

Challenges and opportunities for innovation, access and delivery of health technologies: Why a global dialogue?

Background paper



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GHIT Fund

Global Health Innovative Technology Fund

Cover:

A cadre and a nurse from Posyandu Kapuk II, West Jakarta, Indonesia, is weighing children while visiting houses to check for children who have not received immunization.

Photo: Fauzan Ijazah.

Challenges and opportunities for innovation, access and delivery of health technologies: Why a global dialogue?

Background paper

Prepared for:

**Uniting efforts for innovation, access and delivery:
A global dialogue.**

Organized by the Government of Japan, the Access and Delivery Partnership (ADP) and the Global Health Innovative Technology (GHIT) Fund in Bangkok on 30 and 31 January 2019.

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Contents

Part 1	Introduction	6
a	Background	6
b	Purpose of paper	7
Part 2	Innovation: From knowledge to technologies	8
a	Stage 1: Basic research	8
b	Stage 2: Discovery, pre-clinical and clinical product development	8
c	Stage 3: Regulatory review	9
Part 3	Access and delivery: From technologies to health impact	11
a	Stage 4: Manufacturing and distribution	11
b	Stage 5: Uptake in national health systems	12
c	Stage 6: Provider and population	14
Part 4	System-wide challenges	15
a	Insufficient consideration of interlinkages between stages	15
b	Insufficient consideration of interlinkages between technologies:	15
c	Risk of misaligned incentives	16
d	Balancing private and public interests	16
e	Ensuring sustainable funding	17
f	Facilitating coordination and priority-setting	18
g	Monitoring the overall innovation-access-delivery ecosystem	18
Part 5	Conclusions: Why a global dialogue?	19
	Works cited	20

Junaidi, a TB MDR patient, with his wife, Casweli (35) and his son Saka Januar (5 months), at their home in East Jakarta, Indonesia.

Photo: Fauzan Ijazah.

a **Background**

This paper seeks to inform and frame the discussions that will take place at the meeting, *Uniting efforts for innovation, access and delivery: A global dialogue*, organized by the Government of Japan, the Access and Delivery Partnership (ADP) and the Global Health Innovative Technology (GHIT) Fund in Bangkok on 30 and 31 January 2019. This initiative seeks to provide a forum for dialogue across a broad range of stakeholders involved in innovation, access and delivery of essential health technologies. Participants are expected to include representatives from biomedical R&D funders, research organizations, product development partnerships (PDPs), and access stakeholders – defined in this context as actors involved in the selection, regulation, pricing, procurement and delivery of health technologies at country and global levels. As occasions for dialogue across the full range of interdependent stakeholders are relatively rare, this meeting seeks to provide an opportunity for learning and better alignment across this complex ecosystem.

Malaria, tuberculosis (TB) and the neglected tropical diseases (NTDs) are key priorities of the GHIT Fund and ADP partnership, both supported by the Government of Japan since 2013. These diseases take a heavy toll on households, impeding human and economic development among the world’s poorest populations. For example, despite major progress against malaria over the past decade, estimated cases in 2016 hit a plateau at 216 million [1]. TB is the leading cause of death from a single infectious agent, with an estimated 10 million people having developed TB in 2017 [2]. The NTDs¹ collectively affect over one billion people, primarily those living in poverty [3]. Vulnerability to these diseases is often a marker of destitution and social marginalization, and episodes of illness can drive a household even further into poverty. Ending these epidemics by 2030 has been globally agreed as a target within the Agenda for Sustainable Development.² While this paper focuses on specific diseases, many of the issues raised here are also applicable to achieving innovation, access and delivery for other health challenges such as the non-communicable diseases, antimicrobial resistance, and outbreaks.

Health technologies, including drugs, vaccines, diagnostics and other medical devices, can play an important role in preventing and treating these diseases. The Lancet Commission on Investing in Health concluded that “the international community can best support convergence by funding the development and delivery of new health technologies and curbing antibiotic resistance [6].” Technologies are not the only intervention needed for public health – for example, strengthening health systems and addressing the broader social, economic and political determinants of health are also essential. Nevertheless, the specific focus on technologies in SDG targets 3.8³ and 3.b⁴ underscores the wide recognition that neither universal health coverage nor SDG 3 as a whole can be achieved without more equitable innovation and access to health technologies [7].

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1. WHO’s list of neglected tropical diseases includes: Buruli ulcer; Chagas disease; dengue and chikungunya; dracunculiasis (Guinea worm disease); echinococcosis; foodborne trematodiasis; human African trypanosomiasis (sleeping sickness); leishmaniasis; leprosy (Hansen’s disease); lymphatic filariasis; mycetoma, chromoblastomycosis and other deep mycoses; onchocerciasis (river blindness); rabies; scabies and other ectoparasites; schistosomiasis; soil-transmitted helminthiasis; snakebite envenoming; taeniasis/cysticercosis; trachoma; yaws (endemic treponematoses) [3]. However, there is no single fixed list of which diseases are considered to fall within the category of neglected tropical diseases. The G-FINDER report, which tracks investment in neglected disease R&D, extends beyond these to also include HIV, tuberculosis, malaria and hepatitis, among other pathogens [4]. The US Priority Review Voucher’s list of qualifying NTDs overlaps considerably with the WHO list but also has important differences and is evolving [5].
2. SDG Target 3.3: By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases.
3. SDG 3.8 Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all.
4. SDG 3.b Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all.

During the past several decades, we have witnessed reinvigorated efforts to improve innovation, access and delivery of health technologies for at least some of these diseases. Investment in basic research and health technology development has begun to refill empty pipelines [4]. Interventions to improve affordability, quality, supply security and regulatory processes have been implemented. Billions of dollars of domestic and international funding have been invested in programmes to deliver treatment and care at country level. These efforts have contributed to major accomplishments, such as significant decline in the global incidence of malaria, TB and several NTDs (e.g. rabies, visceral leishmaniasis, human African trypanosomiasis), and even elimination of certain diseases (e.g. malaria, dracunculiasis, onchocerciasis) in previously endemic countries [1, 2, 8].

However, progress is slow and precarious. Growing resistance of the malaria parasite to previously-effective drugs and insecticides raises the possibility that epidemics could resurge [1]. TB cases have been declining very slowly while multidrug-resistant forms of the disease are spreading [2]. Some NTDs such as mycetoma or snakebite envenoming have received very little attention or funding, and efforts to address them remain nascent. Meanwhile, macro trends such as climate change and urbanization raise new risks of the spread or resurgence of some diseases. Achieving equitable innovation, access and delivery remains a major challenge, requiring aligned action by many countries and diverse actors, long-term and sustainable commitment of resources, and overcoming numerous obstacles.

b Purpose of paper

The purpose of this paper is to provide meeting participants with a common, comprehensive starting point from which to launch discussions on how to address shared challenges and seize opportunities in ensuring more effective and equitable innovation, access and delivery of health technologies for the target diseases. It does so by providing an overview of each step of the long path we must travel in order to progress from understanding a pathogen to mitigating its health consequences. The paper also provides examples of how those challenges have been addressed in specific instances, potentially offering lessons to be applied elsewhere. Building on other frameworks [7, 9–12], this document traces the evolution of a health technology through six stages: basic research; discovery, pre-clinical and clinical development; regulatory review; manufacturing and distribution; national health systems (including supply chains); providers; and patients. This paper identifies the many types of actors involved at each stage, including governments, intergovernmental organizations, foundations, NGOs, private sector, academic and scientific organizations, public and private health care providers and patients. Actors are identified to highlight the coherence challenges arising from the number, range, and differing time-frames, mandates and interests of the various actors across the innovation-access-delivery spectrum. The paper then identifies systemwide issues (spanning more than one technology or stage) that merit attention, and related challenges and opportunities to address them.

To cover such a broad topic, the paper necessarily simplifies and sacrifices depth in order to provide a comprehensive and high-level view of a complex system. For example, in reality the stages do not necessarily take place in a linear fashion and often involve iterative feedback loops. Some of the divisions between stages are necessarily somewhat arbitrary. The framework is intended to facilitate discussion rather than to capture the system's full complexity.

The paper is based on existing literature and initiatives, developed based on the author's knowledge of the field, and strengthened by comments from four anonymous peer reviewers and the meeting co-organizers. The paper is not a systematic literature review, nor does it provide a comprehensive catalogue of how to overcome challenges or seize opportunities. Rather, it seeks to provide a high-level synthesis to facilitate participant discussions across a broad set of topics, using examples to illustrate challenges and potential lessons.

a **Stage 1: Basic research**

Basic scientific understanding of diseases primarily affecting the world's poor is vital to develop health technologies. Without understanding the characteristics of a pathogen and the disease it causes – for example, the relevant biology, biochemistry, epidemiology, genetics and immunology – it is difficult to develop drugs, vaccines, diagnostics or other interventions (e.g. insecticides, bednets, water filters) for disease control. Despite significant scientific advances, sustained investment in basic research remains critical for many of the diseases under consideration here, particularly in light of evolving antimicrobial resistance. G-FINDER estimates that 48 percent of global investments in neglected diseases targeted basic research [4].

Key **actors** involved in basic research are primarily public and academic research scientists (including their professional societies), public and philanthropic research funders, and scientific journals, with product development partnerships and private firms also playing a role. Most funding for basic research comes from government science and technology funders, with the largest basic research investments by far coming from the US National Institutes of Health (NIH).

Important **challenges** in this stage include inadequate total investment in basic research for neglected diseases relative to burden of disease. Most scientific funding is provided by public and private funders based in high-income countries where neglected diseases are not endemic. Relatively little research investment originates in disease-endemic countries, and relatively few researchers are based in these countries, where capacity and scientific infrastructure can be limited. Since the scientific community involved in improving understanding of these pathogens is relatively small, arrangements to encourage collaboration, rapid open sharing of research and knowledge are critical to accelerate progress.

Some **examples** of addressing these challenges include the rise of open access publishing as a norm over the past decade, supported – and indeed required by – major research funders including the US NIH, UK Medical Research Council, the European Union and individual member states, and the Bill and Melinda Gates Foundation (BMGF), among others. Professional societies, such as the tropical medicine societies, also play a critical role in facilitating scientific collaboration and rapid sharing of research findings. Public research funders in disease-endemic emerging economies have also begun increasing their investments, for example the Indian public sector, which primarily invests in basic research and increased its spending from US\$32 million in 2008 to \$50 million in 2013 [13].

b **Stage 2: Discovery, pre-clinical and clinical product development**

After adequate knowledge of a pathogen is accumulated, potential drug targets, biomarkers, or compounds are identified and product development transitions into the pre-clinical and clinical stages. At this stage, potential products are tested at a small (pre-clinical, Phase 1) and later at a larger scale (Phase 2 and 3) for safety and efficacy.

Key **actors** at this stage include public and academic labs conducting earlier-stage pre-clinical work, small and medium enterprises (SMEs) that may spin off from such labs, PDPs, large firms (particularly for later-stage clinical development), and early and later-stage research funders.

Important **challenges** at this stage include inadequate total investment in product development for neglected diseases, which offer little to no market return. Young *et al.* estimated that an additional \$1.5–\$2.8 billion per year would be needed, above existing investments of about \$3 billion per year, to successfully bring 18 neglected disease products to completion [14]. Other challenges include ensuring collaboration between researchers to accelerate progress, including facilitating access to promising compounds and compound libraries, as well as sharing data from pre-clinical and clinical research. Collaboration is also important to test compounds and existing

medicines in combination to ensure that appropriate regimens (rather than only single drugs) can be provided to patients upon regulatory approval (see discussion in Part 4(b) below). If there is intellectual property covering a candidate technology, such as an early-stage compound or diagnostic platform, it may be challenging to obtain relevant IP rights to develop the technology further for neglected diseases, especially if the technology also has a potential market in high or middle-income countries (“dual use” technologies). Finally, conducting clinical trials in disease-endemic countries requires identifying and investing in local capacities, adapting trial design to local contexts, and can also involve overcoming significant logistical hurdles such as intermittent electricity, poor roads and insecurity in conflict-affected regions [15]. At the same time, such studies must meet rigorous international standards such as those set by WHO or the International Council for Harmonisation (ICH). An additional challenge is securing adequate arrangements to ensure the end-product will be affordable and available when it completes the development process. As noted in Part 4(d), as public and philanthropic financing increases for these product areas, securing agreements from product developers to meet core product development expectations is important.

Examples of addressing these challenges include the increase in public and philanthropic investment in pre-clinical and later-stage clinical R&D over the past two decades, whereas previously the public sector largely left clinical research to be funded by private firms. In addition, whereas neglected disease product development was earlier financed by high-income countries, often out of development aid budgets, there has been growing engagement from newer players. This includes government science, technology or research ministries investing in R&D, including South Africa’s Medical Research Council and Japan’s GHIT Fund [16]. There have also been growing numbers of clinical trials run in developing countries, suggesting increasing capacity [17, 18]. The European-Developing Countries Clinical Trial Partnerships (EDCTP) initiative has funded over 100 clinical trials in sub-Saharan Africa since its establishment in 2003 [17]. This trend also raises its own challenges, however, such as ensuring ethical treatment of human subjects, capacity of national ethical review boards, and sustained access to experimental technologies where relevant [18].

Finally, academics, PDPs, firms and funders have been increasingly engaging in open-science approaches that facilitate knowledge-sharing, including but not limited to publishing results in open-access journals. For example, the Open Malaria Box developed by the Medicines for Malaria Venture (MMV) made a set of compounds openly available to any researcher interested in conducting research on their utility for malaria or other NTDs. The Drugs for Neglected Diseases initiative (DNDi) NTD Drug Discovery Booster project brings together eight pharmaceutical companies to screen their compound libraries for chemicals potentially useful against Chagas disease and leishmaniasis [19]. The Foundation for Innovative New Diagnostics (FIND) and Critical Path Institute have built an open-access platform with genomic sequencing data on drug-resistant TB specimens, facilitating the development of diagnostics and drug-susceptibility testing [20]. The TB Alliance is developing new compounds in regimens rather than only as single drugs, and seeking approval of regimens that can facilitate better patient outcomes and rational use [21].

c **Stage 3: Regulatory review**

Once a product has completed clinical trials, originator or generic versions of the product must obtain regulatory approval from a stringent regulatory authority (SRA, e.g. US Food and Drug Administration, European Medicines Agency, Japan’s Pharmaceuticals and Medical Devices Agency), the national regulatory agency (NRAs) in the country of intended use, and often both. SRA approval is usually required for procurement using donor funds, and NRA approval for use in country. Post-marketing pharmacovigilance (e.g. Phase IV trials) to detect adverse events is also necessary once a product is used by a larger population.

Key actors at this stage are SRAs and NRAs, developers and manufacturers of products, WHO and funders supporting regulatory strengthening initiatives.

Key **challenges** in this phase include: for SRA approval, authorities are asked to assess technologies for diseases that are usually not endemic in their jurisdictions. For NRA approval, different regulatory standards and processes across multiple countries can increase costs and time, and developers or manufacturers may be either unable or unwilling to invest the necessary resources to obtain NRA approval in all countries that need a product. Among product developers, experience with regulatory filings is concentrated in large firms, and can be challenging for PDPs or SMEs with limited experience in regulatory submissions. Some NRAs in neglected disease-endemic countries may not have experience, technical expertise or institutional processes to review dossiers for health technologies that have not yet been approved elsewhere in the world. Both SRAs and NRAs have the potential for significant time lags.

Furthermore, country approaches to regulating non-pharmaceuticals (e.g. diagnostics, medical devices, insecticides or bednets for vector control) vary widely, with some countries having no clear regulatory process in place for assessing such products. There may also be challenges approving products that are introduced in novel delivery formulations, or for which approval is sought only for regimens, not single compounds.

Finally, responsibility and capacity for pharmacovigilance may be poorly-defined or inadequate. Whereas responsibility for pharmacovigilance in well-established high-income markets usually falls jointly on a product originator and the government, in the absence of an originator producer, it is unclear where responsibility for post-marketing pharmacovigilance should or does lie. For example, tracking adverse events is particularly challenging when a PDP has developed a product jointly with a large firm, and then licensed the production and supply of the product to several generic firms.

Examples of approaches to overcoming these challenges include the EMA's Article 58 process, in which the EMA works jointly with a relevant NRA to issue an opinion on whether a new health technology demonstrates adequate safety and efficacy. For example, Sanofi and DNDi submitted a new sleeping sickness drug, fexinidazole, to the EMA, which reviewed the dossier with the NRA of the Democratic Republic of the Congo [22]; the EMA issued a positive opinion on the drug in late 2018. In addition, regional regulatory initiatives have been launched, such as the African Union Model Law for Medical Products Regulation, supported by NEPAD and ADP. In addition to promoting more efficient regulatory processes, the AU Model Law also provides guidance on quality assurance, pharmacovigilance and ethical review for clinical trials. Regulatory harmonization efforts in the East African Community and Southern African Development Community have been credited with significantly reducing time to registration, and include a capacity-building component [23]. On pharmacovigilance, specific initiatives have targeted strengthening national PV systems, such as ADP's support for developing a surveillance system in Indonesia to monitor and enable the introduction of bedaquiline for MDR-TB treatment [24]. Funders including USAID, Japan and the BMGF have supported initiatives to strengthen regulatory capacity.

Furthermore, WHO's Prequalification Programme has cleared the path for large-scale donor procurement of health technologies by providing donors with quality assurance (disease areas under the programme include malaria, TB and the neglected tropical diseases) [25]. The WHO Prequalification Collaborative Registration Procedure shares information with NRAs to accelerate national approval of WHO prequalified products [26]. However, as the PQ Programme relies on donor funding and addresses only a subset of diseases and product types, it is not a replacement for NRA capacity.

a **Stage 4: Manufacturing and distribution**

Once a product has received regulatory approval, it must be manufactured in adequate volumes in a timely manner for distribution to endemic countries. Key **actors** in this stage include generic or innovator manufacturing firms, regulatory agencies, and procurers (national governments, donors, global funding or procurement initiatives).

Key **challenges** at this stage include ensuring the quality, quantity and affordability of the product. A 2017 WHO study estimated that 10.5 percent of products tested in low- and middle-income countries had failed quality tests and could be considered substandard [27]. Quality assurance processes are required throughout the supply chain, from manufacturer to clinic, but not always implemented.

Furthermore, adequate supply is difficult to ensure when demand projections are uncertain (as is often the case with new technologies and for neglected diseases), markets are globalized (such that a spike in demand in one country can create shortages for another), and depend on the particularities of a given product. For example, as countries began shifting treatment protocols to adopt artemisinin combination therapy for malaria starting around 2003, the rapid increase in global demand could not immediately be met with the long two-year plant-based manufacturing process required for the drug. The global artemisinin market was volatile for a number of years, characterized by shortages and gluts, price spikes and falls for raw materials [28].

There are many reasons for supply challenges. For example, supply can be delayed or halted when orders are low-volume or unpredictable, when delays in payments increase risk for manufacturers, or when producers stop manufacturing due to insufficient profits. Supply security may be more vulnerable when there is only a single supplier for a product, or when producers rely on a small number of API or other raw materials producers. Increasing global concentration of API manufacturing in China means that any problems with Chinese API producers can have worldwide supply ramifications. The issue of shortages has recently garnered increasing attention at the global level, as reflected in 2016 World Health Assembly Resolution 69.25 focusing on this issue [29].

Finally, products must be affordable, especially since products for neglected diseases are targeted exactly at the households and countries with the least ability to pay. Unaffordable health technologies are a barrier to access. Prices are influenced by many factors including costs of production, low volume demand, or monopolies impeding competition.

Total health spending in low-income countries (LICs, under \$1,005 GNI per capita (pc)) was just \$35 per capita, in lower-middle income countries (LMICs, GNIpc \$1,005-3,955) it was \$83, and in upper-middle income countries (GNIpc \$3,956–\$12,235) \$470 (2016 World Bank data). At present, an estimated one fourth of total health expenditure goes towards pharmaceuticals in LMICs, with higher ratios at lower levels of country income [30]. With an increasing number of new health technologies that can offer benefits in developing countries, combined with other demands such as expansion towards universal health coverage, national health budgets are under increasing strain. At the same time, development assistance for health reached a plateau in 2010 after a decade of rapid growth, and significant further increases from traditional donors seem unlikely [31]. These trends raise new questions for affordability, since a price considered affordable by donors may not be so to governments, or a price affordable to a health system may not be affordable when it must be paid out of pocket.

Some **examples** of approaches to addressing these challenges include WHO's Global Surveillance and Monitoring System, which collects information from countries on substandard and falsified medicines, issues rapid alerts when they are detected, and conducts capacity building at country level [32]. While a global back-up system to detect substandard medicines is critically important, it cannot replace national quality assurance systems and strong regulatory functions and institutions.

In addition, pooled procurement initiatives such as the Global Drug Facility (for TB), Gulf Cooperation Council, PAHO Revolving Fund, PEPFAR for HIV commodities, or UNICEF/GAVI for vaccines can address quality, quantity and affordability challenges. For example, both PAHO and UNICEF/GAVI pool vaccine demand from countries, negotiate lower prices from suppliers in exchange for reliable and large demand, and provide guaranteed payment to suppliers [33]. Despite widespread interest in pooled procurement, however, practical challenges (such as harmonizing national legislation in pooling countries) have impeded the creation of many other such initiatives [34].

UNITAID has also funded a wide range of projects to improve the quality, security of supply, and affordability of health technologies for HIV, TB, malaria and related co-morbidities. A sample of UNITAID-funded projects includes demand forecasting for artemisinin, improved process chemistry to reduce the price of antiretrovirals for HIV, funding for the WHO Prequalification programme, and overcoming patent-related barriers to competitive pricing through the Medicines Patent Pool [35].

“De-linkage” (financing R&D separately from product prices) has been proposed as a means to achieve affordable pricing, and was supported in the 2016 Political Declaration of the UN High-Level Meeting on Antimicrobial Resistance [36]. For malaria, TB and NTDs, de-linkage is already implemented at least partially when public and philanthropic funders have paid for the R&D (e.g. through PDPs), allowing the final product to be sold at or near the cost of production. For example, the RTS,S (Mosquirix) malaria vaccine candidate is a product of joint efforts by GlaxoSmithKline and the Malaria Vaccine Initiative (part of PATH), and was funded largely by the BMGF. GSK announced it would supply the vaccine at a no-profit/no-loss price that reflects the cost of production, with a small 5 percent margin for reinvestment in developing the next generation of malaria vaccines. The price is not intended to cover the R&D investments into RTS,S. Gavi, the Global Fund and UNITAID are contributing funding for an RTS,S pilot in Kenya, Malawi and Ghana [37].

Governments, R&D funders, PDPs, companies and others have adopted many strategies to address affordability concerns. These include measures to encourage competitive markets (including voluntary or compulsory licensing of patents), setting target prices in TPPs, audited cost-plus pricing agreements, no-profit/no-loss pricing, improving manufacturing efficiency, technology transfer, tiered pricing and donations. While a thorough review is beyond the scope of this paper, it should be noted that each of these strategies has strengths and weaknesses, and the best path to achieve affordability often depends on the specific product and market niche.

Overall, many global initiatives have been implemented to address challenges relating to quality, quantity and affordability, but these have generally focused on a few products (i.e. vaccines, drugs for HIV, TB, malaria). For products not yet covered by any such arrangements, lessons may be drawn from the wealth of experience built over the past two decades.

b Stage 5: Uptake in national health systems

After technologies are developed, manufactured and registered, uptake of new products at national level can begin. Uptake often requires national policy decisions such as whether to change a national treatment guideline, allocate budget, and train health workers to adopt new technologies. In countries with a significant private for-profit health care sector, such as private pharmacies dispensing malaria drugs or clinics providing TB treatment, authorities must also decide how to regulate use of a new product. After health technologies are procured, they enter into national supply chains.

Key **actors** in this stage include ministries of finance, ministries of health (including guidelines

committees, health technology assessment bodies, procurement agencies), national insurance agencies, NRAs, importers, distributors/wholesalers, pharmacies, health care facilities, and international development organizations supporting any of these actors (e.g. WHO, PEPFAR, UNICEF, Global Fund).

Key **challenges** at this stage include: ensuring robust processes to select the health technologies most suitable for use in a country, including health technology assessment on a product's overall value and whether national guidelines require amendment. National guidelines in many countries are shaped by WHO guidelines, and there can be long timelines to update two sets of guidelines after a product receives regulatory approval. With the growing number of available health technologies, countries face rising challenges selecting the most suitable technologies under constraints on budgets and health system capacities. Furthermore, training health workers and ensuring appropriate use of technologies is necessary, but can be costly and time-consuming. Some technologies can produce net savings across a health system through efficiency gains, but others may imply increased costs far beyond the price of the product itself.

In addition, product quality needs to be ensured upon arrival in-country and throughout the supply chain. For example, products such as vaccines that require a cold chain may arrive in-country at an appropriate quality level but become ineffective during transport or storage. Other supply-chain challenges include generating reliable estimates of volumes needed and products available/used; minimizing corruption such as siphoning off products for resale; preventing shortages; and addressing stockouts. Prices can also increase substantially due to mark-ups at each stage. Some products may put a heavier burden on the health system; for example, if they are large in volume or require careful handling in transit or disposal. Missing health infrastructure can also pose problems, such as a lack of appropriate tools for diagnosis or treatment monitoring, or reliable electricity and a clean water supply.

Examples of addressing these challenges include: WHO's normative work, including the Model List of Essential Medicines and disease-specific guidelines, which help countries prioritize and select technologies. Coordination between product developers and WHO can ensure that WHO guideline committees review available evidence in a timely manner in anticipation of product launches to minimize any delays in uptake. Health technology assessment (HTA) is increasingly being adopted in developing countries to support governments in selecting the most appropriate tools for their contexts. National HTAs such as Thailand's Health Intervention and Technology Assessment Program's (HITAP) International Unit and the UK's NICE International programme also support the strengthening of HTA capacity elsewhere through international collaborations.

Some projects are also generating evidence on the full cost – or cost savings – of a technology when it is adopted within a health system. For example, the International Vector Control Consortium (IVCC) is generating evidence on the implementation costs and potential savings from newer pesticides and bednets for malaria prevention [38]. Such cost-effectiveness analyses are particularly important when the prices of new products are higher than older ones, thereby discouraging uptake, though they may offer cost savings elsewhere in the health system.

In addition, a number of organizations have developed specialized expertise in supply-chain and quality assurance training and institutional strengthening programmes. Technological innovation, such as vaccine vial monitors that indicate when a vaccine has been exposed to excessive heat, can also facilitate quality assurance. Civil society organizations have also worked to monitor and address medicines stockouts, as in Malawi [39]. Finally, broader investments in health system strengthening – from hiring adequate numbers of health workers to upgrading infrastructure of healthcare facilities, from strengthening logistics to strengthening governance – should yield benefits for technology uptake.

c Stage 6: Provider and population

Once a technology is nationally adopted and progresses through the supply chain to reach a health care facility (e.g. hospital, clinic, health post, pharmacy, drug seller), the health care provider-patient interface becomes critical. Key **actors** in this stage include health care providers (e.g. physicians, nurses, pharmacists, community health workers) and populations.

This is a vast field, much of it beyond the scope of this paper. Yet as the last link in the long chain between scientific knowledge and health impact, it is critical. For the sake of focus, we limit the discussion here to issues closely related to technology.⁵

Challenges at this stage include ensuring adequate provider capacity to use new technologies. Also important are the adaptability and acceptability of the product to the patient, as well as the patient's ability to use the product appropriately (e.g. adherence to treatment). Ensuring health technologies are adapted for use in specific subpopulations, such as children or pregnant women, is also a persistent challenge. For example, paediatric formulations are often developed after adult formulations or not at all due to limited market potential, the need to develop doses at different ages/weights, special risks and ethical challenges in paediatric clinical trials, among many other reasons [40]. Improving the speed and accuracy of diagnosis so that providers can respond more quickly to patient needs is also a challenge, especially if sensitive, specific diagnostics have not been developed or if diagnosis relies on centralized reference labs.

Examples of addressing these challenges include product developers prioritizing shorter, safer treatment regimens that facilitate patient adherence. For example, MMV developed tafenoquine as a single-dose treatment for P.vivax to prevent relapse, replacing a drug that needed to be taken for up to 14 days [41]. A critical tool that is increasingly used is the Target Product Profile (TPP), a document that early in the R&D process identifies key desirable product characteristics (discussed further below). Furthermore, many PDPs have recognized unmet needs and included paediatric product development projects in their portfolios. In 2007, WHO launched the first Model List of Essential Medicines for Children [42].

The importance of developing point-of-care (POC) diagnostics that can provide rapid results has also received significant attention. The FIND-Fujifilm TBLAM project is developing a POC diagnostic that may be able to detect TB infection in the urine within an hour, including in difficult-to-diagnose HIV-positive individuals [43]. Finally, research and training on how technologies can best be delivered – included within the broader categories of “operational research”, “implementation research” or “delivery science” – can contribute to addressing a number of the challenges identified here [44].

Multi-drug administration campaign, Tanzania school.
Photo: Natasha Scripture.



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5. Non-technology-related challenges at the provider-population interface include barriers in population access to health care from geographical or linguistic distance, inadequate patient trust in the provider and health system, long waiting times, user fees, cost of transportation or competing obligations to seeking health care (e.g. childcare or paid labor).

This paper has thus far examined one health technology or one stage at a time. However, it is also important to recognize interlinkages and interdependence between technologies and stages. In this section, we take a higher-level view of the “innovation-access-delivery (IAD)” ecosystem to identify needs, challenges and promising approaches and opportunities.

a **Insufficient consideration of interlinkages between stages**

As reflected in the meeting title, improving health requires an end-to-end approach that links innovation, access and delivery. However, in reality there are many different efforts and actors at each stage of the process, and interlinkages between them tend to be weak. For example, for neglected diseases, availability, and affordability of the end product needs to be considered at the discovery and clinical development stage (Stage 2 above), at which point researchers can take into consideration the feasibility of ultimately producing a product at low cost and potentially in small quantities. However, too often affordability is not apparent or taken into consideration until much later, during the manufacturing phase (Stage 4). Similarly, manufacturers willing and able to supply adequate volumes of quality-assured products are needed when a product is developed in Stage 2, but in the absence of traditional markets it is often unclear where the funding will come from to purchase products until Stage 4 or 5. Whether a product will be acceptable to patients and whether the health system can incorporate a new technology should ideally be considered from Stage 2, but problems may not be apparent until Stages 5 or 6 when a technology reaches the country or clinic level.

Examples of overcoming some of these challenges include the Meningitis A vaccine project, which identified a target price at which African countries in the meningitis belt could sustainably afford a vaccine (\$0.50/dose), and designed the R&D process to successfully meet that price target [45]. The development of Target Product Profiles (TPPs) has also frequently been used to incorporate health system and end-user needs at earlier stages of R&D. For example, the GHIT Fund requires TPPs early in the product development cycle [46]. The UNICEF-UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR) Global Health Observatory initiative is working to develop a centralized compendium where potential product developers can easily find TPPs. In terms of overall coordination, the PDP Funders Group and Heads of International Research Organizations (HIRO) are examples of bodies that regularly bring together major funders, though further information is needed on the extent to which they address the issues identified here [47].

Discussion question (a): What kinds of mechanisms would bring actors together to facilitate consideration of interlinkages between the stages and ensure more coordinated action?

b **Insufficient consideration of interlinkages between technologies**

Health technologies are often used jointly, such as drugs in combination therapy (e.g. for TB, Hepatitis, HIV) or diagnostics with treatments. But technologies are usually developed individually by different firms or organizations. Competition between firms or organizations can discourage the collaboration and knowledge-sharing that would accelerate scientific progress. These dynamics can lead to delays in achieving health impact. For example, the regulatory approval in 2012 and 2013 of two new TB drugs developed by the firms Johnson & Johnson (bedaquiline) and Otsuka (delamanid) was very welcome, offering the first new TB drugs with a novel mechanism of action in two generations. However, TB treatment requires at least three classes of antibiotics used in combination, and years of further studies were required to test whether they could be used together to develop optimized regimens with them [48].

Examples of overcoming these challenges include the licensing of patents through the Medicines Patent Pool to enable the development of fixed-dose combinations of products from different firms. Formal and informal collaborations between developers of diagnostics and treatments, such as FIND and drug-focused PDPs, also regularly take place and can facilitate the development of complementary technologies. Earlier-stage structured collaboration and sharing

of clinical data and patents between product developers has also been proposed for TB by the International Union Against TB and Lung Disease and others [49].

Discussion question (b): What kinds of funding, incentives, or collaborative mechanisms are needed to ensure that complementary health technologies are developed?

c Risk of misaligned incentives

A range of traditional and relatively new funding streams and incentives operate in the R&D system for malaria, TB and NTDs. In addition to the traditional pull offered by patent monopolies and markets, there is now increased availability of public and philanthropic grants for product development, the US FDA Priority Review Voucher (PRV), and loans that reduce risk. These push-and-pull mechanisms operate in a complex environment and may not always be fully aligned. They may even work at cross purposes. For example, patents and resulting monopolies may be an incentive to invest in R&D, but they also create barriers to follow-on innovation and can enable high pricing. PRVs have been sold for \$67.5 million-\$350 million [5] and can therefore increase investment in R&D for neglected diseases, but may encourage secrecy and inhibit collaboration (e.g. with PDPs). The current PRV also does not require worldwide novelty of a product, nor must awardees price at affordable levels or actually supply the products to meet demand. For example, supply and production of miltefosine (a drug developed in the 1990s that can treat visceral leishmaniasis (VL)) continues to be a major challenge; Knight Therapeutics received a PRV for the drug and sold it for \$125 million, but is not supplying it in VL-endemic countries [50]. For technologies that have a market in high- or middle-income countries, such as TB treatment, the existence of at least some market pull can incentivize private R&D investment but may simultaneously impede affordable pricing.

Examples of addressing these challenges include: the UNITAID Medicines Patent Pool's agreement with Viiv to charge tiered royalties on the HIV drug dolutegravir, which is made available as a generic in both LICs and MICs, but with higher royalties payable in a subset of MICs [51]. Tiered pricing can also improve affordability in some MICs, though tiering by itself is not a guarantee of affordability [52]. For example, the Pan American Health Organization Revolving Fund negotiates vaccine prices on behalf of participating Member States in the region. Prices are generally higher than those paid by Gavi for the poorest countries, but are also lower than those paid in other middle-income countries; PAHO-negotiated prices for the pneumococcal vaccine (PCV) has facilitated uptake in the region [53]. A second example is the use of PRV to increase access to Chagas treatment: the private company Chemo Group had jointly developed benznidazole for Chagas disease with DNDi and the NGO Mundo Sano; when Chemo received a PRV for registering the drug in the US, it agreed to share proceeds with the two non-profit groups to support patient access to treatment and make the drug affordable and available [54].

Discussion question (c): How can greater alignment between various push-and-pull incentives and funding strategies be ensured?

d Balancing private and public interests

Most initiatives for innovation and access involve public or philanthropic actors working with commercial partners (in contrast, delivery tends to involve primarily public and non-profit actors). Such public-private collaborations can bring complementary capacities and new resources to efforts to discover, develop and produce health technologies. But they also raise challenges, such as whether the distribution of risk and reward is appropriate for the contributions each partner has made. Also, the opportunity cost for the commercial partner in pursuing projects without significant market returns may be high, even when direct costs are subsidized or fully covered by outside funders. Such opportunity costs can not only discourage some commercial partners from engaging at all, they can also raise the risk that launched projects will not be completed.

In addition, for technologies that can be used in both profitable high-income and less profitable lower-income markets, questions arise regarding which customers should take priority when supply is limited, or what prices are acceptable when public funds have subsidized R&D. Such concerns with dual use products can also manifest earlier in the product cycle, where risks associated with clinical testing of a new product for an NTD may not be viewed as worthwhile, since it could introduce regulatory delays to approval of a product for an indication that could generate significant returns in developed country markets.

Examples of addressing these challenges include research funders and PDPs including provisions in agreements with firms that provide a number of safeguards, such as rights to transfer a technology to another organization if development does not proceed in a timely manner, affordability provisions, IP licensing in some LMICs, data-sharing requirements, among others [55]. Data is insufficient on how well these provisions have worked, however, and concerns have arisen regarding the feasibility of enforcing these contracts. For vaccines, Gavi's long-term purchase commitments, including the Advanced Market Commitment for PCV, is intended to ensure adequate private investment in production capacity to avert shortages.

Discussion question (d): What strategies have been successful in appropriately balancing public health objectives and commercial interests in the areas of malaria, TB and NTDs?

e **Ensuring sustainable funding**

The majority of R&D for malaria, TB and NTDs is funded by public and philanthropic sources based in high-income countries, with a significant minority from firms and disease-endemic countries [4]. In the absence of self-sustaining commercial markets, and with DAH having reached a plateau, it is unclear how to increase total investments to meet the estimated \$6 billion per year that is needed (double the current levels). Neglected disease R&D relies heavily on US government sources, which accounted for 47 percent of all funding and 73 percent of public sector funding [4]. PDPs operate on a very unstable financial foundation with heavy reliance on the BMGF as the single largest funder of these initiatives, accounting for 54 percent of PDP funding in 2016 [4]. While the US FDA PRV offers an interesting possible revenue source, it also raises a number of other difficult issues (see above). In addition, because it is only available after a product is successfully developed, it cannot replace more reliable, sustained funding.

There have also been increasing calls for MICs to finance more global health R&D [56]. Total levels are growing, but slowly, and they remain a small fraction of HICs spending [4]. The WHO Consultative Expert Working Group on R&D: Financing and Coordination (CEWG) called for binding international obligations for R&D investment in 2012, but there was inadequate support among Member States to take this forward [56]. For health technology delivery, domestic resources and DAH play a significant role in LICs (~30 percent of total health spending), while DAH plays a shrinking role in lower-middle and upper-middle income countries (~3 percent and 0.3 percent of total health spending, respectively [57]). In MICs, funding for delivery will increasingly need to draw from domestic resources, but these are under heavy strain from rising health care costs and competing health priorities.

Examples of addressing these challenges include multi-year commitments from funders to provide some stability to long-term R&D via PDPs, and for delivery through Gavi and the Global Fund. UNITAID's funding model, based primarily on an air ticket levy charged in high-, middle- and low-income countries, was also intended to make funding more sustainable and predictable. Where significant donor funds have been mobilized (e.g. for HIV, TB, malaria and childhood vaccines), global markets for health technology innovation and manufacturing have been created. Another model is cost-sharing between public and private partners. For example, the Pediatric Praziquantel Consortium to develop a paediatric formulation of this drug for schistosomiasis is supported by Merck KgAa, BMGF, GHIT and EDCTP. Finally, while data is relatively scarce, the trends regarding MICs funding

for R&D are encouraging: in 2016, R&D investments in neglected diseases by the governments of Brazil, India and South Africa reached a record high of \$78 million [4]. The G20 countries may become an increasingly significant source of R&D investment from the MICs in the future.

Discussion question (e): How can total funding for innovation, access and delivery be increased to reach adequate levels, and/or be made more sustainable and reliable?

f Facilitating coordination and priority-setting

Global R&D efforts in the neglected diseases have increased considerably over the past two decades. This brings new actors to the table but also increases the need for coordination to accelerate scientific progress and achieve the most with a tight resource envelope. Indeed, given limited financial and human resources, priorities for R&D and access investments are also necessary. These points were highlighted by the CEWG report [56], the UN Secretary-General's High-Level Panel on Access to Medicines [58], and a number of other analyses and expert bodies. However, challenging questions arise regarding who should set priorities, on what basis, and at what level of specificity (e.g. by pathogen/disease or technology, short list or long list). Research funders are autonomous, and funding decisions are not always coordinated or aligned.

Examples of coordination among funders include the PDP Funders Group and HIRO (both mentioned above). Examples of efforts to set priorities include WHO's list of priority pathogens for antimicrobial resistance and pathogens of pandemic potential [59] and, at a more granular level, development of target product profiles for some of these pathogens [60]. At a regional level, priorities for R&D were identified in the 2013 report (updated from 2004), "Priority Medicines for Europe and the World" published by WHO and funded by the European Union [61]. While these are important contributions to priority-setting, it is more difficult to assess the extent to which developers have responded to these priorities. More granular priority-setting, at the level of technologies, formulations or subpopulations, may still be needed.

Discussion question (f): How can priority-setting be done in a legitimate manner, and help to coordinate autonomous research funders, countries and other actors?

g Monitoring the overall innovation-access-delivery ecosystem

Successfully addressing malaria, TB and the NTDs requires hundreds of actors to work collectively towards innovation, access and delivery of health technologies. Decision-making happens across many years, countries, organizations, public and private sectors, and on local, national and global scales. The complexity of the system makes it difficult to understand, let alone strengthen. For example, it is difficult to find and interpret basic information regarding which actors are conducting what kind of R&D, which projects donors are funding, which technologies are or are not reaching which people, and what health impacts might result. Understanding how well the "innovation-access-delivery" ecosystem is functioning requires regularly updated information and analysis, but these are costly to generate.

Examples of addressing these challenges include the G-FINDER project [62], funded by the BMGF, which has annually tracked and analysed investments into neglected disease R&D over the past decade, and has begun expanding into other areas such as emerging infectious disease. In-depth tracking of R&D in disease-specific areas is also carried out, such as the Treatment Action Group's annual report on TB [63]. The WHO Global Observatory on R&D was launched upon a request from the 2013 World Health Assembly, and combines data from multiple sources to paint a picture of global innovation activities, including publications, product pipelines and investments [64].

Discussion question (g): What further information and analysis is needed to better monitor, understand and improve the functioning of the "innovation-access-delivery" ecosystem?

This paper has sought to provide a high-level overview of the challenges and potential opportunities to ensure more effective innovation, access and delivery of health technologies, in order to give meeting participants a common starting point for discussions. The chain of events from understanding a pathogen to reducing its negative health impact is long, complex and rife with pitfalls. Obstacles exist for each disease, at each stage, in each country. At the macro level, barriers to a better-functioning innovation ecosystem also persist. Nevertheless, for nearly every challenge, examples of initiatives to address the problem have been identified. Some of them have demonstrated success. While much remains undone to address the terrible toll from these diseases, there is also a rich foundation of experience from which to draw inspiration for further progress.

A broad variety of actors and stakeholders share ambition and commitment to addressing the burden of malaria, TB and the NTDs as a critical contribution to improving health equity, achieving universal health coverage and the broader SDGs of the 2030 Agenda. Yet they work at different points in the long continuum from research to access and delivery, and are often separated by time, geographic and social distance, and organizational and funding silos. Because decisions by actors in one niche of this complex ecosystem can impact actors in another, ensuring that the ecosystem at large is effective in achieving its shared goal requires intensified global dialogue.

Such a global dialogue can facilitate the achievement of at least five objectives.

- 1. Learning:** A global dialogue can provide an opportunity for actors to learn from each other's successes in addressing shared challenges, and accelerate the identification of effective practices and the articulation of shared principles.
- 2. Coordinated action:** A number of issues identified here would benefit from coordinated action. For example, better alignment of incentives and funding policies by major research funders would ensure that actors are not working at cross-purposes when trying to stimulate R&D in areas of low market returns. Coordination between product developers and end-users can ensure that products are well-adapted for use at country level and acceptable to patients. Similarly, coordination across stages between earlier-stage product developers and later-stage procurement agencies can facilitate the uptake of new technologies.
- 3. Collective action:** Similarly, a number of issues would benefit from more collective action. For example, joint adoption of certain policies, such as open-access publication or data-sharing, could accelerate the implementation of progressive policies. At the same time, joint action by major funders can improve efficiency and reduce the need for grantees to comply with a web of different policies. Harmonization of national regulatory requirements can accelerate access and decrease costs to developers. Agreeing upon priority areas for research – whether for basic research, product development, or implementation/delivery research – could reduce the risk of duplication, facilitate tracking progress and help to ensure major gaps do not go unfilled. Finally, joint endorsement of a set of principles could help to align actors and solidify widely held norms.
- 4. Identify issues requiring further dialogue and/or analysis:** Global dialogue can also identify issues that may not yet be ripe for coordinated or collective action, but where further attention, dialogue or analysis is needed. It can also help to set the agenda and identify important participants for future disease-specific or health technology-specific convenings and dialogues.
- 5. Community and network-building:** The global system of actors engaged in innovation, access and delivery of health technologies may function better if its constituent parts are connected through stronger networks and communities. A global dialogue provides the opportunity for organically strengthening relationships and establishing new ones, and for strengthening the trust required to collaborate and achieve outcomes.

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