Global Health
Technologies Coalition

Briefing Paper, Volume 1: Developing technologies to address poverty-related and neglected diseases and conditions

Perspectives from nonprofits on accelerating product development and improving access for low- and middle-income countries

Financing and Coordination of Health Research
May 2013

Contents

About the Global Health Technologies Coalition

The Global Health Technologies Coalition (GHTC) is a group of more than 25 nonprofit organizations working to increase awareness of the urgent need for tools that save lives in the developing world. These tools include new vaccines, drugs, microbicides, diagnostics, and other devices. The coalition advocates for increased and effective use of public resources, incentives to encourage private investment, and streamlined regulatory systems. The GHTC is housed at PATH.

The Global Health Technologies Coalition can be found online at **www.ghtcoalition.org**.

More information about these issues can be shared by request from **info@ghtcoalition.org**.

Acknowledgments

This paper was authored by Claire Wingfield from PATH in consultation with Kaitlin Christenson from the Global Health Technologies Coalition (GHTC) and with support from Sasha DeLeon. We would like to thank our advisory committee members: Rachel Cohen (Drugs for Neglected Diseases initiative), Mary Moran (Policy Cures), Eileen Quinn (PATH), Judit Rius (Médecins Sans Frontières), John-Arne Rottingen (Harvard University), Jane Rowley, Katharina Scheffler (Deutsche Stiftung Weltbevoelkerung), and Rachel Wilson (PATH). We would also like to thank the nonprofit product development organizations who participated in this analysis: Aeras, Dengue Vaccine Initiative, Drugs for Neglected Diseases initiative, European Vaccine Initiative, Foundation for Innovative Diagnostics, Global Alliance for TB Drug Development, Infectious Disease Research Institute, International AIDS Vaccine Initiative, International Partnership for Microbicides, Medicines for Malaria Ventures, PATH, Population Council, Sabin Vaccine Institute, and TuBerculosis Vaccine Initiative. Finally, we would like to recognize contributions made by those who advised this work in an informal capacity: Nick Chapman (Policy Cures), Danny Edwards (Council on Health Research for Development), Javier Guzman (Policy Cures), Kim Lufkin (GHTC), Zafar Mirza (World Health Organization [WHO]), Robert Terry (WHO), and the GHTC staff.

Suggested citation: Global Health Technologies Coalition (GHTC): *Developing Technologies to Address Poverty-Related and Neglected Disease and Conditions. Perspectives from Nonprofits on Accelerating Product Development and Improving Access for Low- and Middle-Income Countries. Vol. 1*. Washington, DC: Global Health Technologies Coalition; 2013. Available at http://ghtcoalition.org/NPPD-briefing-paper-series.php.

Financing and coordination of health research

Perspectives from nonprofits on accelerating product development and improving access for low- and middle-income countries

Introduction

Life expectancy in most countries has increased by approximately ten years over the past four decades—but the gap between the richest and poorest countries remains wide.[1] While progress has been made to address poverty-related and neglected diseases and conditions, millions of people continue to die of preventable and treatable conditions because the current drugs, diagnostics, vaccines, and devices targeting many neglected diseases are not adequate to address the health needs of low- and middle-income countries (LMICs). Actors from the private, public, and philanthropic/nonprofit sectors are working to develop and deliver new and innovative tools to address the health needs of LMICs, but these efforts are challenged by insufficient funding, weak and disjointed infrastructure, and limited scientific capacity in the settings where research must take place.

Purpose and aims

This paper is the first in a series that will demonstrate how nonprofit product development organizations (NPPDs) work to advance R&D for poverty-related and neglected diseases and conditions in LMICs. This series is meant to inform global policy and financing debates, including but not limited to discussions on the recommendations outlined in the 2012 report from the WHO Consultative Expert Working Group (CEWG) on R&D.[2] The main functions of the CEWG were to identify major challenges to advancing R&D for health needs of LMICs and make recommendations to improve the coordination of priorities and activities, financing of all phases, and monitoring of R&D investments.

For the purposes of this series, nonprofit product developers are defined as nongovernmental organizations that partner with the public, philanthropic/not-for-profit, and private sectors to develop technologies—diagnostics, drugs, devices, vaccines, and microbicides—targeted at neglected diseases and conditions of high morbidity and mortality in LMICs. The series will:

- Provide examples and lessons learned from NPPDs to clarify challenges and identify potential solutions to improve financing and coordination of R&D for poverty-related and neglected diseases and conditions in LMICs.[a]
- Inform the establishment of a global R&D observatory at WHO as called for in the draft resolution that will be considered at the 66th World Health Assembly in May 2013.[3]
- Inform the implementation of R&D demonstration projects, also called for in the draft resolution.
- Inform the potential future establishment of additional long-term, sustainable coordination and financing mechanisms to be assessed and considered at a later date, as described in the same draft resolution.

a The list of diseases is based on the list referenced in Policy Cures's *Neglected Disease Research and Development: A Five-year Review* (available at: http://www.policycures.org/downloads/GF2012_Report.pdf) and is not an exhaustive list of neglected diseases. Those covered by surveyed NPPDs include bacterial pneumonia and meningitis, dengue fever, diarrheal diseases, helminth infections, HIV, kinetoplastids, leprosy, malaria, trachoma, and tuberculosis. We also included technologies that address maternal, newborn and child health, and sexual and reproductive health conditions.

This first paper sets the stage for subsequent papers by providing examples of how NPPDs approach product development and the key challenges identified by NPPDs that they and their partners face in developing and introducing technologies targeting the health needs of LMICs.

Methodology

This analysis relies on publicly available data and information collected through a survey sent to 15 NPPDs. See Table 1 for a list of the organizations included in this analysis. The NPPDs were surveyed to capture their perspectives on the research gaps in the current global pipeline, key challenges they encounter as technologies advance through the pipeline, and potential solutions to solving those challenges. The NPPDs profiled in this paper represent a cross-sampling of the nongovernmental organizations engaged in this work and do not account for all of the NPPDs working in this space. The NPPDs included in this analysis work across different technologies and health areas of great importance in LMICs. Although many academic institutions can also be considered NPPDs and have valuable evidence to share, they are beyond the scope of this paper.

Table 1: Listing of NPPDs surveyed for this report

NPPD	Focus area(s)	Mission statement	Number of portfolio products*
Aeras	Tuberculosis (TB) vaccines and biologics	Dedicated to the development of effective TB vaccines and biologics to prevent TB across all age groups in an affordable and sustainable manner.	16
Drugs for Neglected Diseases initiative (DNDi)	Neglected tropical diseases with the highest death rates (human African trypanosomiasis, leishmaniasis, Chagas disease); filarial infections; and pediatric HIV drugs	To develop new drugs, or new formulations of existing drugs, for patients suffering from the most neglected communicable diseases. Acting in the public interest, DNDi bridges existing R&D gaps in essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners.	26
Dengue Vaccine Initiative (DVI)	Dengue vaccines	A consortium of organizations working to lay the groundwork for dengue vaccine introduction in endemic areas so that, once licensed, vaccines to prevent dengue will be swiftly adopted by countries most in need.	6
European Vaccine Initiative (EVI)	Vaccines against diseases of poverty (including Chagas disease, Dengue fever,, Malaria, Leishmaniasis, and universal flu)	To contribute to the global efforts to control diseases of poverty by creating an environment conducive to accelerating the development and clinical assessment of vaccine candidates for diseases of poverty; promoting the affordability and accessibility of vaccines for diseases of poverty in low-income populations; aligning all major stakeholders and acting as a focal point to ensure the successful development of vaccines for diseases of poverty for low-income populations; and communicating to stakeholders and public the importance of EVI's work and progress toward the deployment of affordable and efficacious vaccine candidates for diseases of poverty.	12

* Self-reported by NPPDs and may reflect variability in how products are defined across these organizations.

Table 1: Listing of NPPDs surveyed for this report *(continued)*

NPPD	Focus area(s)	Mission statement	Number of portfolio products*
Foundation for Innovative New Diagnostics (FIND)	TB, human African trypanosomiasis, leishmaniasis, Chagas disease, malaria, and acute febrile syndrome	To drive the development and early implementation of innovative diagnostic tests that have a high impact on patient care and disease control in low-resource settings.	15
Global Alliance for TB Drug Development	TB drugs	TB Alliance's mission is to discover and develop better, faster-acting, and affordable drugs to fight TB. Through innovative science and with partners around the globe, it leads a global effort to ensure development of and equitable access to faster, better TB cures that will advance global health and prosperity.	22
International AIDS Vaccine Initiative (IAVI)	Preventive HIV vaccines	To ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world.	5
Infectious Disease Research Institute (IDRI)	Infectious disease diagnostics, vaccines, and therapeutic products	To apply innovative science to develop products to eliminate infectious diseases of global importance.	12
International Partnership for Microbicides (IPM)	Antiretroviral-based microbicides	To prevent HIV transmission by accelerating the development and availability of safe and effective microbicides for use by women in developing countries.	10
Jhpiego	Maternal and newborn health	To improve the health of women and families in developing countries.	11
Medicines for Malaria Venture (MMV)	Antimalarial drugs	To reduce the burden of malaria in disease-endemic countries by discovering, developing, and facilitating delivery of new, effective, and affordable antimalarial drugs.	60
PATH	Drugs, diagnostics, vaccines, and devices for infectious diseases, maternal and child health, and reproductive health	To improve the health of people around the world by advancing technologies, strengthening systems, and encouraging healthy behaviors.	200
Population Council	HIV/AIDS and reproductive health prevention technologies	To improve the well-being and reproductive health of current and future generations around the world and to help achieve a humane, equitable, and sustainable balance between people and resources.	18
Sabin Vaccine Institute	Neglected tropical diseases vaccines	To reduce needless human suffering from vaccine-preventable and neglected tropical diseases by developing new vaccines, advocating for increased use of existing vaccines, and promoting expanded access to affordable medical treatments.	7
Tuberculosis Vaccine Initiative (TBVI)	TB vaccines	TBVI supports, integrates, translates, and prioritizes R&D efforts to discover and develop new TB vaccines that are accessible and affordable for all people.	43

* Self-reported by NPPDs and may reflect variability in how products are defined across these organizations.

The funding landscape

The landscape of R&D for poverty-related and neglected diseases and conditions has changed dramatically since the 1990s. Since that time and up until 2009 there had been a steady increase in funding for R&D targeting the health needs of LMICs, which has helped fuel the growth of technology pipelines and a surge in the number of organizations filling these pipelines.

As a result of these investments, a number of new technologies have been introduced including new and improved vaccines for meningitis A, Japanese encephalitis, and cholera; improved drugs and drug combinations against malaria; and diagnostics and testing platforms for visceral leishmaniasis and TB. Additionally, significant progress has been made in the development of much-needed technologies—such as preventive vaccines for HIV and malaria; improved vaccines for TB, bacterial pneumonia, and diarrheal diseases; microbicides to protect women and their partners against HIV and unintended pregnancies; diagnostics for neglected diseases such as onchocerciasis (or river blindness) and Chagas disease; and devices aimed at improving maternal health outcomes and family planning options. Despite this progress, a funding gap continues to persist between what is invested for research that targets LMICs' health needs and what is needed.

For example, 8.7 million people fell ill and 1.4 million died from TB in 2011.[5] More than 95 percent of these deaths occurred in LMICs. These morbidity and mortality figures indicate that, despite having drugs, diagnostics, and a vaccine available to combat TB, these tools are inadequate because they do not meet the health needs of people living in LMICs. Yet the global TB research investment continues to fall US$1.35 billion short of the annual US$2 billion funding target recommended by the Global Plan to Stop TB.[6] This statistic is emblematic of the inadequate funding trends across R&D targeting the health needs of LMICs.

The R&D value chain

Organizations conducting R&D targeting LMICs come from governments, academic institutions, nonprofit organizations, and private companies in high-, middle-, and low-income countries. Because the perceived financial risks are often too high relative to the potential economic returns, and the scientific challenges are daunting for many poverty-related diseases and conditions, it is impossible to rely solely on one organization or sector to meet the health needs of LMICs. Therefore, many organizations partner to share risk, leverage expertise, and maximize impact. These organizations work across the product development value chain, from upstream research exploring fundamental understanding of a disease that will provide the foundation for developing new technologies to more downstream operational research aimed at optimizing the use of new technologies within a health system. NPPDs play an important (and often unique) role in bridging the gap between early basic science and late-stage research. Along the value chain, NPPDs and their private- and public-sector partners conduct trials of new tools across all phases of clinical and field trials to prove the concept, evaluate safety and efficacy, and validate that the proper production process is in place to ensure manufacturing quality.

The public sector is consistently the largest overall funder of R&D for poverty-related and neglected diseases and conditions, accounting for almost two-thirds of the US$3.048 million spent in 2011. The US government, predominately through the US National Institutes of Health (NIH), accounts for approximately 70 percent of public-sector funding.[4] Other sectors play an important role in funding for R&D for LMICs; in particular, the philanthropic sector, and specifically the Bill & Melinda Gates Foundation, has played a critical role in driving growth over the last 15 years, outspending most governments. In fact, the Bill & Melinda Gates Foundation was the second largest funder of R&D from 2007 to 2011.[4] However, recent trends show that spending from the private sector is rising—up by $107.3 million (28 percent) in 2010, while investments from the public and philanthropic sectors have been falling—down by almost $80

million and $136 million, respectively, in 2010.[7] Overall, the pool of funders for R&D for poverty-related and neglected diseases and conditions is small, with 12 funders accounting for almost 90 percent of all investments in 2010 and 2011.[4] This overreliance on a relatively small number of funders magnifies the implications of funding shifts by those donors (e.g., a 10 percent cut by the NIH would have a disproportionate impact on the overall funding picture). Given the current global financial climate, this funding concentration can result in donor fatigue and shrinking available funds just as many technologies are about to enter into more expensive, late-stage clinical development and prepare for product registration where increased investments are needed.

Nonprofit product development organizations' approaches to product development

A clear public health need or gap may exist, but if there is no perceived commercial market, need does not necessarily translate into demand.[8] It is in this space that NPPDs offer unique value. NPPDs facilitate partnerships that harness the expertise, resources, and investments of the public, philanthropic, and private sectors in order to share risks and costs and drive R&D efforts toward highly focused, well-defined goals, and engage the most appropriate partners with relevant expertise. In contrast to typical commercial product development, NPPDs focus on affordability and access, bringing financial resources through public and philanthropic donors, as well as other assets, such as technical expertise or field presence, to the partnership. Because private-sector companies are less likely to assume the full risks and costs of product development targeting LMICs, NPPDs take on this risk by covering costs throughout the product development cycle. In exchange, NPPDs negotiate licensing agreements and intellectual property rights to ensure that the eventual product will be made available at a price that is affordable and in adequate supply in LMICs. This process typically de-links the costs of R&D from the price level of the final product. De-linking R&D costs from product prices is about creating "competitive intermediaries" between developers and the commercial market, ensuring that developers recoup costs while ensuring that products are affordable and accessible to patients. For example, PATH's Drug

DNDi's policy on intellectual property and licensing

DNDi has developed an intellectual property policy to guide its R&D activities and associated contractual agreements with the following objectives:

- The need to ensure that treatments are ultimately affordable to patients who need them and that access to these treatments is equitable.
- The desire to develop drugs as public goods when possible.

The policy, which reflects the fact that DNDi outputs are likely to have negligible commercial value and that R&D agreements will often be made with public-sector entities, calls for a pragmatic approach so that decisions regarding ownership of patents and of licensing terms are made on a case-by-case basis.

Based on this policy, DNDi has managed to negotiate favorable licensing terms with several pharmaceutical companies and, after a number of years of experience in such negotiations, has come to define a "gold standard" of licensing terms, which can be summarized as follows:

- Perpetual royalty-free non-exclusive sub-licensable licenses in the specific disease areas determined in the contract.
- Worldwide research and manufacturing rights.
- Commitment to make the final product available at cost, plus a minimal margin, in all endemic countries, regardless of income level.
- Non-exclusivity, enabling technology transfer and local production.

For example, the antimalarial ASAQ was developed as a public good in order to have the product accessible on the widest scale possible. This "public good" driving principle also supported technology transfer to an African manufacturer to secure a second manufacturing source, strengthening production capacity in one of the highest malaria-burden regions and possibly driving prices further down through competition.

DNDi's full intellectual property policy can be found at http://www.dndi.org/images/stories/pdf_aboutDNDi/ip%20policy.pdf.

Development program (created through PATH's affiliation with OneWorld Health) signed a collective licensing agreement with the Special Programme for Research and Training in Tropical Diseases (commonly referred to as TDR) at WHO to develop a new injectable formulation of paramyosin—a treatment for visceral leishmaniasis—after it was unable to find a sponsor for a large-scale trial. Paromomycin intramuscular injection is now included on the WHO Model List of Essential Medicines and is available to health systems at cost.

There are a number of similarities—to varying degrees—in approaches among NPPDs, including:

- Having multiple candidates in their portfolio at various stages of development.
- Utilizing financial and in-kind resources from the public, private, and philanthropic sectors.
- Working across the product development process, managing long-term projects and filling the research gaps by linking early basic research to product development and introduction.
- Strengthening the capacity of research and manufacturing partners in endemic countries.
- Negotiating licensing agreements with partners to ensure the availability, affordability, and accessibility of resulting new technologies.
- Working with regional and national regulatory authorities and global and regional regulatory stakeholders to clarify pathways and improve alignment of requirements throughout the product development process.
- Advocating for policies and investment to strengthen R&D for poverty-related and neglected diseases and conditions, and bring attention to the health needs of LMICs.

NPPDs range in scope and focus. Some, like Aeras, Dengue Vaccine Initiative (DVI), International AIDS Vaccine Initiative (IAVI), Medicines for Malaria Venture (MMV), TuBerculosis Vaccine Initiative (TBVI), and Global Alliance for TB Drug Development (TB Alliance), are focused on a specific type of technology for one disease. Other NPPDs focus on one technology field but across multiple disease areas, such as Drugs for Neglected Diseases initiative (DNDi), European Vaccine Initiative (EVI), Foundation for Innovative New Diagnostics (FIND), and Sabin Vaccine Institute. Others work across multiple diseases/conditions and technology areas, like Infectious Disease Research Institute (IDRI), Population Council, Jhpiego, and PATH, which develop vaccines, drugs, diagnostics, and devices to address many health issues.

Most of the NPPDs surveyed for this paper are virtual research organizations, meaning that they do not conduct in-house research but work through collaboration with partners from a wide range of research settings.[9] Other NPPDs—like Aeras, IAVI, IDRI, and PATH—have in-house laboratory capabilities that allow them to conduct on-site product development activities, such as manufacturing and testing.[10] Regardless of the approach, NPPDs work in partnership with one another and across sectors, formally and informally, throughout the entire product life cycle to develop much-needed tools and to create an enabling environment for R&D targeting the health needs of LMICs. These partnerships may be formalized by agreements granting access to intellectual property or outlining specific activities to be undertaken, such as technology transfer or technical assistance, or they may include *ad hoc* information-sharing.[11] For example, IAVI and Aeras have recently renewed a formal agreement for sharing knowledge and resources across the clinical trials networks of both organizations, developing joint training programs, increasing coordination and collaboration within vaccine R&D and manufacturing efforts, and sharing specific common support services.

NPPDs maintain portfolios to make sure only the most promising products advance through the pipeline. This portfolio approach, also employed by the private sector, allows funders to spread their investments across a suite of products and mitigate individual risk of failure, as the NPPD can shift funds from a failing project to more promising products within their portfolio.[12] The growth in the number of NPPDs over the past two decades has had a significant impact on the number of technologies and scope of the R&D activities targeting poverty-related diseases and

conditions. For example, an estimated 576 to 740 million people worldwide are infected with human hookworm, but the Sabin Vaccine Institute is the only collaboration working on a vaccine for the infection. Aeras, in collaboration with TBVI, has led the TB vaccine community to develop and publish the *Rational Approach to Selection and Clinical Development of TB Vaccine Candidates,* which provides comprehensive, measurable, and globally acceptable criteria for selecting, assessing, and advancing the best vaccine candidates that are in the pipeline.[13]

As shown in Table 2, the NPPDs surveyed report engaging in research activities in various phases of product development. The majority focus on preclinical and clinical development and more than half have also engaged in field testing of technologies. Not all of the NPPDs in this analysis have introduced a new technology from their pipeline, so some are not yet actively pursuing post-marketing or operational research activities.

NPPDs play a critical role in bringing together the fragmented resources and expertise of the R&D field to increase scientific understanding and control of poverty-related and neglected diseases and conditions—in addition to innovating and introducing technologies that would not be developed otherwise for commercial reasons. They strive not only to fill the pipeline with new and improved technologies but also to improve the scientific foundation for many of these conditions and diseases through technical assistance and open knowledge innovation that generate knowledge that is free to use without legal or contractual restrictions. For example:

Table 2. NPPD's research activities across R&D phases

Organization	Discovery/ Preclinical	Clinical development	Design/ Field testing	Phase IV/ Post-marketng surveillance	Operational research
Aeras	✓	✓			
DNDi	✓	✓	✓	✓	
DVI					✓
EVI	✓	✓			
FIND	✓	✓	✓	✓	
IAVI	✓	✓	✓		
IDRI	✓	✓	✓		
IPM	✓	✓			
Jhpiego	✓	✓	✓		
MMV	✓	✓	✓	✓	✓
PATH	✓	✓	✓	✓	✓
Pop Council	✓	✓	✓	✓	
Sabin	✓	✓			
TB Alliance	✓	✓			
TBVI	✓	✓			

- The PATH Malaria Vaccine Initiative (MVI) and IAVI, together with Imperial College London, are collaborating on the development of a T-cell assay reference center that is helping to advance vaccine research beyond the needs of the two organizations.
- MMV launched the Malaria Box, a library of more than 400 compounds with antimalarial activity. Access is offered free of charge on the condition that the resulting data is published and placed in the public domain to facilitate malaria and neglected disease drug discovery and research.
- EVI coordinates TRANSVAC, a vaccine development platform that may be accessed for free by vaccine developers and producers in Europe. TRANSVAC services include access to adjuvants, animal model testing, and standardized reagents for several commonly used assays and analytics.
- IDRI, FIND, PATH, DNDi, DVI (as part of the International Vaccine Institute), MMV, and Sabin Vaccine Institute are all members of the World Intellectual Property Organization (WIPO) Re:Search, which provides access to intellectual property for pharmaceutical compounds and technologies, as well as technical assistance and data available for R&D for neglected diseases through a publicly available database.
- TB Alliance in partnership with the Gates Foundation and the Critical Path Institute founded the Critical Path to TB Drug Regimens (CPTR). Under CPTR, drug developers allow their drug compounds to be tested in combination to find the best regimen, regardless of sponsor and intellectual property rights.

Several NPPDs have been successful in bringing new technologies to patients. MMV and Novartis partnered to co-develop a child-friendly fixed-dose combination artemisinin-based malaria therapy (Coartem® Dispersible), and since 2009, more than 171 million doses have been distributed. Coartem® Dispersible is estimated to have saved 340,000 people from dying of malaria. In 2007, DNDi and Sanofi launched ASAQ, a fixed-dose combination of artesunate and amodiaquine, available for $1 in the public sector for a full treatment malaria course for adults and for $0.50 for children. More than 200 million doses have since reached patients in need. In 2010, the Meningitis Vaccine Project (MVP)—a partnership between PATH and WHO—developed and launched MenAfriVac®—the first ever vaccine designed specifically to address the health needs of Africa—for less than $0.50 per dose.

MenAfriVac®: meeting the health and economic needs of LMICs

The Meningitis Vaccine Project (MVP)—a partnership between PATH and the World Health Organization—was created to accelerate the development and introduction of MenAfriVac®, a safe and affordable vaccine that would provide long-lasting protection against meningococcal A, which threatens the lives of 450 million people living in 26 African countries that comprise the "meningitis belt." With significant investment from the public-, private-, and philanthropic/nonprofit sectors, MVP partnered with an Indian vaccine manufacturer, Serum Institute of India Ltd., to leverage their manufacturing capabilities to bring the vaccine to the global market at an affordable price. MVP facilitated the transfer of a critical technology created by the US Food and Drug Administration to the Serum Institute of India, Ltd., which strengthened their capacity to scale up the manufacturing process, and produce and distribute the vaccine for less than $0.50 per dose.

As a result of the commitments made by MVP and its partners, MenAfriVac® was developed for less than one-tenth the cost of a typical new vaccine in less than ten years, and is expected to provide $570 million in cost savings to the global health community during the next decade.[14]

The vaccine's impact on improving health outcomes in the region is becoming evident. First introduced in Burkina Faso in December 2010, the vaccine has now been deployed in ten African countries, resulting in a dramatic fall in cases of meningitis A in the region. More than 100 million doses of the meningitis A vaccine have been delivered, with no cases being reported in the those who received the vaccination.

Table 3. NPPD pipeline

Illness	Devices	Diagnosis	Drugs	Microbicides	Multi-purpose prevention technologies	Platform technologies[a]	Vaccines	Other
Bacterial pneumonia and meningitis[b]						●	●	
Dengue fever							⊙	
Diarrheal diseases[c]			●			●	●	
Helminth infections[d]		●	■			⊡ ◆	❖	⊡
HIV/AIDS	○	△ ●	■ ●	✦ ○	✦ ○ ●	◆ ○ ●	▲	⊡
Kinetoplastids[e]		△ ● ◆	■			◆	◆ ❖	
Leprosy		◆					◆	
Malaria		△ ➤ ●	■ ⊖ ●			◆ ⊖	⊡ ●	
Maternal, newborn and child health	➤ ●	➤ ●	●		➤	➤		➤
Sexual and reproductive health	➤ ● ○	●	○	○	✦ ○ ●			
Trachoma						◆		
Tuberculosis		△ ◆ ➤ ●	◆ ■			⊡ ●	□ ⊡ ◆ ▶	⊡

Key

□ Aeras	⊡ EVI	◆ IDRI	⊖ MMV	❖ Sabin
■ DNDi	△ FIND	✦ IPM	● PATH	■ TB Alliance
⊙ DVI	▲ IAVI	➤ Jhpiego	○ Population Council	▶ TBVI

a This category includes adjuvants, diagnostic platforms and delivery devices. These are technologies that can potentially be applied to a range of disease and products but which have not yet been attached to a specific product for a specific disease.

b *Streptcoccus pneumonia, Neisseria meningitdis*, both bacteria.

c Rotavirus, Enterotoxigenic E.Coli, Cholera, Shigella, *Cryptosporidium*, Giardia, multiple diseases.

d Roundworm, Hookworm, Whipworm, Strongyloidiasis & other intestinal roundworms, Lymphatic filariasis, Onchocerciasis, Schistosomiasis, Tapeworm, multiple diseases.

e Chagas' disease, Leishmaniasis, Sleeping sickness, multiple diseases.

NPPD survey findings

Table 3 shows the breadth and depth of the pipeline of NPPDs surveyed for this paper. In partnership with other actors and each other, the NPPDs reported contributing to the development of more than 450 technologies across neglected and infectious diseases, as well as maternal, newborn, and child health and sexual and reproductive health conditions.[b] Despite the progress made by NPPDs and partners, their efforts alone are not sufficient to address the many health needs and systemic challenges facing LMICs. When asked to identify the significant gaps in current research efforts, the NPPDs identified many of the same issues, even when the organizations had a different health and/or technology focus.

Key gaps and challenges

Among the NPPDs surveyed for this paper, the most commonly cited gap in current research efforts is the **incomplete scientific foundation** for developing new health technologies for LMICs. For many of the NPPDs working on developing tools for neglected diseases, there is a fair amount of scientific uncertainty because research aimed at improving the fundamental understanding of the pathogens and disease processes still is limited for these diseases. Respondents noted that an incomplete understanding of the mechanisms of action or how these pathogens cause disease makes it difficult to identify potential targets for vaccines and drugs, and to design diagnostics that can confirm infection, disease, and drug resistance. For example, it is understood that humans can make neutralizing antibodies against HIV, but researchers are trying to discern how to turn that knowledge into a potential vaccine candidate. This may be even more of a challenge for less researched neglected tropical diseases. EVI, DNDi, and IDRI noted that they are still learning about the complex development and life cycles of certain disease-causing pathogens, making it difficult to understand how best to interrupt the disease process.

Inadequate research tools pose significant challenges to product developers. Aeras, TBVI, and MMV noted that the lack of comprehensive laboratory models, both animal and in vitro, and markers of protection pose significant challenges for evaluating their respective products. MMV and DNDi reported needing better diagnostics for case detection and characterization, including drug resistance data and laboratory assays for assessing efficacy of new tools. These data are critical for evaluating products, informing target product profiles, and capturing surveillance data that can describe true disease burden and impact for diseases. NPPDs and other developers use this information to manage their portfolio of projects for each disease target.

Some NPPDs also identified a number of **nonclinical research challenges**. According to these respondents, more research is needed to identify how to develop sustainable markets for products and establish innovative financing mechanisms that would attract investment into product development from all sectors across all phases of research. The International Partnership for Microbicides (IPM), which has microbicide candidates in late-stage clinical trials, identified the need for more acceptability studies to engage end users in the design and validation of new products to facilitate their uptake. Jhpiego and PATH felt that NPPDs would benefit from more creative exploration of introduction and utilization strategies, particularly for devices—some of which are consumer products to be sold in the private sector—that have no central procurement mechanism and therefore lack strong incentives for public- and private-sector investment.

The NPPDs were asked to identify the key systemic and infrastructure challenges they face as technologies advance through the pipeline. **Funding** was at the top of the list. Numerous respondents noted that there are too few funders investing too few resources in R&D for neglected diseases and poverty-related conditions. Lack of funding threatens to stall or interrupt progress. This may be particularly true during the time from discovery through proof-of-concept Phase I and II

b Diseases include bacterial pneumonia and meningitis, dengue fever, diarrheal diseases, helminth infections, HIV, kinetoplastids, leprosy, malaria, trachoma, and tuberculosis.

clinical studies—or what some researchers refer to as the "valley of death"—where there is a dearth of funding for technology projects that no longer count as basic research but are not yet far enough to advance to later-stage efficacy trials.

Of the funding that is available for R&D targeting poverty-related and neglected diseases and conditions, a significant portion does not lend itself to product development. Public funding has shifted substantially from product development to basic research, which accounted for almost one-third of total investment (31.2 percent) in 2011 versus just over 26 percent in 2007.[4] The NIH is by far the largest public-sector funder but directs most of its investments to investigator-driven basic research. This type of funding is not as flexible as unrestricted core funding that provides broad support to an entire project, and which can more suitably support the portfolio approach used by NPPDs. It is important to note that the NPPDs are not encouraging the NIH and other academic labs to shift more of their existing funds to product development, and recognize that basic research is necessary for the breakthroughs that lead to new products. But they support more funders investing throughout the product development process, including late-stage development and introduction, because the lack of diversity of funders investing in product development and introduction for LMICs risks creating a situation where research is guided by an individual donor's priorities.

The challenge of trying to navigate **weak and disjointed regulatory systems** is a major obstacle for the NPPDs and their partners. Several NPPDs cited the lack of consistent regulatory requirements and limited capacities of national regulatory authorities as major contributors to delays and increased costs. These delays can also have significant impact on health systems. For example:

- MVI had to clear 40 independent review boards—many reviewing the same information against different standards—in order to initiate clinical trials of RTS,S.
- WHO—which works with national regulatory authorities to monitor and strengthen capacity—temporarily removed the national regulatory authority of India of its functional status as a vaccine regulator because the authority was not fulfilling all of the critical control functions necessary to effectively monitor and evaluate vaccine research and production. It took approximately 18 months and significant investment from many stakeholders—including MVP and its partners, as well as the Indian government—to improve standards. This delayed the registration of the MenAfriVac® vaccine, which may have exacerbated a potentially preventable outbreak of meningitis A.
- IPM would need to file regulatory dossiers with multiple independent regulatory agencies in order to register a microbicide in each country where it could have potential public health impact. Each dossier submission costs time and money and delays the availability of these technologies.

The costs of regulatory challenges cannot be understated and have ripple effects beyond the specific country of focus. Each delay increases the complexity, duration, and cost of conducting research targeting the health needs of LMICs. NPPDs and their partners bear costs related to regulatory requirements throughout the product development process in order to secure approval to initiate studies, register a product, and monitor the safety and efficacy after product approval. Timely review and approval by regulatory authorities is critical to meeting clinical development milestones and facilitating the timely introduction and uptake of new and improved technologies. Unfortunately, regulatory authorities in many endemic countries do not have the resources to conduct thorough reviews of the diverse products currently in the NPPD pipeline. This is compounded by the fact that stringent regulatory authorities in wealthy countries neither have the mandate nor the resources and expertise to adequately address this gap.

In addition to weak regulatory capacity at the country level, respondents felt that **limited local research and manufacturing capacity** constrain NPPDs and their partners' ability to keep the pipeline filled and bring new and improved technologies to patients. Many local research sites

have not conducted stringent product registration studies that meet international standards for good clinical and laboratory practice. Since clinical trials for products must be conducted in the settings in which diseases are endemic, investments must be made to strengthen local capacity. This includes training and improving facilities in high-burden settings to meet these standards. Likewise, manufacturing partners in many of these countries lack the experience and expertise to produce products that meet standards necessary to secure approval from WHO and international procurement agencies, such as the GAVI Alliance and UNICEF. This too means NPPDs and their partners must invest in strengthening local manufacturing to ensure a sustainable supply of quality-assured products.

Potential solutions

Many of the NPPDs have tried to address the challenges of inadequate funding, weak regulatory systems, and limited local capacity. A number of these efforts have been successful in overcoming obstacles, but are limited in scope and reach.

NPPDs note that more predictable, stable, and long-term funding and innovative financing across all phases of product development are necessary to enable the development and delivery of new health technologies designed for LMICs. It is critical to diversify funding sources and improve coordination across funders to allow for a more **sustainable and consistent funding base**. The NPPDs call for greater leadership from governments in endemic countries in partnering with "traditional" donors to identify unmet R&D needs and comprehensively finance R&D targeting the health needs of LMICs. This includes investment in developing products, as well as sustainable markets that will drive innovation and investment from all sectors.

Many of the NPPDs report that there is a need for **centralized coordination mechanism(s)** tasked with identifying overarching R&D needs, gaps, and priorities in line with a proposed recommendation from the CEWG to establish a global R&D observatory. Many of the NPPDs also note that if this coordination body were housed within an organization that is properly staffed and funded, it would be a valuable asset by coordinating R&D efforts toward clearly defined goals for needs-driven innovation and equitable access. However, there was not consensus among the NPPDs about which organization should or could fill this role. Some NPPDs specifically called on WHO to act as the centralized mechanism.

Almost all of the NPPDs note that, although their primary goal is the development of new tools, they also work to strengthen research, manufacturing, and in some cases regulatory capacity in endemic countries. NPPDs and their partners need sufficient resources to invest in **strengthening the research and manufacturing capacities of their local partners**. For instance:

Strengthening scientific capacity in developing countries

IAVI and its partners have developed an international network of clinical facilities and labs, in service to its mission to ensure the development of AIDS vaccines. Seven research centers are located in five East and Southern Africa countries and are each linked to national institutions or academic research centers. All affiliated labs are in compliance with Good Clinical Laboratory Practice requirements, the international standard. This collaboration has resulted in thorough training for clinicians, nurses, scientists, and technicians to conduct AIDS vaccine trials and studies at the highest ethical, scientific, and quality standards. IAVI's clinical partners in Africa and globally have evaluated 13 AIDS vaccine candidates over the last decade. IAVI has also taken a comprehensive public health and development-driven approach to engaging communities in AIDS vaccine research, training counselors and health care providers in communities and investing in "training the trainers" programs. Ending the HIV/AIDS epidemic, according to IAVI, will require the contributions of researchers from countries most burdened by the disease. The success of the AIDS vaccine enterprise and resulting economic development will hinge on the establishment of sustainable, local, scientific, and technological capacity in developing and emerging economies.

- IPM established its South Africa office to implement sustained investment and capacity-building activities in communities with high HIV prevalence. To date, IPM has helped strengthen capacity at 17 research centers (including 10 newly established centers) in seven countries in Africa. The organization has also trained more than 600 staff and community advisors on microbicides and clinical trial implementation. As a result, many of these centers are now equipped to conduct high-quality clinical trials in line with Good Clinical Practice guidelines and provide other needed health services to the community.
- The European and Developing Countries Clinical Trials Partnership (EDCTP)[c] works with a number of the surveyed NPPDs to enhance the research capacity at sites in which trials are ongoing or planned. Some NPPDs that work in areas outside of the EDCTP's current scope have advocated for the expansion of EDCTP's mandate from Phase II and III studies to include Phase I and IV studies and across more diseases beyond HIV, TB, and malaria.[15] This would allow for NPPDs working in neglected tropical diseases and poverty-related conditions to utilize the capabilities built at these sites.
- IDRI has undertaken partnerships to share adjuvant technology—substances that can help augment the breadth and magnitude of the protective immune response to vaccines—and expand vaccine capabilities. The Cantacuzino Institute in Romania was close to developing an avian flu vaccine and partnered with IDRI to develop the emulsion technology to increase the availability of dosages for influenza. Gennova Biopharmaceuticals Ltd. in India is working with IDRI on the same emulsion technology but in an effort to advance vaccine capabilities for a range of diseases. Both projects are just the start for multicountry vaccine collaborations for IDRI.
- PATH worked with the Chengdu Institute of Biological Products—a vaccine manufacturer in China—to increase access to the Japanese encephalitis vaccine. PATH supported the construction of a new factory and helped the manufacturer prepare data and submit an application for prequalification from WHO—a prerequisite for procurement by UN agencies. A final decision from WHO is expected within the year and, if granted, it will become the first vaccine made in China to be prequalified by WHO. As a result of this partnership, the Japanese encephalitis vaccine has been introduced in five new countries where approximately 81 million children have been vaccinated since 2006.

Most of the NPPDs noted the need to **strengthen regulatory pathways and capacities** that shorten review timelines without compromising the ultimate quality of a product. Overcoming regulatory challenges will require policy change, clarification of pathways for all types of technologies, and adequate and sustainable funding to support capacity strengthening and alignment of regulatory requirements. The NPPDs see an opportunity to scale up and expand existing projects like the African Vaccine Regulatory Forum (AVAREF)[d] and the African Medicines Regulatory Harmonization Programme,[e] that bring together representatives from public and private sectors in high-, middle-, and low-income countries to improve regulatory processes and strengthen local capacity. For example, MVI and partners worked closely with AVAREF and regulators from seven African countries to conduct a joint review of a clinical trial evaluating the effectiveness of RTS,S—a malaria vaccine candidate being evaluated in Phase III clinical trials. This joint review helped African scientists and regulatory officials increase their capacity to oversee clinical trials, align national regulatory requirements, and expedite the study

c EDCTP aims to accelerate the development of new or improved drugs, vaccines, microbicides, and diagnostics against HIV/AIDS, tuberculosis, and malaria, with a focus on Phase II and III clinical trials in sub-Saharan Africa. EDCTP is up for renewal in 2014 under the EU Framework Programme for Research and Innovation. For more information, visit http://www.edctp.org/.

d AVAREF is an *ad hoc* scientific advisory body convened by WHO to provide support to regulators in making informed regulatory decisions with regards to authorizations of clinical trials, evaluation of registration dossiers, or any other challenging issues regarding evaluation of vaccines. For more information, visit http://www.who.int/immunization_standards/vaccine_regulation/africa_network/en/.

e The overall aim of the African Medicines Regulatory Harmonization Programme is to support African countries to improve public health by increasing access to good quality, safe, and effective medicines through harmonizing medicines regulations, and expediting registration of essential medicines. For more information, visit http://www.amrh.org/

Table 4. Summary of challenges and potential solutions for R&D targeting LMICs

Challenges	Potential solutions
Gaps in scientific understanding and tools	Coordination of efforts towards identifying needs-based priorities and monitoring investments in R&D targeting health needs of LMICs.
Insufficient funding levels	Sustained investment across the product development value chain from "traditional" donors and endemic countries.
Weak and disjointed regulatory systems	Scale up innovative regional programs like AVAREF and ensure global and regional regulatory stakeholders and stringent and national regulatory bodies have adequate resources to support local capacity strengthening and alignment of requirements.
Limited local research and manufacturing capacity	Scale up research networks like EDCTP and ensure NPPDs and partners have adequate resources to support capacity strengthening of local research and manufacturing partners in line with international standards.

review process. Today, the large-scale efficacy trial evaluating the vaccine has enrolled more than 15,000 children and infants at 11 sites in seven African countries. These types of models should be fully equipped with the resources to expand across various types of technologies, diseases/conditions, and regions, and their efforts should be coordinated to avoid duplication and maximize impact.

Conclusion

There was broad agreement across the NPPDs surveyed about the most significant challenges they face in advancing technologies, as well as some potential solutions to address these issues (see Table 4).

The examples and perspectives cited in this paper provide a high-level overview of the greatest gaps and challenges faced by NPPDs, but are not intended to serve as a comprehensive list of all challenges inhibiting the development of products targeting the health needs of LMICs. Further papers will explore these issues in greater detail.

This analysis is meant to inform global policy and financing debates, including but not limited to discussions of the recommendations outlined in the report from the CEWG, by describing how NPPDs advance R&D for poverty-related and neglected diseases and conditions in LMICs. Some of the challenges cited in this analysis are similar to those cited by the CEWG, including lack of diversified funding mechanisms that encourage sustained investment and inadequate investment from LMICs, as well as limited local research and manufacturing capacity. However, NPPDs highlighted additional critical gaps and challenges that were not addressed by the CEWG, such as the scientific uncertainty that underlies neglected disease research, and solutions that could be taken up by the global R&D observatory such as strengthening national regulatory capacity and improving alignment of regulatory processes.

The GHTC will explore the identified gaps, challenges, and solutions outlined in this paper in greater detail in a series of subsequent papers intended to share the perspectives from NPPDs on:

- Financing of R&D and the mechanisms they consider to have achieved a demonstrable impact on accelerating the development of and improving the accessibility of technologies targeting poverty-related and neglected diseases and conditions.
- Ensuring the availability, accessibility, and affordability of technologies through a variety of mechanisms—including but not limited to licensing agreements and initiatives that promote open knowledge innovation.
- Addressing regulatory challenges and innovative pathways faced by NPPD and partners throughout the product development process.
- Strengthening the research and manufacturing capacity of local partners in LMICs.

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