{J}] • Strategize ways to attract and retain young researchers in HIV vaccine discovery research[{O}]
INNOVATIVE FINANCING	• Identify means to further reduce the cost of antiretroviral medicines and per-person treatment costs through better program management to maintain the treatment bottom line[{A},{B}] • Develop innovative funding mechanisms to spur additional health R&D for HIV and other health problems confronting low- and middle-income countries, with particular emphasis on developing affordable new tools to address priority issues[{A}] • Strategize how to cultivate emerging economies as international AIDS donors within a framework of global solidarity and shared responsibility[{A}] • Investigate ways to reduce dependency on overseas development assistance for national-level AIDS responses[{B}] • Find ways to divert resources towards cure research and development[{E}] • Find ways to better integrate the private sector into the poverty-related	• Identify ways to reduce the cost of antiviral medications, particularly second- and third-line regimens[{A},{B}] • Develop strategies to manage intellectual property that are oriented towards public health goals, such as the full use, as required, of flexibilities permitted under international regulations such as the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) administered by the World Trade Organization[{A}] • Identify ways to build-up local pharmaceutical capacity and take full advantage of the flexibilities permitted under the TRIPS agreement to shift from international to domestic drug production[{A},{B}] • Develop a monitoring system to ensure that national HIV spending is focused on effective investment and increases in domestic spending, including developing innovative and sustainable AIDS funding sources[{A}] • Determine how to improve the efficiency of AIDS spending through such means as capturing productivity gains, further reducing the costs of antiretroviral medicines, improving service delivery and integrating services, e.g. through couples counselling and testing, or opioid substitution therapy [{A},{B}] • Identify key product development partnerships (PDPs) to engage talented researchers in private industry[{F}] • Find ways to reduce restrictions on funding requirements to ensure that the best research candidates are prioritized (under the EU 7th Framework Programme)[{F}] • Streamline administrative processes to expedite funding flows to reach researchers[{F}] • Explore pooled funding mechanisms to encourage collaboration[{F}]

R&D Areas	HIV/AIDS	
	Goals	***R&D Priorities for Achieving Goals***
	neglected disease R&D landscape[F] • Identify methods to improve coordination efforts between funders and researchers to jointly develop product development portfolios[F] • Identify the right balance of funding between product development and basic science [F] • Determine how to align efforts of aid organizations and science and technology agencies [F] • Find ways to improve financing coordination efforts amongst various stakeholders[F] • Find ways to create new product development public-private partnerships (PDPPPs)[G] • Identify means to leverage philanthropic donations to strengthen national pharmaceutical innovation systems[G] • Develop new mechanisms and pathways to ensure the urgent approval of neglected tropical disease drugs in developing countries [H] • Better understand the current diagnostic market dynamics and trends[L],[N] • Utilize available procurement data to inform future funding and procurement strategy[N] • Find ways to improve the quality and completeness of data collection and data analysis for procurement[N] • Determine how to generate additional funding for HIV vaccine programs,	• Assess the potential for new policies to encourage local production of medicines to treat neglected diseases[G] • Utilize technology transfer and licensing agreements to promote local drug production[G] • Find way to create centers of regulatory excellence in African subregions [H] • Identify possible methods to provide automatic WHO prequalification for novel neglected disease products[H] • Find ways to include regulators from endemic countries in regulatory reviews of neglected disease products [H] • Determine ways to select Western medicines regulatory agencies to review prequalification decisions[H] • Generate neglected disease data that can be cross-applied to core commercial compounds[I] • Find ways to upgrade the capacity of clinical trial sites in developing countries[I] • Identify PPPs that are willing to commit to a long-term funding mechanism (entirety of R&D process) [I] • Identify and find ways to collaborate with industry partners that will contract with PPPs to develop drugs for neglected diseases[I] • Find ways to incentivize funds from G8 countries to create the Industry R&D Fund (IRFF)[I] • Create a central clearinghouse for information regarding: targets or compounds related to neglected disease research, funding sources, and services and skills offered [I] • Identify new, innovative public-private partnerships (PPPs) for drug development, and create policies to encourage PPPs[I] • Investigate ways to provide shared platform services to PPPs (e.g. legal, human resources, etc.) to accelerate R&D processes [I] • Develop strategies to support to PPPs in negotiating industry deals[I] • Create and assess the potential of an IRFF to underwrite industry participation in PPPs[I] • Evaluate how the provision of PPP-sponsored start-up funds to new small companies influences their participation in neglected disease R&D [I] • Find ways to sell “fast-track” regulatory review of commercial drugs to finance neglected disease R&D[I]

R&D Areas	HIV/AIDS	
	Goals	***R&D Priorities for Achieving Goals***
	particularly vaccine discovery research{O}	• Evaluate whether awarding prizes to multinationals who invest in neglected disease drug development inspires greater investment and prioritization of R&D for neglected diseases {I} • Explore strategies to reduce financial obligations on patent and maintenance fees{I} • Identify ways to engage companies in using preferential pricing arrangements{G} • Assess how access to treatment could enhanced through intergovernmental organization-sponsored buyer co-payments{G} • Determine how to engage venture capitalists to invest in neglected disease R&D{G} • Utilize information on price variation by country and by test to improve cost-effectiveness of procurement{N} • Find ways to better account for market consolidation in procurement decisions to balance competition with market stability{N} • Determine ways to support improved accuracy of GPRM procurement data{N} • Identify methods to address and resolve potential overlap in Global Fund PQR and UNICEF procurement data{N} • Identify methods to encourage more complete reporting in Global Fund PQR{N} • Strategize ways to overcome inconsistent or insufficient data entry for procurement, e.g. using drop-down lists{N} • Determine how to account for funding timeframes in reporting procurement data{N} • Further analyse direct-from-manufacturer procurement to procurement through suppliers, agents, or intermediaries to assess potential for improved cost-effectiveness{N} • Determine the activities needed to complement procurement of HIV simple/rapid, EIA and supplemental tests, e.g. positive and negative controls{N}

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.
D. HIV Vaccines & Microbicides Resource Tracking Group (TWG). Investing to End the AIDS Epidemic: A New Era for HIV Prevention Research and Development. HIV Vaccines & Microbicides Resource Tracking Group; 2012.
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.

G. 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.
H. The George Institute for International Health. Registering New Drugs: The African Context. London; The George Institute for International Health, January 2010.
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. 2nd 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.
N. UNITAID. Diagnostic market analysis: HIV simple/rapid, enzyme immunoassay (EIA) and supplemental tests: available data and implications for future funding. Geneva: World Health Organization: July 2011.
O. Fauci A, Johnston M, Dieffenbach C, Burton D, Hammer S, Hoxie J, *et al*. HIV vaccine research: the way forward. Science. 2008; 321: 530-532.

Synthesis of Disease-Specific R&D Priorities for Neglected Tropical Diseases

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
BASIC SCIENCE	• Investigate how helminth parasites modulate host–parasite interactions at the within-host levels {A} • Determine programme end-points for elimination of helminth infection{A} • Identify the mechanisms of host immune responses to helminths, and translate knowledge of these mechanisms into rational strategies for vaccine development{A} • Better understand the full spectrum of disease symptoms for NTDs{C} • Assess the importance of asymptomatic infection for Chagas disease (CD), Human African Trypanosomiasis (HAT) and Leishmaniasis{D} • Investigate the complex ecology of antimicrobial resistance and foodborne zoonoses{F} • Develop the basic research agenda to allow potential zoonotic pandemic pathogens to be distinguished from harmless microbes by use of molecular sequence data only, or information that can be deduced from these data—eg, structures of key proteins{H} • Identify ways to embed basic research within a superstructure of more integrated interdisciplinary and systems-based research{J} • Better understand the "ecosocial" factors which facilitate resistance; determine the	• Examine the impact of helminth parasites on the host immune response of concurrent infection with other helminth and non-helminth pathogens, the impact of parasite control interventions on such host–parasite interactions, and how concurrent infections affect clinical outcomes and the host's ability to seroconvert upon vaccination{A} • Identify how to annotate parasite genomes and transcriptomes, and to develop new tools for parasite functional genomics in key species{A} • Define the determinants and mechanisms of helminth-induced pathologies, including carcinogenesis, and excess human mortality{A} • Define parasite (and vector/intermediate host) population and ecological genetic structures in the contexts of genetic responses to interventions within and between parasite populations, parasite transmission, and epidemiology{A} • Conduct studies on the pathogenesis, genetics, population structure, vector–parasite–host(s) interactions and immunology to further support the basis for translating basic research into operations/implementation of existing or improved control measures{A} • Conduct detailed studies to elucidate the spectrum of symptoms for cysticercosis and taeniasis, including stroke associated with NCC to inform burden of disease studies{C} • Investigate the impact of schistosomiasis on malnutrition and cognition in relation to single infections and polyparasitism{C} • Conduct studies that investigate the process of HAT entry into the central nervous system (CNS) and subsequent pathogenesis that produces a debilitating and lethal second-stage of the disease{D} • Better understand the zoonotic microbiome from people and that of the animals they contact, and what causes zoonotic microbes to proliferate in some conditions{F} • Study the effects of the use of antibiotics in animal production, and find ways to enhance the translation of this science by involving physicians, veterinarians, and ecologists in the design and interpretation of studies{F} • Explore the use of alternatives such as probiotics, diets to promote healthy or protective gastrointestinal flora, new methods of immune-system modulation,

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	strategies – biological, chemical, genetic, cultural and social – that exist to better control pathogens and vectors[J]	bacteriophages, bacterial cell wall hydro lases, and anti-microbial peptides to help reduce the need for antimicrobial use in people and animals[F] • Analyze zoonotic viral traits and phylogenetic relations, and how these correlate with emergence and pathogenicity after a virus spills over[H] • Further elucidate the relationship between host range and plasticity as they relate to the likelihood of pathogens transmitting between different host taxa, and develop predictive correlations for these events[H] • Provide better estimates of a virus's ability to evolve by investigating the factors that allow a pathogen to successfully jump species, including high mutability and an absence of proofreading to correct mutations[H] • Better understand host—receptor interactions, including understanding of the interactions for commonly expressed receptors (eg, sialic acids or heparan sulfate proteoglycans) or ease of adaptation of the virus to a new host receptor[H] • Investigate viruses' capacity to exploit new routes of transmission, and include human behaviour as a critical component that should be integrated into any predictive model[H] • Conduct research that allows scientists to better predict the virulence of zoonotic pathogens, and increases our ability to assess the likelihood that a wildlife or livestock virus will cause noteworthy disease if the virus does infect people[H] • Further elucidate patterns of host–virus coevolution among related viruses and their wildlife hosts by analysing genetic sequences and improving understanding of the pathogen's opportunities for transfer[H]
DIAGNOSTICS	• Develop new NTD diagnostics that can be used in remote/difficult settings[B] • Find ways to improve available diagnostic tests, specifically their sensitivity, specificity, multiplex capacity, and ability to measure infection intensity, and detect drug resistance for helminth infections[A] • Determine how to standardize and validate methodologies and cost-effective protocols for diagnosis in the process of monitoring and evaluation (M&E)[A] • Improve existing/develop novel	• Find ways to encourage the convergence of epidemiological and laboratory approaches to develop tools optimal for control programmes that are facilitated by the recognition that parasitological diagnosis at the individual level is not appropriate for implementing and monitoring such interventions[A] • Determine how to apply modern laboratory techniques to diagnosis development, particularly the use of PCR and molecular techniques to produce parasite recombinant proteins as reagents for serodiagnostic tests[A] • Better understand the performance characteristics of currently available tools for diagnosis for each of the human helminth infections, and identify critical gaps in diagnostic technology[A] • Find ways to overcome key challenges in diagnostic development for helminth infections, including quantifying intensity of infection, response to anthelmintic

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	diagnostic assays M&E of the impact of control programmes on helminth infection and associated morbidity, and for supporting decisions towards control/ elimination end-points[{A}] • Develop new diagnostics for case detection and characterization, including drug resistance and tests of cure for Chagas disease, Human African Trypanosomiasis and Leishmaniasis[{D}] • Develop improved means to identify specific disease states: from asymptomatic and chronic to cured conditions for CD, HAT and Leishmaniasis[{D}] • Develop diagnostics for point-of-care use for infection and exposure to allow for proper assessments of case fatality ratios and disease burden for vector-borne pathogens[{G}] • Concentrate diagnostic development efforts on products for Amebiasis, CD, Giardiasis, HAT, Leishmaniasis, Taeniasis-cysticercosis, Echinococcosis, Food-borne trematodiases, Loiasis, Lymphatic filariasis, Onchocerciasis, Schistosomiasis, Ascariasis, Hookworm, Trichuriasis, Strongyloidiasis, Toxocariasis, Dengue and other flaviviruses, Rabies, Rift Valley fever, Baronellosis, Bovine tuberculosis, Buruli ulcer, Cholera, Enteric pathogens (Gram neg), Leprosy, Leptospirosis, Trachoma, Treponematoses, Mycetoma and Ectoparasitic infections[{I}]	chemotherapy, (including detection of anthelmintic resistance), disease mapping and surveillance, elimination and the need to collect data amenable to use in mathematical modelling of infection[{A}] • Develop new diagnostic tests using biomarkers of infection that reflect infection intensity[{A}] • Develop and validate clinical, phenotypic and molecular methods for monitoring of drug efficacy and resistance [{A}] • Develop and validate questionnaire-based methods for diagnosis of helminth infections[{A}] • Find ways to link measures of diagnostic performance for the diagnostic tests optimized or developed with statistical/mathematical tools to support monitoring and evaluation of helminth control programmes[{A}] • Determine how to improve the specificity of leprosy diagnosis using clinical or other investigations[{B}] • Develop immunological tests for diagnosis and biomarkers of infection status/exposure and for differentiation of *T. solium* and *T. saginata*[{C}] • Develop more sensitive and specific diagnostics for early detection of *Echinococcus* infection including: o methods (imaging, serology) to assess parasite viability and/or progression of both cystic and alveolar disease; o comparison of the efficacy, sensitivity and specificity of copro-DNA tests to establish strain-specific detection for *E. granulosus* in dogs[{C}] • Find ways to improve diagnostics so they are effective at detecting schistosomiasis in low-prevalence populations, and so they can be used as surveillance tools in order to determine whether effective control has been achieved[{C}] • Develop new, safe diagnostic techniques for acute infection during pregnancy to detect toxoplasmosis in the mother and fetus[{C}] • Develop cost-effective diagnostic and management protocols for CNS toxoplasmosis in high-risk HIV-seropositive patients[{C}] • Develop appropriate and effective methods for the collection of samples for diagnosis of rabies in humans both post mortem (e.g. periorbital biopsies) and antemortem (e.g. nuchal skin biopsies)[{C}] • Find ways to encourage more widespread use of existing techniques for field

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
		collection and storage of samples and tests for rabies diagnosis and surveillance, such as the direct rapid immune-histochemical test, and use of preservatives/specialized paper for stabilization of virus and RNA{C} • Develop inexpensive, robust and reliable diagnostic tests for bacterial zoonoses that can be used in field and hospital settings{C} • Establish locally appropriate cut-off points for acquisition of valid data to inform disease burden studies e.g. the single comparative intradermal test for bovine tuberculosis and serological tests for brucellosis{C} • Design diagnostic strategies to differentiate brucellosis vaccinated animals from naturally infected animals in order to prevent unnecessary livestock slaughter{C} • Develop inexpensive and reliable brucellosis diagnostic tests for use in local hospital and field settings{C} • Develop diagnostics for infants of *T. cruzi*-infected mothers, second-stage human African trypanosomiais, and visceral leishmaniasis in different global regions{D} • Develop an on-site diagnostic dipstick to test for Crimean-Congo haemorrhagic fever (CCHF){E}
DRUGS	• Assess drug efficacy and promptly detect the development of drug resistance{A},{B} • Develop and deliver preventive chemotherapy as an integrated package for co-endemic NTDs{B} • Discover safe and effective medicines that are simpler to administer, can be easily used in remote areas and cheaper than those currently available{B} • Investigate new safe therapeutics to avoid drug resistance, including exploring combinations of approved anti-kinetoplastid drugs, repurposing of existing approved drugs and developing new drugs for Chagas disease, Human African Trypanosomiasis and Leishmaniasis{D},{I} • Develop drugs for chronic Chagas disease,	• Develop new drugs and treatments for onchocerciasis and lymphatic filariasis{A} • Complete a clinical trial of oral antibiotic therapy (using rifampicin and clarithromycin) by 2014 to achieve intensified control of Buruli ulcer{B} • Find new low-cost treatment regimens for African trypanosomiasis, or investigate how to reduce the cost of melarsoprol-free treatment{B} • Develop improved chemotherapy for Taeniasis/Cysticercosis infection in humans and pigs{B} • Develop new or refined preventative chemotherapy options for lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helmnithiases and blinding trachoma{B} • Conduct field-based randomized clinical trials to evaluate the efficacy of oxfendazole and its effectiveness with recombinant vaccines against porcine cysticercosis{C} • Find ways to scale-up multicentric prospective evaluations of available clinical treatment options, including surgery, ultrasound, drug regimens (albendazole, flubendazole and ivermectin, including dosages and combinations) for echinococcosis {C} • Continue to explore new drug candidates for use in the immune-compromised

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	second stage human African trypanosomiasis, visceral leishmaniasis, and cutaneous leishmaniasis[{D},{I}] • Develop new, effective, safe and affordable drugs, preferably oral, for all the trypanosomiases and leishmaniases[{D},{I}] • Develop a macrofilaricide drug[{I}] • Concentrate research efforts towards drug development for Chagas disease, HAT, Leishmaniasis, Taeniasis-cysticercosis, Echinococcosis, Food-borne trematodiases, Loiasis, Lymphatic filariasis, Onchocerciasis, Schistosomiasis, Hookworm, Trichuriasis, Strongyloidiasis, Toxocariasis, Dengue and other flaviviruses, Rabies, Rift Valley Fever, Baronellosis, Bovine TB, Buruli Ulcer, Cholera, Enteric pathogens (Gram Negative), Leprosy, Leptospirosis, Treponematoses, Mycetoma, Paracoccidiomycosis and Ectoparasitic infections[{I}]	*Cryptosporidium* host[{C}] • Evaluate and find ways to implement new biological regimens for humans, including use of monoclonal antibodies as a cost-effective replacement for rabies immunoglobulin[{C}] • Conduct clinical research on optimal drug treatment regimens for etiologically confirmed *M. bovis* and non-tuberculous mycobacterial infections[{C}] • Evaluate the effectiveness of the standard DOTS regimen administered in cases of tuberculosis caused by *M. bovis* and non-tuberculous mycobacterial infections, as few cases are differentiated on the basis of culture results[{C}] • Develop new drugs for Chagas' disease that provide a shorter treatment course with fewer side-effects than nifurtimox and benznidazole, and devise paediatric formulations[{D}] • Find ways to overcome current problems of toxicity, efficacy, administration and length of treatment for CD, HAT and leishmaniases[{D}] • Discover and develop new drugs for kinetoplastid pathogens using the foundation laid by genome sequencing projects and the identification of potential drug targets[{D}] • Determine ways to confirm chemically validated drug targets and rigorously assess new drugs for chances of success by ranking against additional criteria such as druggability, assay feasibility, toxicity, and potential for the emergence of drug resistance for CD, HAT and leishmaniases[{D}] • Improve the usability of currently registered drugs, including a shortened 10-day course (rather than 21–35 days) of melarsoprol that followed pharmacokinetic studies and a clinical trial with a 3-day course of pentamidine for HAT[{D}] • Identify new drug candidates for HAT, particularly new molecules with trypanocidal activity that can penetrate the blood brain barrier[{D}] • Find ways to preserve the utility of drugs for CL and VL forms of leishmaniasis[{D}] • Determine how to overcome challenges of drug resistance, limited efficacy for different strains and species, and cost for VL pentavalent antimonials and lipid amphotericin B formulations[{D}] • For CL, focus on preserving the potency of pentamidine, fluconazole, azithromycin, itraconazole used as systemic therapy for cutaneous, mucocutaneous, diffuse cutaneous and post kala-azar dermal leishmaniasis, and heat therapy, cryotherapy, and intralesional antimony drugs used for cutaneous

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
		forms of the disease[{D}] • Conduct much needed double-blind clinical trials of ribavirin to determine whether ribavirin is improving the survivor rate Crimean-Congo haemorrhagic fever[{E}]
VACCINES	• Develop new models for preventive immunization against NTDs[{B}] • Develop more animal vaccines against transmission of NTDs[{C}] • Focus on new vaccine development for leishmaniasis, Chagas disease, hookworm infection, schistosomiasis, dengue, and enteric bacterial pathogens[{I}]	• Explore anti-helminth vaccines as part of the solution to control helminthic infections of poverty[{A}] • Further assess different vaccine strategies/options/combinations for echinococcosis, e.g. a vaccine for ovine echinococcosis and development of a vaccine for use in definitive canine hosts[{C}] • Develop animal vaccines for toxoplasmosis[{C}] • Develop a livestock vaccine to block animal infection and consequently reduce the excretion of infectious cysts into the environment and transmission of infection to humans[{C}] • Establish reliable, economical and harmonized *in vitro* laboratory tests to ensure the quality and in particular the potency of rabies vaccines[{C}] • Develop combined approaches to dog rabies vaccination and immuno-contraception[{C}] • Develop effective livestock vaccines and vaccination strategies for *M. bovis* that are feasible in most developing countries[{C}] • Critically assess the immunogenic properties of currently available brucellosis vaccines and their effectiveness in areas of high endemicity[{C}] • Find ways to improve the safety and immunogenicity of the current vaccines against *Brucella melitensis* and *Brucella abortus*[{C}] • Develop multivalent, low-cost, locally produced vaccines for enteric diseases that are sufficiently effective to interrupt transmission cycles[{C}] • Investigate vaccines to prevent *Leishmania* infection and disease, and vaccines to block transmission of *Leishmania*[{D}] • Develop prophylactic or therapeutic vaccines for Leishmania and assess the importance of asymptomatic infection in CD, HAT and leishmaniases[{D}] • Examine the host-pathogen relationship when developing prophylactic, therapeutic or transmission-blocking vaccines for CD, HAT and leishmaniasis[{D}] • Develop a vaccine protocol that could be used to reduce transmission of *T. cruzi* to humans for Chagas disease; this is a practical and achievable goal within a short time frame[{D}]

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
		• Develop a live vaccine that could be delivered orally to larger groups of animals against *T. cruzi* infection; the vaccine not need to be 100% effective in preventing infection since reducing the level of infectiousness of dogs for insects could impact transmission{D} • Test the efficacy of a human vaccine for CD and its potential integration with other control mechanisms{D} • Develop a HAT vaccine that blocks initial infection given the repertoire of surface antigens produced by the metacyclic parasites that are transmitted by the tsetse fly is much more limited than the repertoire of the bloodstream forms{D} • Determine how to utilize the findings from basic science studies of HAT to identify targets for vaccine development that would prevent CNS entry or pathogenesis{D} • Develop a transmission-blocking vaccine for HAT that would prevent establishment of the parasite in the tsetse vector{D} • Develop a prophylactic vaccine for leishmaniasis based on the strong naturally acquired resistance that develops following a primary infection as well as demonstrated protection seen in a variety of animal models{D} • Investigate and validate the possibility that no non-living vaccine will be able to generate, and more importantly maintain, the level of cell-mediated immunity necessary to protect against sandfly-transmitted infections in humans{D} • Develop animal models and test leishmaniasis vaccines in dogs as they can be evaluated using natural exposure{D} • Explore killed whole cell vaccines for their low cost, ease of production, have prophylactic and therapeutic potential for leishmaniasis{D} • Focus specifically on vaccine product development for Amebiasis, Chagas disease, HAT, Leishmaniasis, Food-borne trematodiases, Onchocerciasis, Schistosomiasis, Hookworm, Strongyloidiasis, Dengue and other flaviviruses, Rabies, Rift Valley Fever, Bovine TB, Cholera, Enteric pathogens (Gram Neg), Leprosy, Leptospirosis, Rheumatic fever, Trachoma, Treponematoses and Paracoccidiomycosis{I}
VECTOR CONTROL	• Concentrate on developing innovations in vector control for dengue, Chagas disease, lymphatic filariasis, the Leishmaniases and onchocerciasis to	• Identify ways to strengthen national capacities in medical entomology, entomological surveillance and operational research{B} • Develop career paths and incentives for entomologists to pursue public-health entomology instead of academic research{B}

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	reduce transmission[{B},{D},{I}] • Develop safe and effective products for vector control that do not rely on insecticides [{B}] • Find ways to reduce the time needed to bring new products to market by as much as possible[{B}] • Find ways to achieve a collaborative approach among sectors for agriculture, health and the environment to achieve the sound management of pesticides[{B},{D},{F}] • Learn how to better integrate veterinary public health services into the control of neglected zoonotic diseases[{B},{C},{F}] • Develop bold new approaches to gauge the risk of zoonotic pathogens spreading from their natural reservoirs to humans, and their potential to become new human infectious pathogens[{F}] • Investigate new vector control technologies, including markers of successful vector control for Chagas disease, Human African Trypanosomiasis and Leishmaniasis[{D}] • Research vector population characteristics, including insecticide resistance for Chagas disease, Human African Trypanosomiasis and Leishmaniasis[{D},{I}] • Explore new techniques to develop vectors resistant to pathogens by infecting them with naturally occurring intracellular insect parasites (eg,	• Prioritize studies on multi-disease packages and host approaches for selected neglected zoonotic diseases in order to improve and sustain the cost effectiveness of efforts to control these diseases[{B}] • Develop ways to control vectors by treating potential sources of unsafe water with temephos (Abate) and distributing filters to strain water[{B}] • Identify how to improve environmental sanitation against NTDs e.g., storm water drainage (leptospirosis), land drainage (fascioliasis) and community-led total sanitation (cysticercosis) [{B}] • Conduct studies of disease burden in both humans and animals in both urban and rural settings in a manner that brings the human and veterinary health communities together[{C}] • Determine the role of the variety of animals in transmission as reservoirs for *Schistosoma japonicum* and *S. mekongi* (buffalo or others such as dogs, cats or rats) [{C}] • Determine the precise role of carabao (water buffalo) in the transmission of *S. japonicum* in the Philippines[{C}] • Identify agricultural practices that reduce the exposure of livestock to cryptosporidiosis infection in order to interrupt transmission to humans[{C}] • Assess vector infestation in Chagas disease[{D}] • Delineate target vector populations of human African trypanosomiasis[{D}] • Define cost-efficient insecticidal targets for control of human African trypanosomiasis as a prevention strategy[{D}] • Understand the factors that influence house invasion by sylvatic Triatominae and why some bugs may succeed in colonizing a house while others do not[{D}] • Determine how to produce more cost-effective, target-based control technologies for HAT that will impact the *gambiense* reservoir of parasites in the *gambiense* form of disease that resides in humans[{D}] • Determine the effective reservoir of parasites in the *rhodesiense* form of disease resides in domestic or wild animals[{D}] • Develop vector source reduction for leishmaniasis using environmental measures that could include:[{D}] o rendering soil unsuitable for sandfly larvae, thereby reducing the numbers of emerging sandflies[{D}] o spraying of flowering trees[{D}]

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	Wolbachia)[{G}] • Find ways to attempt to control many vector-borne pathogens that are zoonotic and have transmission intensity in vectors driven primarily by wildlife reservoirs[{G}] • Focus new vector control product/transmission-blocking zoonotic animal reservoir product development on Chagas disease, HAT, Leishmaniasis, Taeniasis-cysticercosis, Echinococcosis, Food-borne trematodiases, Lymphatic filariasis, Onchocerciasis, Schistosomiasis, Ascariasis, Toxocariasis, Dengue and other flaviviruses, Rabies, Rift Valley Fever and Bovine TB[{I}]	o indoor residual spraying, insecticide treated nets and vector repellents[{D}] • Determine how to provide more accurate estimates of the distribution of the *Hyalomma* spp tick responsible for Crimean-Congo haemorrhagic fever[{E}] • Determine optimal regimens to control *Hyalomma* spp ticks using insect repellent and livestock insecticidal sprays[{E}] • Identify ways to enlist experts to map the behaviour of the *Hyalomma* spp tick, particularly in response to population and ecological changes[{E}] • Conduct long-term multicentre studies to improve understandings of natural variation, changes with time, interspecies transfer and the dynamics of antimicrobial resistance in wildlife, both naturally occurring and arising from anthropogenic influences[{F}] • Conduct observations studies and experimental work with wildlife that could provide valuable insights into understanding the population and community effects of antimicrobial use and persistence of changes[{F}]
EPIDEMIOLOGY	• Find ways to gather more accurate estimates of the global disease burden for NTDs[{C},{D},{E}] • Develop and refine mathematical models to investigate relationships between infection and morbidities to aid programmes aiming to reduce the burden of disease (elimination of public health problem) [{A}] • Determine how to increase the use and application of epidemiological models to aid M&E and surveillance, the design of cost-effective sampling protocols and the monitoring of intervention efficacy including drug resistance [{A}] • Identify how to produce updated helminth disease prevalence maps[{A}] • Develop tools and systems for post-	• Find ways to ensure mathematical models take into account cumulative effects of chronic disease for evaluation of disease burden and the impact on such burden of control interventions[{A}] • Determine how to link epidemiological models to cost-effectiveness analyses of NTD interventions and their alternatives[{A}] • Find ways to monitor the progress of control interventions and quantify changes in incidence of infection and disease[{A}] • Develop maps of helminth infection and co-infection as well as of intermediate hosts' and vectors' distribution to enable accurate assessment of distribution and burden of disease[{A}] • Assess the contribution of systematic non-compliant persons as well as of migrants and refugees, pregnant/lactating women and under five-year olds to the maintenance of transmission[{A}] • Identify and evaluate climate and environmental changes that impact helminth infections[{A}] • Develop and refine models to investigate relationships between infection and transmission thresholds to aid programmes aiming to eliminate the infection reservoir[{A}]

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	control surveillance[{A}] • Determine how to optimize existing/ develop novel instruments for effective surveillance, including prompt detection of resistance, pharmacovigilance, and post-intervention surveillance systems[{A},{B},{C}] • Collect epidemiological data that shows the differential impact of NTDs according to a patient's sex and age in order to better inform policies, and guide targeted interventions for sustainable control[{B}] • Conduct small-scale focused epidemiological studies on zoonoses to gather basic information for the design of control programmes and awareness generation and to support advocacy[{C}] • Determine how to re-attribute the burden of morbidity and mortality attributed to diseases and conditions (cancers, neurological conditions, injuries) to the neglected parasitic/zoonotic diseases[{C}] • Re-evaluate the societal burden of disease for zoonoses[{C}] • Better understand how changes in the environment affect zoonotic disease trends, and how these changes affect microbial dynamics across the system[{F},{J}] • Utilize combined public health and ecology approaches to drive advances in predicting the emergence and spread of novel zoonoses[{F},{J}] • Understand the relation between environmental changes, wildlife	• Develop metapopulation and spatially-explicit parasite transmission models[{A}] • Develop and validate mathematical models for co-infections[{A}] • Find ways to fill gaps in the knowledge about the burden of Leishmaniasis and its incidence in most endemic countries[{B}] • Find ways to ensure that assessments of the burden of zoonoses take into account their dual burden on the health of humans and of livestock, and thus their total cost to society[{B}] • Develop and validate transmission dynamics models to assess the cost−effectiveness and cost−benefits of alternative control strategies for cysticercosis and taeniasis, echinococcosis[{C}] • Find ways to measure the health and economic burden of echinococcosis caused by both *E. granulosus* and *E. multilocularis*, including productivity losses in humans and animals and cost−effectiveness of current control approaches[{C}] • Determine how to estimate the global burden of foodborne trematodiases (FBT)[{C}] • Evaluate national FBT disease surveillance, and its effectiveness in tracking FBT infections[{C}] • Find ways to quantify the impact of improved water quality and sanitation on toxoplasmosis infection[{C}] • Find ways to quantify the proportion of chronic abortions globally that are attributable to toxoplasmosis[{C}] • Determine how to document the burden of cryptosporidiosis in young children in developing countries[{C}] • Determine the extent of livestock as source of *Cryptosporidium* infections in humans in the developing world[{C}] • Develop and evaluate new technologies for integrated, real-time rabies surveillance and response (e.g. mobile computing technologies)[{C}] • Develop cross-sectoral assessments of the bacterial zoonoses disease burden to allow for realistic evaluation of the cost−effectiveness of disease interventions[{C}] • Construct a common measure of zoonotic disease burden that incorporates human health indices, costs to the public health sector, monetary burden for the livestock sector and costs to the private sector[{C}] • Better understand the human disease burden of zoonotic tuberculosis, and how and why the prevalence of human *M. bovis* and non-tuberculous mycobacterial infections varies in different communities[{C}]

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	population dynamics, and the dynamics of their microbes to forecast risk of human infection with enzootic or endemic zoonoses[{F},{J}] • Investigate the dynamics of zoonotic pathogens in their wildlife reservoir to learn if potential early warning systems can be developed to better inform the risk of an outbreak in livestock or people, and ultimately reduce the number of cases of human disease[{F},{J}] • Determine how to standardize data collection and find ways to increase long-term monitoring and risk assessment for the development of multidrug resistance or multi-bacterial infections in human beings resulting from antimicrobial use in food animals and from wildlife[{F}] • Acquire a robust understanding of how all aspects of climate and climate change affect rates of the processes involved in transmission of vector-borne pathogens[{G}] • Determine the relative importance of host relatedness versus contact frequency in the emergence of zoonotic diseases[{H}] • Develop collaborative models that include researchers, public health agencies, the government, and the public to identify the causes of increases in incidence and subsequent targeting with appropriate control measures to reverse the ecological drivers of vector-borne disease emergence, e.g. risk related to specific types of land use could be ameliorated by urban planning and management of host	• Identify animal-related risk factors for human infection with different mycobacterial species of zoonotic TB, including potential factors associated with small ruminants[{C}] • Generate data and develop methodologies to allow an accurate estimation of the societal burden of brucellosis, focusing primarily on burden of disease in livestock and human populations[{C}] • Develop better methods for surveillance of human enteric infections, including syndromic classification and etiology if possible, based in representative community settings, both urban and rural, and across the whole age range[{C}] • Clarify the reservoirs for animal and human enteric infections and the pathways of transmission among animals, from animals to humans, from humans to humans and from humans to animals[{C}] • Determine how to implement ongoing surveillance for enteric disease drug resistance and determine the most effective means to disseminate this information[{C}] • Measure the effectiveness of Community-Led Total Sanitation (CLTS) on incidence and prevalence of zoonotic and marginalized diseases through epidemiological studies and community-based randomized trials[{C}] • Assess the DALY burden borne by individuals affected by zoonotic diseases[{C}] • Assess the monetary impact of zoonoses to livestock and human productivity[{C}] • Study risk factors in both people and animals with a view to successfully targeting at-risk groups for high-priority intervention of zoonoses[{C}] • Investigate methods for quantifying the rate of underreporting of zoonotic diseases in humans[{C}] • Develop transmission dynamics models to predict the effectiveness of alternative control measures for zoonoses[{C}] • Conduct cohort studies on several zoonoses in which the symptoms in humans appear several years after infection[{C}] • Conduct randomized trials to estimate the effectiveness of alternative control strategies, including integrated/combined strategies for zoonoses[{C}] • Investigate surveillance methods for Chagas disease and human African trypanosomiasis, and economic analysis of treatment and vector control methods for CD, HAT and leishmaniasis[{D}] • Determine how to provide a more accurate estimate of global Crimean-Congo

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	and vector communities through landscaping, hunting, or restoration of ecological communities [{G},{J}] • Assess the utility of GIS and bioclimatic monitoring systems to measure, anticipate and plan for infectious disease outbreaks, and to build infrastructural capacity in disease endemic countries (e.g. HealthMapper, Global Health Atlas, TREES Project)[{J}] • Determine the socioeconomic impact of zoonotic diseases on livestock production and the consequences that control measures of such disease have for the livestock trade[{J}] • Determine zoonotic diseases' impact on wildlife populations and biodiversity[{J}] • Investigate how social variables (gender, ethnicity, culture) influence human-animal interactions, the transmission of disease, cultural aetiologies of disease and patterns of health-seeking[{J}] • Identify the social and mental health consequences of disability caused by infectious disease (e.g. social stigma, fear) [{J}]	haemorrhagic fever (CCHF) prevalence and distribution using improved surveillance methods[{E}] • Investigate why the burden of CCHF is higher in Turkey than elsewhere so that other countries can draw conclusions about their own risks, e.g. whether it is due to the environment, the virus, a genetic factor, or something to do with the tick vector[{E}] • Find ways to encourage collaboration between public health scientists, who normally use epidemiological techniques with human case data, and disease ecologists who often work with wildlife or livestock data to model risk in human beings[{F}] • Determine how to expand the breadth of analyses investigating the relationship between climate and vector-borne pathogens to include all potential factors affecting incidence of infection and prevalence of disease, both biological and non-biological[{G}] • Develop vector-borne disease predictions based on climate that are truly cross-disciplinary, evidence-informed collaborations, marrying biologists' pursuit of improved models of vector abundance, infection prevalence, and pathogen evolution (eg, drug resistance) with understanding from medical and social scientists about developments in treatment and interventions, land-use change, and human societal factors[{G}] •
PUBLIC HEALTH AND OPERATIONAL RESEARCH	• Find ways to optimize the deployment of existing intervention tools to maximize impact (including impact against polyparasitism) and sustainability, with focus on pharmaceuticals, vaccines, vector control and ecohealth approaches (sanitation, clean water, improved nutrition, education)[{A},{B}]	• Develop surveillance systems for monitoring the sub-optimal response by *Onchocerca volvulus* to ivermectin[{A}] • Conduct operations research to address challenges and needs to help fill programmatic gaps in *O. volvulus* and lymphatic filariae control[{A}] • Investigate how helminth parasites modulate host–parasite interactions at the population level [{A}] • Determine how to incorporate environmental considerations and health education into helminth control programs to facilitate programme integration and

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	• Develop strategies incorporating delivery of multiple interventions at various levels to maximize sustainability of control programmes in general, and of integrated neglected tropical diseases (NTD) control in particular[{A},{B}] • Examine community-directed intervention successes, issues, challenges and needs for NTDs[{A}] • Develop strategies (taking gender issues into account) to increase awareness of ill-health processes, community participation, ownership and empowerment, as well as equity in access to health services for communities and risk groups[{A}] • Find ways to build adequate research capacity for the management of helminthiases and other infectious diseases of poverty[{A}] • Identify ways to steer intervention from disease control towards permanent elimination[{A}] • Find ways to combine five public-health strategies and deliver them locally to overcome NTDs: (i) preventative chemotherapy; (ii) innovative and intensified disease-management; (ii) vector control and pesticide management; (iv) safe drinking-water, basic sanitation and hygiene services, and education; and (v) veterinary public-health services[{B}] • Determine how to change paradigms of reactive approaches to disease outbreaks	sustainability[{A}] • Identify the social and environmental structures that contribute to the maintenance of helminth infection (including polyparasitism) for developing multi-disciplinary interventions[{A}] • Develop strategies incorporating delivery of multiple interventions at various levels to maximize sustainability of control programmes in general and of integrated NTD control in particular[{A}] • Determine how to strengthen understanding of the sociological, behavioural, political and economic drivers of helminth infection and control to improve community knowledge/education, achieve empowerment/equity/gender, participation and ownership; and increase intervention coverage, compliance and sustainability[{A}] • Find ways to continuously update and share data platforms to optimize data management, analysis, and (mathematical/statistical/ geographical/climate change) modelling, integrating scientists, stakeholders and end-users[{A}] • Develop appropriate health research policies and capacity building in disease-endemic countries to provide conducive environment and adequate expertise for sustained disease control efforts[{A}] • Determine how national programmes can develop a culture of integrated and coordinated planning and NTD programme management to enable programmes to scale up effectively and encourage commitment from governments[{B}] • Find ways to achieve universal coverage of prevention and control interventions for neglected tropical diseases [{B}] • Find ways to increase access to essential medicines of assured quality at affordable prices and a well-trained and motivated work force to delivery NTD treatment services[{B}] • Determine ways to involve sectors other than health, including finance, education, agriculture and veterinary public health, water and sanitation, and environmental management in NTD research and control[{B},{J}] • Develop methods to overcome obstacles and risks to implementation, e.g. the effects of natural disasters and human conflicts that result in the displacement of millions of people, and disrupt public-health interventions and disease surveillance[{B}] • Investigate how to build sufficient human-resources capacity (both technical and

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	and instead implement sustainable preventive measures that are guided by entomological and epidemiological surveillance[B] • Develop procedures and alternative strategies that can be used if drug resistance is detected[B] • Find ways to expand the surveillance for zoonotic diseases in humans and animals[C] • Develop guidelines for implementing integrated surveillance to better define the problem of zoonoses[C] • Develop plans for prevention and control activities for zoonoses[C] • Conduct, maintain and report inventories of control activities and tools currently being deployed for zoonotic diseases[C] • Conduct more extensive studies on the costs of zoonotic intervention, the cost–benefits and cost–effectiveness[C] • Conduct operational research on integrated disease and vector control for Chagas disease, Human African Trypanosomiasis and Leishmaniasis[D] • Determine how to promote the One Health perspective to understand the ecology of zoonotic diseases at the human being–animal interface, and integrate knowledge of animal and human medicine, agriculture, ecology, sociology, microbial ecology, and evolution, and the underlying issues that drive increased transmission of pathogens	managerial) required to support the scaling up of interventions at all levels of national health-care systems as well as to mobilize resources[B] • Develop closely coordinated programme planning, service delivery and shared indicators for monitoring and evaluation of the control of lymphatic filariasis and onchocerciasis[B] • Identify opportunities to implement control measures for Buruli ulcer together with other public health programmes[B] • Identify how to implement advocacy and awareness campaigns that will be followed by intensified leprosy detection and treatment at the local level in countries that report more than 1 000 new cases annually[B] • Find ways to coordinate operational research to increase early diagnosis and the quality of leprosy services[B] • Intensify leprosy research by investing in the development of diagnostics and treatment, and working to prevent neuritis[B] • Find ways to ensure control and research efforts for African trypanosomiasis are based on sustainable public health objectives, not only on the actual burden of the disease[B] • Develop and validate standard methodology for Taeniasis/Cysticercosis intervention in endemic communities[B] • Determine how implement combined strategies for Taeniasis/Cysticercosis elimination, including achieving routine vaccination of pigs in endemic areas, better management of pig farms and pork production practices, improved sanitation, and health education[B] • Design and identify ways to scale-up innovative and intensified disease-management for Buruli ulcer, Chagas disease, both forms of human African trypanosomiasis, the Leishmaniases (cutaneous, mucocutaneous and visceral forms), leprosy and yaws[B] • Determine how to improve individual case management by finding ways to diagnose cases early, provide treatment to cure or reduce infection and morbidity, manage complications, and adopt strategies to respond appropriately to different levels of endemicity and health-system capacity[B] • Find ways to scale up interventions for control and elimination of neglected zoonotic diseases when feasible in select geographical and epidemiological settings[B]

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	in humans, wildlife, and livestock[{F},{H},{J}] • 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[{F}] • 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 [{F},{G},{H},{J}] • 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[{G},{J}] • 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[{H}] • 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	• 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[{B}] • 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[{B}] • Determine ways to maintain and generate needed expertise at the national level and to improve programmes' abilities to adapt to local conditions[{B}] • 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[{B}] • Find ways to scale-up environmental interventions for NTDs[{B}] • Determine how to improve husbandry practice and upgrade abattoirs and meat inspection, particularly for echinococcosis, cysticercosis and bovine tuberculosis[{B}] • Determine the economic cost of neglected zoonoses for both the human and animal populations involved[{C},{J}] • 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[{C}] • Investigate promotion of health literacy and social mobilization to ensure maximal engagement of the affected populations in the selected interventions[{C}] • 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[{C}] • 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[{C}] • 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[{C}]

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	the spread of infectious diseases{J} • Develop methods to ensure that research findings, clinical experience and learning from both human and veterinary domains are connected{J} • 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{J} • Develop research frameworks to assess the reciprocal impact of global initiatives, national health systems and intersectoral governance on infectious disease control{J} • 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{J} • Learn how to improve access and appropriate use of quality medical technologies for infectious disease control{J} • Determine how stand-alone disease control information systems be integrated into existing national health information systems and into general health decision-making processes{J} • Investigate how to develop research frameworks to assess the interaction between Global Health Initiative-targeted	• 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{C} • Find ways to increase interest in the discovery and development of new diagnostic tools, vaccines and new trematocidal drugs for foodborne trematodiases{C} • Determine how to improve access to clean water, adequate sanitation and sewage treatment, and enhanced food safety measures to have an impact on foodborne trematodiases{C} • Develop integrated control approaches and intersectoral collaboration between public health and veterinary medicine for foodborne trematodiases, including collaboration on considerations of feasibility, efficacy and cost–effectiveness{C} • 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 trematodiases{C} • Analyze gender (male and female) differentials on access to and compliance with FBT treatment for foodborne trematodiases (FBT){C} • Develop appropriate and gender-sensitive tools and methods to assess the socioeconomic impact of FBT on individuals, households, communities and societies{C} • 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{C} • Assess the cost–effectiveness of integration of existing serological test regimes for toxoplasmosis into antenatal care programmes in low-income settings{C} • Develop culturally acceptable health education programmes to improve food hygiene in the home, especially for pregnant women, to prevent toxoplasmosis infection{C} • 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{C} • Assess the impact of community-level water and sanitation improvements on the

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	services and non-Global Health Initiative-targeted services so that overall service delivery is improved[{J}] • Develop leadership strategies and mechanisms to share common values of equity and the right to healt, community involvement and sustainability across diverse actors through an outcome-oriented approach[{J}] • 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[{J}] • 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)[{J}] • 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?)[{J}] • Investigate the impact of product	prevalence of human cryptosporidiosis infection in both urban and rural settings[{C}] • 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[{C}] • Find ways to establish prioritization and cooperation of rabies control between health, veterinary and wildlife agencies[{C}] • Evaluate the cost−effectiveness of different WHO-recommended pre and post-exposure regimens or rabies, including indirect costs associated with hospital visits[{C}] • Investigate the economics of dog oral vaccination strategies and identify appropriate settings for implementing oral vaccination campaigns in dogs[{C}] • 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[{C}] • 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[{C},{F},{G}] • Develop approaches to raise awareness among physicians of the need for differential diagnosis of *Brucella* in cases of non-specific febrile illness[{C}] • 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[{C}] • Develop infrastructure and capacity to identify zoonotic enteric pathogens in the relevant animal populations[{C}] • 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[{C},{J}] • Develop ways to improve the communications between veterinary and human health professionals, to include integrated training modules and mechanisms for exchange of information[{C},{J}] • Identify how to create joint veterinary/human health outbreak investigation teams, with access to quality laboratory capacity for diagnosis allied to

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	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{J} • Determine the most effective ways to implement the criteria for innovation (effectiveness, affordability, acceptability and sustainability) in national and global innovation systems{J} • 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{J} • Identify strategies and social entrepreneurship models that are available for local communities to innovate in the prevention, control and treatment of infectious diseases{J} • 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{J} • 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){J}	enhancement of veterinary and human grassroots public health educational services (educational extension model) to improve animal and human health outcomes{C},{J} • 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{C} • 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{C} • Create new approaches to community sanitation measures and the provision of clean water supplies{C} • Estimate the duration of “open defecation free” (ODF) status following CLTS{C} • Estimate the cost–benefit of CLTS as compared with other approaches{C} • Study the human-animal interface to clarify the social, cultural, behavioural, economic and gender dimensions of improving community access to proper sanitation through CLTS{C},{J} • Evaluate the impact of CLTS on specific communities dependent on equines and camelines, smallholder pig farmers and those dependent on aquaculture{C} • 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{C} • 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{C} • Find ways to extend the concept of zoonoses to cover diagnosis, data-sharing, monitoring and surveillance systems, training, interventions and delivery{C} • Conduct long-term (longitudinal) studies assessing health education “multipacks”, i.e. for diseases with similar or overlapping bio-social determinants{C} • 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{C} • Organize and conduct comparative studies on traditional versus participatory research for zoonoses and marginalized infections{C} • Conduct evaluation research (assessment of methodologies for

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	• Determine the most effective way to link the local milieu of innovation in the public and private sectors in LMICs with international partners[J] • Develop sophisticated regulatory and intellectual policies to provide the framework for an open innovative platform[J] • Develop and refine processes to assess health interventions and technologies as inputs to budget decision making and the design of publicly subsidized health benefits[K]	programme/project evaluation) for zoonotic diseases[C] • Assess the specific contribution of educational components within integrated interventions[C] • Expand systems research to determine how best the different sectors can interact[C] • Find ways to integrate animal and human disease expertise with social science perspectives[C] • 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[C] • Create opportunities to evaluate and modify zoonotic control strategies as experience is gained in implementation[C] • 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[C] • Expand research on the use of new communication technologies such as smart phones to enhance surveillance, reporting and evaluation of zoonoses[C] • 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[E] • 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[F] • 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[F] • 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[F] • Develop guidelines for safe or best practices that include ecological knowledge to

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
		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{F} • 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{G} • Develop behavioural change strategies promoting personal protective behaviours to prevent the emergence of endemic or exotic pathogens{G} • 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{J} • Determine the best open-access models for sharing of new knowledge and products, and the delivery of new innovations{J} • Find ways to highlight the importance of innovation by engaging key players in global networks{J} • Develop and work towards a "one world-one research" community agenda{J} • 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.) {J} • 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{J} • Create monitoring systems to track pharmacological side effects and community attitudes towards health technologies and to strengthen capability to translate technologies into local solutions{J} • 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,

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
		particularly in disease endemic countries[{J}] • 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[{J}]
INNOVATIVE FINANCING	• 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[{B}] • Find ways to advance political will and commitment to increase the capacity of helminth disease research in disease-endemic countries[{A},{B}] • Determine how to generate investments in South–South collaborations for helminth R&D[{A}] • Determine how to increase investments in new drug and diagnostic test research and development programmes for enteric infections[{C}] • Determine how to increase R&D funding available for trypanosomatid diseases so that it is comparable with malaria, tuberculosis and HIV/AIDS[{D}] • Determine how to fill the funding gap for NTD product development within the US President's Global Health Initiative[{I}] • Identify how to allocate greater funding priority to research that adopts interdisciplinary approaches that encourage collaboration between government ministries and agencies, and	• 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 [{A}] • 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[{A}] • 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[{A}] • 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[{A}] • Develop innovative strategies for funding integrated and sustainable dog vaccination programmes, including education and social mobilization campaigns[{C}] • 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[{C}] • 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[{D}] • Develop strategies to increase the diagnostic and vaccine market for Crimean-Congo haemorrhagic fever[{E}] • 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[{I}]

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	that better incorporate ecology into disciplines – including public health, medicine, social sciences, veterinary sciences and agriculture[{J}] • Determine how to inspire greater investment in human capital and knowledge systems[{J}] • Determine the best mix of infectious disease control funding mechanisms to strengthen health system financing, and in what contexts[{J}] • Determine how global funding can be used to build mechanisms for innovation and health R&D in the lowest income countries[{J}] • 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[{J}] • Create incentives to invest in implementation research to complement advances in product development for infectious diseases of poverty[{J}] • Develop methods to avoid wastage and improve the efficiency of R&D funding for infectious diseases of poverty[{J}] • Find ways to strengthen the data reservoir concerning funding flows to infectious disease R&D[{J}] • Develop processes and methods to ensure that R&D funding is relevant to the needs on the ground[{J}] • Find ways to ensure that research capacity building activities are seen as integral to	• 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[{J}] • Find ways to reduce duplication and improve coordination of R&D funding for priority conditions by integrating goals and reducing overlap[J}] • Find ways to reduce competition for funds as a source of wastage[{J}] • Find ways to improve the coordination of priorities for action in order to harmonize approaches to R&D funding e.g. through the proposed model of the WHO Expert Working Group on Research and Development Financing[{J{] • 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[{J}] • Develop a classification system to organize data on R&D for health[{J}] • Find ways to resolve the issue of separating ultimate funders from recipients of funds and from intermediaries (such as PDPs) [{J}] • Develop information systems to help capture data on funding flows for R&D on health[{J}] • Investigate methods to build new funding capacity for supporting R&D in emerging economies such as Brazil, China and India[{J}] • Identify high-level actions on which policy-makers, funders and researchers should focus when developing their health research related strategies • Create and use a new index of infectious diseases of poverty to serve as a surrogate marker of national socioeconomic development[{J}] o Establishment of a framework of indicators for the index, based on a series of commissioned reviews and other research[{J}] o Identify institutions and other stakeholders, and provide funding to support development, piloting and small scale validation, in partnership with relevant stakeholders for the index[{J}] o Develop a stakeholders' platform to review, agree and recommend a strategy and framework for scale-up and implementation of the index[{J}] • 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

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
	the funding agenda[J] • Develop a strategic approach to the funding and support of research and to the generation and use of research outputs[J] • Find ways to reallocate part of public and donor monies toward the most cost-effective and equity-enhancing health interventions and technologies[K] • 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[K]	policies[J] • 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[J] • 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[J] • To facilitate LMIC health research ownership and strengthen partnerships with international donors, LMICs could:[J] o develop research priorities congruent with the burden of infectious diseases of poverty in their own populations; o find ways to increase their own research activity and improve research leadership; o develop regional partnerships to build research infrastructure, human resources and research capacity; o create policies and develop plans to guide national and international investments towards the identified research priorities; o develop plans to increase their national support for research and translation of research to strategies for health[J] • Create an innovation platform to foster a culture of innovation to benefit public health[J] o 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 o 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. o 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[J] • Create an easily accessible, online global platform that supports a database and detailed analysis of resources and financial investment in health research that can

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
		provide policy-makers, funders and researchers with information they need to guide their activities, identify funding gaps and mitigate duplicated efforts{J} • 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{K} • Develop platforms to direct donor support to countries creating or developing their own health technology assessment systems{K} • 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{K} • Investigate ways to increase the allocative efficiency of both global health donors and national health systems{K} • 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{K} • 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{K} • 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{K} • Build and find ways to support regional networks of policy makers and practitioners, such as HTAsiaLink{K} • 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{K} • Find ways to facilitate dialogue between health systems and industry to ensure that the benefits of new technology and system needs are mutually understood

R&D Areas	NEGLECTED TROPICAL DISEASES	
	Goal	***R&D Priorities for Achieving Goals***
		and reflected in price and availability[{K}] • Develop methods to ensure that health technology assessment facilities are of use both to countries with health technology assessment agencies and those without them[{K}] • 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[{K}] • 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[{K}] • Find ways to guarantee HTAFs' ability to ensure independence and transparency[{K}] • 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[{K}] • 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[{K}] • Develop methods to ensure HTAFs operate in close coordination with the WHO and the PAHO[{K}]

A. World Health Organization. Research Priorities for Helminth Infections. Technical Report of the TDR Disease Reference Group on Helminth Infections (DRG4). Technical Report Series No. 972. Geneva: World Health Organization; 2012.
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.
E. Burki T. Ticks and Turkey. Lancet. 2012; 380:1897-98.
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.
I. Hotez P. New Antipoverty Drugs, Vaccines, and Diagnostics: A Research Agenda for the US President's Global Health Initiative (GHI). PLoS Negl Trop Dis. 2011;5(5): e1133. doi:10.1371/journal.pntd.0001133.
J. World Health Organization. Global Report for Research on Neglected Diseases of Poverty. Geneva: World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases; 2012.
K. Glassman A, Chalkidou K. Priority setting in health: Building institutions for smarter public spending. Washington: Center for Global Development; 2012.

Synthesis of Disease-Specific R&D Priorities for Childhood Pneumonia and Diarrhoea

R&D Areas	CHILDHOOD PNEUMONIA AND DIARRHOEA	
	Goals	***R&D Priorities for Achieving Goals***
BASIC SCIENCE	• Find ways to optimize the current combination of zinc and ORS therapies{P} • Identify the developmental stages/ages at which children are most at risk of long-term cognitive impacts from diarrhoea • Elucidate the causal factors leading to death from pneumonia{Q} • Conduct research to refine pneumonia classification{Q} • Identify biomarkers that can rapidly differentiate bacterial from viral pneumonia to assist in focusing diagnostic development and antibiotic therapies{Q} • Develop an adaptable research approach to the etiological investigation of pneumonia, particularly for pneumonia of unknown etiology and emerging lung infections{Q} • Elucidate the pathophysiology of pneumonia and immune regulation of the inflammatory response to lung infection{Q} • Conduct research into the role of innate immunity in severe cases of childhood pneumonia{Q}	• Assess whether a mixture of zinc and ORS be developed that successfully reduces duration and stool output{P} • Determine whether there is a critical window for early childhood diarrhoea that can affect future physical and mental development, e.g. at 0–6 months, 6 months –2 years, or 3–5 years of age{P} • Find ways to gather more detailed information about the etiology and pathophysiology of the disease{Q} • Find ways to refine classifications of pneumonia using clinical signs and a more sophisticated radiological interpretation{Q} • Assess and validate the diagnostic potential of IL-1 receptor antagonist, IL-1beta, IL-6, IL-8, G-CSF, TNF-alpha, and soluble triggering receptor expressed on myeloid cells (sTREM) for cases of severe bacterial infections in the developing world{Q} • Investigate the relative contribution of multiple viruses in the genesis of respiratory pathology and their interactions with bacterial pathogens{Q} • Determine why H5N1 influenza causes severe pneumonia in children, whereas the SARS-CoV causes milder disease{Q} • Investigate factors that influence the control of inflammation{Q} • Better understand the balance of roles between TLRs and cytokines in modulating lung inflammation to help explain the mechanisms of action of zinc{Q}
DIAGNOSTICS	• Find ways to improve point-of-care diagnostic techniques{A} • Develop means to improve diagnostic ability to identify the bacterial aetiology of pneumococcus{J}	• Find ways to use new diagnostic tools inter-alia in studies estimating burden of disease as well as vaccine effectiveness studies to accurately interpret the impact of a vaccine on IPD{J} • Identify diagnostics that do not require samples from within the lung, yet may be more sensitive than blood culture isolation, to aid monitoring efforts of vaccine

R&D Areas	CHILDHOOD PNEUMONIA AND DIARRHOEA	
	Goals	***R&D Priorities for Achieving Goals***
	• Develop a gold standard against which to test new diagnostics for childhood pneumonia[{Q}] • Develop a rapid, easy to use, inexpensive diagnostic test for childhood pneumonia[{Q}]	impact on invasive pneumococcal disease (IPD)[{J}] • Determine the causal attribution of organisms identified in blood or nasal secretions in the etiology of pneumonia[{Q}]
DRUGS	• Investigate new ways to treat childhood pneumonia[{A}] • Develop Amoxicillin 250 mg dispersible tablets as the key target product for treating pneumonia[{N}]	• Develop non-liquid and mucosal antibiotic paediatric formulations to treat childhood pneumonia[{A}]
VACCINES	• Find ways to improve efficacy of low-cost pneumococcal conjugate vaccines for childhood pneumonia[{A}] • Find ways to achieve the Global Immunization Vision and Strategy targets for vaccines against measles and pertussis[{H},{M}] • Assess the potential impact of all emerging vaccines and immunotherapy against *Staphylococcus aureus* and determine an investment strategy based on key prioritization factors[{I}] • Develop an essential multi-component vaccine for *S. aureus*[{I}] • Develop a multivalent pneumococcal conjugate vaccine covering all serotypes and/or a cross-protective common protein vaccine to significantly reduce the burden of pneumococcal disease in children under age 5 years[{J}] • Investigate the health systems and contextual factors that affect the	• Develop common-protein pneumococcal vaccines[{A}] • Find ways to improve existing vaccines (eg, measles or *Haemophilius influenzae* type b) to enable needle-free delivery and heat stability[{A}] • Develop more combination vaccines and vaccines against major viral pathogens[{A}] • Find ways to introduce pneumococcal conjugate vaccine (PCV) and Haemophilus influenzae type B (Hib) vaccines into the national immunization programmes of high-mortality countries[{H}]Investigate and resolve issues relating to optimal antigenic target identification, criteria for acceptable efficacy, identification of the target population in children as well as adults, commercial development limitations, optimal timing of immunization strategy, storage and cold chain requirements, cost of development and cost effectiveness for a potential *S. aureus* vaccine[{I}] • Identify the right combination of, and find ways to combat, more than one virulence factor for *S. aureus* in the human host[{I}] • Direct pneumococcus vaccine research efforts towards developing a low cost pneumococcal protein vaccine (PPV)[{J}] • Investigate how increasing the number of doses or alter the timing of doses given as part of the oral rotavirus primary vaccine series affects performance[{K}] • Assess the role of zinc and probiotic supplementation at the time of rotavirus vaccination[{K}] • Evaluate the potential interference of maternal antibody and breastfeeding in rotavirus vaccine efficacy[{K}] • Investigate how adding an additional dose of vaccine at a later age may improve the

R&D Areas	CHILDHOOD PNEUMONIA AND DIARRHOEA	
	Goals	***R&D Priorities for Achieving Goals***
	distribution of vaccines[J] • Develop strategies to improve the performance of oral rotavirus vaccines[K] • Design approaches to monitor the safety of rotavirus vaccines and understand the relationship between rotavirus vaccines and intussusception[K] • Identify modifiable factors to maximise rotavirus vaccine protection and reduce the effectiveness gap between low-income and high-income settings[L],[M] • Investigate ways to increase the availability of high-quality zinc supply in-country[N] • Develop tools to guide the design and implementation of high-impact demand generation programs at scale for zinc and ORS[N] • Develop novel vaccines against the animal coronaviruses that could be precursors of future SARS-like diseases[Q] • Develop an effective RSV vaccine to guard against pneumonia and bronchiolitis due to RSV infection[Q]	duration of protection from vaccination[K] • Find ways to establish background rates of intussusception in select countries of Africa and Asia[K] • Examine treatment patterns for intussusception, rates of surgery and outcomes[K] • Evaluate and validate the Brighton case definition for intussusception in a variety of settings[K] • Conduct self-controlled case-series studies to examine if a short-term increase in risk of intussusception following rotavirus vaccination exists in other settings[K] • Investigate the recommended age restrictions for when to give the first and last doses of the rotavirus vaccine to minimise risk of intussuseption and optimize the timeliness of vaccination in low-income countries[K],[L] • Conduct research on modifiable strategies to increase rotavirus performance in under-resourced settings, e.g. changes to the age that children receive vaccine, delaying breastfeeding for a few hours after vaccination, decoupling of rotavirus vaccination from oral poliovirus vaccination, and provision of concomitant zinc and probiotics[L] • Assess how a booster dose of rotavirus vaccine given with measles vaccination might increase protection after age 1 year in low-income settings[L] • Map the availability (registration and over-the-counter (OTC) status) of zinc in high-burden countries and conduct quality surveys of specific products to inform appropriate quality standards[N] • Identify mechanisms to provide technical support to selected manufacturers to meet defined quality standards of zinc supplements[N] • Design and coordinate regional regulatory activities for zinc (e.g., joint regulatory reviews for product registration and OTC status)[N] • Determine how to best support in-country design and implementation of strategies targeting increased uptake of zinc/ORS among consumers and providers in private and public sectors[N] • Conduct systematic reviews of existing research/evidence on consumer and provider preferences, adherence, other data to inform strategy development for zinc and ORS[N] • Find ways to overcome barriers of antigenic diversity within animal coronaviruses to identify antigens for vaccine targeting[Q] • Better understand immune responses to bacterial respiratory pathogens[Q]

R&D Areas	CHILDHOOD PNEUMONIA AND DIARRHOEA	
	Goals	***R&D Priorities for Achieving Goals***
VECTOR CONTROL	• None identified	• None identified
EPIDEMIOLOGY	• Identify ways to scale-up global disease surveillance{D} • Consolidate data and fill knowledge gaps about mortality attributed to CD&P{D} • Develop approaches to monitor the long-term impact of rotavirus vaccines in resource-limited settings{K},{L} • Better understand the epidemiology of fata pneumonia{Q} • Assess the impact of antimicrobial resistance on the management of childhood pneumonia{Q}	• Investigate how disease burden changes as socio-demographic conditions evolve{D} • Observe how the incidence of other diseases and changes in risk factors impact CD&P{D} • Determine how to utilize current data to identify groups at greater risk or missed by services, and develop targeted approaches to reach them{H}Conduct studies to monitor trends in diarrhea and rotavirus disease burden pre- and post-rotavirus vaccine introduction{K} • Determine how to use surveillance platforms to conduct epidemiologic studies to estimate rotavirus vaccine effectiveness under conditions of routine use{K} • Determine how to evaluate the total population impact of rotavirus vaccination including indirect benefits{K} • Develop means to interpret the changing ecology of rotavirus strains after vaccine introduction in the context of vaccine effectiveness studies or changes in absolute disease burden{L} • Determine the extent to which the roll-out of rotavirus vaccination reduces the burden of acute dehydration as well as diarrhoea{P} • Determine whether the community-led total sanitation approach lead to decreased diarrhoea risk{P} • Assess whether access to, and benefits received from, nutritional supplementation programmes reduce global burden of diarrhoeal disease{P} • Identify the risk factors for diarrhoea mortality{P} • Find ways to build-up capacity for local and regional surveillance of antibiotic resistance, particularly in settings with high levels of penicillin insensitivity{Q}
PUBLIC HEALTH AND OPERATIONAL RESEARCH	• Identify the barriers to increases in coverage and ensure that hard to reach populations have access to effective interventions—ie, oral rehydration solution, zinc, *Haemophilius influenza* type b and pneumococcal vaccines, WHO's seven-point plan, and WHO's strategy for acute respiratory infection{A},{B},{C},{F},{H},{M},{P}	• Investigate the effectiveness of culture-appropriate health education and public health messages on changes in health-seeking behaviour, hospital admission, and mortality, and which communication strategies are best to spread knowledge and generate care-seeking behaviour{A},{H}.{M} • Identify the main barriers to increase demand for and compliance with vaccination schedules for available vaccines in different contexts and settings{A},{C} • Determine the added effect of integrated Community Case Management or Integrated Management of Childhood Illness on early and equitable administration of appropriate treatment for acute diarrhoea and for pneumonia{A},{C},{M}

R&D Areas	CHILDHOOD PNEUMONIA AND DIARRHOEA	
	Goals	***R&D Priorities for Achieving Goals***
	• Identify contextual or cultural factors that positively or negatively affect care-seeking behaviour and which factors most effectively drive care-seeking behaviour{A},{P} • Identify the best indicators for measurement of uptake of interventions and effectiveness of communication strategies{A},{H},{M} • Determine how to best support implementation of the WHO/UNICEF *Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea*{B},{M} • Identify the children at greatest risk of CD&P, and who are the hardest to reach and the most neglected{B},{H} • Determine how to scale-up implementation and operations research to inform progress in mortality reduction{C} • Explore solutions to pragmatic issues in the areas of programme management and resource allocation for CD&P{E} • Determine ways to ensure all children have access to life-saving vaccines and essential treatments such as amoxicillin for pneumonia and oral rehydration solution and zinc for diarrhoea{F},{H},{N} • Develop integrated programmes to tackle the shared risk factors of diarrhea and pneumonia{G},(H),{M} • Find ways to prevent children from becoming ill from pneumonia and	• Identify the effect on child health outcomes of interventions to support mothers, for example to reduce maternal depression, strengthen maternal coping, and develop problem-solving skills for child health{A} • Determine the capacity of health systems worldwide to correctly diagnose and manage childhood pneumonia, and the obstacles to correct diagnosis and case management in developing countries{A} • Identify how trained community health workers can be effectively trained and sustained and whether they can be trained to adequately assess, recognize danger signs, refer, and treat acute respiratory infections, including safe and effective administration of antibiotics{A},{C},{F} • Find ways to evaluate the effectiveness of a community-led approach to total sanitation{A} • Identify and find ways to provide access to interventions for children in the most hard-to-reach places{B},{F} • Determine how to strengthen primary care responses to CD&P{B} • Find ways to remove or reduce financial barriers to access{B} • Identify ways to expand the role of non-governmental providers{B} • Determine how to best utilize new mobile technologies to achieve sustainable, quality services for CD&P{B} • Find ways to improve the acceptability and effectiveness of oral rehydration solution and zinc to treat childhood diarrhea{C} • Determine the key barriers to health-care seeking and access for pneumonia{C},{E} • Find ways to track trends in emerging diseases as new interventions are introduced{D} • Determine whether the effectiveness of IMCI and related initiatives could be improved if operationalized as a programme in the model of PEPFAR or PMI{E} • Investigate how to improve the coordination of CD&P efforts and secure sufficient access to services{E} • Identify ways to enhance the production, distribution, and promotion of key commodities{E} • Determine how to strengthen weak monitoring and assessment systems{E} • Determine how to promote awareness and accelerate action to address the social and environmental determinants of health, for example by reducing harmful indoor air pollution produced by burning firewood{F}

R&D Areas	CHILDHOOD PNEUMONIA AND DIARRHOEA	
	Goals	***R&D Priorities for Achieving Goals***
	diarrhoea by ensuring universal coverage of immunization, HIV prevention and healthy environments{H} • Develop clear country-level strategies and work plans, with key responsibilities assigned{H} • Find ways to scale-up implementation research and identify optimal modes of delivery for existing interventions{H} • Find ways to adopt effective case management at the community and health facility levels{H},{M} • Design advocacy campaigns promoting exclusive breastfeeding and zinc supplementation to reduce rates of low birth weight and under-nutrition{H},{M} • Evaluate the effectiveness of new technologies that can reduce indoor air pollution and conduct additional research to demonstrate the health benefits of these interventions{H},{M} • Formulate new strategies to promote hand washing with soap and water, particularly among caregivers in developing countries{H},{M} • Develop means to ensure individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility{H} • Develop communication strategies that translate research evidence into meaningful information for communities and individuals in highest-mortality countries{H},{M}	• Identify ways to increase demand from families and communities for quality health services{F} • Find ways to strengthen partnerships between public and private actors to encourage innovations in, and expand the reach of, health services{F} • Determine how to ensure that women and children know their rights to quality health care and are empowered to hold their leaders to account for any failure to deliver on their commitments{F} • Determine how measure the results of tackling diarrhoea and pneumonia and compare the progress to the promises that have been made{F} • Determine how integrated programs can best address common risk factors including a lack of exclusive breastfeeding of children younger than six months, under-nutrition and zinc deficiency{G},{H},{M} • Develop or update country-level situational analyses for pneumonia and diarrhoea{H} • Identify areas of harmonization and collaboration between programmes and sectors, including the private sector, academia and civil society{H} • Develop a set of common indicators for tracking progress on CD&P{H} • Learn how to best coordinate the implementation of interventions by applying lessons from other integrated disease prevention and control efforts{H} • Develop tools and platforms to track the execution and progress of coordinated implementation efforts{H} • Design collaborative platforms that engage and embed critical partners in overall work, including the involvement of multiple sectors and programs, private and civil society organizations, and UN agencies and development partners{H} • Development methods to select priority interventions based on local context within national action plans{H} • Find ways to establish better linkages between existing programmes to lead synergies and efficiencies that will maximize the benefits{H} • Design mechanisms for close collaboration between the Ministry of Health (MoH) and other sectors, especially the ministries responsible for water, education, energy and the environment{H} • Determine how to build research capacity in the countries most affected{H} • Prioritize community-based action research, sociocultural research on knowledge, attitudes, perceptions, cultural practices and health seeking behaviours, and

R&D Areas	CHILDHOOD PNEUMONIA AND DIARRHOEA	
	Goals	***R&D Priorities for Achieving Goals***
	• Find ways to gather local effectiveness and impact data from developing countries in Africa and Asia currently introducing rotavirus vaccines to effectively monitoring vaccine performance and identify ways to improve impact{K} • Find ways to generate momentum and enthusiasm for rotavirus vaccination in the least developed countries with the high mortality rates{L} • Develop platforms for concerted action between vaccine manufacturers, financial donors and decision-makers to achieve rotavirus vaccination goals in a timely manner{L} • Develop strategies to rise national coverage of pneumonia and diarrhoea interventions to levels found in the richest groups{M} • Investigate how to best implement integrated community case management (iCCM) programmes in developing countries{M},{P} • Find ways to scale-up rigorous monitoring, evaluation and documentation of existing iCCM programmes{M},{P} • Find ways to advance and support sustainable procurement of medicines and medical devices{N} • Find ways to establish guidance to governments and United Nations agencies on what are priority areas for action related to selection and supply	research on delivery strategies, on overcoming barriers to interventions and on better ways for implementation{H} • Countries with a high under-five mortality rate should develop and adopt plans to expand adequate case management of pneumonia at the hospital, health facility and community levels to achieve 90% coverage{H},{M} • Find ways to improve the management of HIV infection and increae use of *P. jiroveci* pneumonia prophylaxis to reduce the mother-to-child transmission of HIV{H},{M} • Create incentives to stimulate demand and improve caregiver knowledge, attitudes and practices towards immunization{H} • Create incentives for households and health workers in favour of immunization{H} • Conduct social research to improve the delivery of immunization services and the ability to meet the needs of diverse communities{H} • Identify reasons for vaccine hesitancy and take steps to increase community confidence and demand for immunization{H} • Conduct communications research to inform individuals and communities about the benefits of immunization and to hear their concerns{H},{L} • Conduct operational and social science research to identify successful strategies to reduce inequities and improve the quality and delivery of immunization services{H} • Investigate the use of more effective information through modern communication technologies to improve programme efficiencies and increase coverage and impact{H} • Identify community-based decision-makers and groups to strengthen community-based support for breastfeeding{H} • Conduct assessments and formative research to strengthen community-based breastfeeding initiatives{H} • Carry out national level formative research on pneumonia and diarrhoea to foster and strengthen care seeking/demand for case management and community knowledge of prevention measures{H},{M} • Develop generic communication messages/materials and adapt these tools to meet the needs of local communication strategies{H} • Periodically assess implementation/impact of communication efforts{H} • Find ways to build capacity for community-based groups, peer counsellors and community leaders to lead prevention measures{H}

R&D Areas	CHILDHOOD PNEUMONIA AND DIARRHOEA	
	Goals	***R&D Priorities for Achieving Goals***
	chain of medicines procurement[N] • Investigate opportunities for interagency collaboration through UNICEF IPC[N] • Develop quality improvement (QI) methods that can be used to instill appropriate stewardship of antibiotics in the absence of a formal antimicrobial stewardship programs (ASP)[O] • Find ways to utilize QI methods to rapidly improve adherence to national guidelines on the judicious prescribing of antibiotics for community-acquired pneumonia (CAP)[O] • Conduct studies on the efficacy of simple public health measures (e.g. social distancing, masks and hand hygiene) on transmission of respiratory viruses[Q] • Elucidate the role of zinc in pneumonia treatment[Q] • Define the parameters of equity and develop systems to monitor changes (e.g. identify the main determinants of risk that might be geographic or ethnographic) [Q] Find ways to improve the quality of inpatient pediatric care[Q]	• Evaluate and explore options available to potentially expand developing countries' cold chain and storage capacity prior to vaccine introduction programs[K],[L] • Conduct research to gather more evidence on the quality of care when community health workers are given increasingly complex tasks or deliver multiple interventions as part of iCCM[M] • Determine how to recruit, retain, supervise and motivate community health workers to provide high-quality care within iCCM programs[M] • Develop an urgently needed operations research "learning agenda"[M] • Conduct environmental impact evaluations of the production, distribution and use of medicines and medical devices (including carbon footprint and environmental toxicity), sustainability aspects related to labor and trade, and ways in which selection and procurement can reduce impact[N] • Identify and test alternative delivery strategies designed to ensure that ORS and zinc are reaching hard to reach populations and being used by the poorest of the poor (for example, home distribution of ORS and zinc)[P] • Identify the key barriers against the appropriate use of ORT[P] • Determine which factors drive care-seeking behaviour during childhood diarrhoeal disease and how ORS and zinc programs can be positioned to best respond to these factors[P] • Identify the factors have led to the decline in ORS use rates in countries where rates were high and now are low[P] • Identify which factors most effectively drive caregiver demand for ORS and zinc[P] • Identify the attributes of successful and sustainable childhood diarrhoea programs, e.g. determine which designs and strategies were used in programs and interventions that led to drastic reductions in diarrhoeal disease burden[P] • Determine the added impact of iCCM on early and equitable administration of appropriate treatment for acute diarrhoea[P] • Determine how the perception of diarrhoea as an illness affects:[P] o Key household practices like hand washing o Willingness to pay for point-of-use water disinfection products o Care seeking, and o Compliance to ORS and zinc treatment • Determine how best to move caregivers from knowledge of ORS and/or zinc treatment to actual trial and eventual adoption as routine practice, and identify the

R&D Areas	CHILDHOOD PNEUMONIA AND DIARRHOEA	
	Goals	***R&D Priorities for Achieving Goals***
		stages of behaviour change in order to tailor messages accordingly:{P} • Determine whether moving from general and generic to more specific targeted messaging would influence practices, when they are best delivered, and what would this include{P} • Determine what would be needed to move a caregiver from awareness to trial of ORS and zinc, and what the relative impact of mass media vs. group vs. one-on-one communication strategies would be{P} • Determine whether communication strategies vary in effectiveness between rural and urban populations{P} • Determine the individual risk effects of malnutrition, poor sanitation, low level of education, and reduced levels of vitamins and micronutrients in acquiring diarrhoea in children living in the developing world{P} • Identify which contextual or cultural factors positively or negatively influence ORS and zinc utilization or compliance{P} • Evaluate if early initiation and exclusive breast feeding is associated with reduced burden of diarrhoea and improved growth{P} • Determine the best indicators for measuring the effectiveness of communication messages for childhood diarrhoea and the effectiveness of different communication channels in terms of (a) awareness of, (b) readiness to try, and (c) actual use of ORS and/or zinc{P} • Assess the potential impact of economical oxygen concentrators on child mortality from hypoxia{Q} • Assess the use of zinc supplementation in outpatient settings where most children with pneumonia are treated{Q} • Determine the acute effects of zinc as a treatment for pneumonia{Q}

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.

B. Chan M, Lake A. Integrated action for the prevention and control of pneumonia and diarrhoea. The Lancet. 2013 Apr [cited 2013 May 4]. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60692-3.

C. Chopra M, Mason E, Borrazzo J, Campbell H, Rudan I, Liu L, et al. Ending of preventable deaths from pneumonia and diarrhoea: an achievable goal. The Lancet. 2013 Apr [cited 2013 Apr 25]. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60319-0.

D. Fischer Walker C, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta Z, et al. Global burden of childhood pneumonia and diarrhea. The Lancet. 2013 Apr [cited 2013 Apr 25]. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60222-6.

E. Gill C, Young M, Schroder K, Carvajal-Velez L, McNabb M, Aboubaker S, Qazi S, Bhutta Z. Bottleneck, barriers, and solutions: results from multi-country consultations focused on reduction of childhood pneumonia and diarrhoea deaths. The Lancet. 2013 Apr [cited 2013 Apr 25]. Available from: http://dx.doi.org/10.1016/ S0140-6736(13)60314-1.
F. Kikwete J. Playing our part to save children's lives. The Lancet. 2013 Apr 12 [cited 2013 May 4]. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60719-9.
G. Samarasekera U, Horton R. Continuing the child survival revival. The Lancet. 2013 Apr 12 [cited 2013 May 4]. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60718-7.
H. World Health Organization/The United Nations Children's Fund (UNICEF). Ending preventable child deaths from pneumonia and diarrhoea by 2025: The integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD). Geneva: World Health Organization; 2013.
I. Huda T, Nair H, Theodoratou E, Zgaga L, Fattom A, El Arifeen S, et al. An evaluation of the emerging vaccines and immunotherapy against staphylococcal pneumonia in children. BMC Public Health. 2011; 11(Suppl 3):S27. Available from: http://www.biomedcentral.com/1471-2458/11/S3/S27.
J. Webster J, Theodoratou E, Nair H, Seong A, Zgaga L, Huda T, et al. An evaluation of emerging vaccines for childhood pneumococcal pneumonia. BMC Public Health. 2011; 11(Suppl 3):S27. Available from: http://www.biomedcentral.com/1471-2458/11/S3/S27.
K. Tate J, Patel M, Cortese M, Lopman B, Gentsch J, Fleming J, et al. Remaining issues and challenges for rotavirus vaccine in preventing global childhood diarrheal morbidity and mortality. Expert Rev Vaccines. 2012;11(2):211-220.
L. Patel M, Glass R, Desai R, Tate J, Parashar U. Fulfilling the promise of rotavirus vaccines: how fare have we come since licensure? Lancet Infectious Dis. 2012; 12: 561-70.
M. United Nations Children's Fund (UNICEF). Pneumonia and Diarrhoea: Tackling the Deadliest Diseases for the World's Poorest Children. New York: UNICEF; 2012.
N. United Nations Children's Fund (UNICEF). Update on Work on Medicines. Presentation. New York: UNICEF IPC; Dec 2012.
O. Ambroggio L, Thomson J, Kurowski E, Courter J, Statile A, Graham C, et al. Quality improvement methods increase appropriate antibiotic prescribing for childhood pneumonia. Official Journal of the American Academy of Pediatrics. 2013; 131:e1623. doi: 10.1542/peds.2012-2635.
P. Wazny K, Zipursky A, Black R, Curtis V, Duggan C, Guerrant R, et al. Setting research priorities to reduce mortality and morbidity of childhood diarrhoeal disease in the next 15 years. PLoS Med. 2013; 10(5): e1001446. doi:10.1371/journal.pmed.1001446.
Q. Scott J, Brooks A, Peiris J, Holtzman D, Mulholland E. Pneumonia research to reduce childhood mortality in the developing world. J Clin Invest. 2008; 118: 1291-1300. doi:10.1172/JCI33947.