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Strategies towards ending the burden of neglected infectious diseases

- Assessing the success of the Product Development Partnership model and its approaches

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Declaration of own work

I, Kei Katsuno, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: Kei Katsuno Date: September 30, 2024

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Abstract

Delivering the right treatments for infectious diseases to those who need them most remains a challenge. Further, new tools are needed to sustain and expand treatment and control efforts. In this context, a product development partnership (PDP) is a non-profit organizational structure that enables the public, private, academic, and philanthropic sectors to aggregate funding to develop, test, and bring to licensure new health technologies for diseases of the developing world whose solutions lack commercial market potential. Yet, as of now, relatively few novel products have successfully crossed the finish line to reach health practitioners and patients. Therefore, it is critical to assess both the strengths and weakness of PDPs to understand what we need as a global health community, and how these organizations could further accelerate R&D for infectious diseases.

This research aimed to analyse the effectiveness of PDPs in advancing R&D for infectious diseases using a mixed methods approach that integrates both qualitative and quantitative methods. The study involved semi-structured interviews with key stakeholders, including PDP representatives, funders, and policymakers, alongside a quantitative analysis of PDP performance metrics to assess trends and critical success factors.

The results underscore PDPs' potential to enhance collaboration across sectors and facilitate resource mobilization for neglected diseases. However, the research also highlights key challenges, including sustainable funding, insufficient incentives for private-sector engagement, and limited coordination among stakeholders. Based on the findings, the study presents six policy recommendations: (1) sustainable/incremental funding for PDPs, (2) foster collaboration and partnership, (3) develop incentives for PDPs, (4) ensure quality control and quality assurance, (5) support sustainable business models, and (6) prioritize capacity building through strong and equal partnerships, particularly in low- and middle-income countries.

These recommendations offer actionable insights for PDPs, policymakers, funders, and global health stakeholders, providing a pathway for more effective global health R&D and the accelerated development of essential health solutions for neglected diseases.

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List of acronyms and abbreviations

AMC	Advanced Market Commitment
AMR	Anti-microbial resistance
BMBF	German Ministry of Education and Research
BMGF	Bill and Melinda Gates Foundation
BMS	Bristol-Myers Squibb
CEPI	Coalition for Epidemic Preparedness Innovations
CHF	Swiss Franc
CL	Cutaneous leishmaniasis
CRO	Contract Research Organization
DCL	Diffuse cutaneous leishmaniasis
DNDi	Drugs for Neglected Diseases initiative
EDCTP	European & Developing Countries Clinical Trials Partnership
EMA	European Medicines Agency
EUR	Euro
EVI	European Vaccine Initiative
FIND	Foundation for Innovative New Diagnostics
FT	Financial Times
GAVI	Global Alliance for Vaccines and Immunization
GHIF	Global Health Investment Fund
GHIT	Global Health Innovative Technology Fund
GHPD	Global Health Product Development
GMRI	Gates Medical Research Institute
GNF	Genomics Institute of the Novartis Research Foundation
HAT	Human African Trypanosomiasis
HICs	High-income countries
IAVI	International AIDS Vaccine Initiative
IPM	International Partnership for Microbicides
IVCC	Innovative Vector Control Consortium
IVI	International Vaccine Institute
JPMA	Japan Pharmaceutical Manufacturers Association
JPY	Japanese Yen
LEAP	Leishmaniasis East Africa Platform
LMICs	Low- and middle-income countries
MCL	Mucocutaneous leishmaniasis
MDGH	Medicines Development for Global Health
MDR-TB	Multidrug-resistant tuberculosis
MMV	Medicines for Malaria Venture
MSF	Médecins Sans Frontières (Doctors Without Borders)
NCE	New Chemical Entity
NIH	National Institute of Health
NITD	Novartis Institute for Tropical Diseases
NL-DGIS	Netherlands Directorate-General for International Cooperation
NRDD	Nature Reviews Drug Discovery
NTDs	Neglected Tropical Diseases

ODL	Orphan Drug Legislation
OECD	Organisation for Economic Co-operation and Development
PDPs	Product Development Partnerships
PEPFAR	President's Emergency Plan for AIDS Relief
PKDL	Post-kala-azar dermal leishmaniasis
PQ	Prequalification
PRI	Programme related investment
PRV	Priority Review Voucher
QA	Quality assurance
QC	Quality control
R&D	Research and Development
SRA	Stringent regulatory authority
TBDA	TB Drug Accelerator
UK-DFID	United Kingdom Department for International Development
UK-FCDO	UK Foreign, Commonwealth & Development Office
USD	United States Dollar
VL	Visceral leishmaniasis
WHO	World Health Organization
WT	Wellcome Trust
XDR-TB	Extensively drug resistant tuberculosis

1. Chapter 1 Introduction

1.1 Introduction - Global Health R&D to Combat Infectious Diseases

Infectious diseases are a persistent threat to global economic growth, health, security, and human development in many of the low- and middle-income countries. Each year, infectious diseases such as TB, malaria, and neglected tropical diseases (NTDs) kill almost nine million people, many of them children under the age of five. They also cause enormous burdens of life-long disability that disproportionately impact those who are poor[1]. Stepping up research and investments into Global Health Product Development (GHPD) that can effectively treat infectious diseases could have an enormous impact on fulfilling global commitments to lift people out of poverty and and improve economic outlook for future generations.

Considerable progress has been made in controlling certain infectious diseases in many nations. However, progress has stalled in many areas. Delivering the right treatments to those that need them most remains a challenge. Further, new tools are needed to eliminate these diseases. Many infectious diseases are still under-researched and poorly understood, and the innovations to address them are of limited commercial interest. This thesis focuses on one mechanism through which research and development of new vaccines, diagnostics, and medicines is carried out to combat infectious disease.

Neglected tropical diseases (NTDs): A diverse group of infectious diseases that are prevalent in tropical and subtropical conditions throughout the world – affect more than one billion people and cost developing economies billions of dollars every year. The list of NTDs defined by the WHO, a mixture of viral, bacterial, fungal and parasitic diseases are as follows: Buruli ulcer, Chagas disease, Dengue and Chikungunya, Dracunculiasis (guinea-worm disease), Echinococcosis, Foodborne trematodiases, 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 helminthiases, Snakebite envenoming, Taeniasis/Cysticercosis, Trachoma, Yaws (Endemic treponematoses).[2]

1.2 An Innovation Gap – and the roles of Product Development Partnerships (PDPs)

Despite the widespread need for new vaccines, diagnostics, and medicines for infectious diseases, innovator companies and manufacturers see few incentives to invest in developing and producing such products. Most existing diagnostics cannot be properly used in low- and middle-income countries. Moreover, available medicines for infectious disease have safety and efficacy limitations. Other than HIV/AIDS medicines and dengue vaccines, most of the required tools for infectious diseases could not yield enough of a market return to make them an appealing investment[3].

The need for innovation in GHPD efforts goes beyond just expediting the development of new drugs. We need to be improving upon the products already on the market. Many of the available treatments for infectious diseases were developed decades ago and their effectiveness is diminishing due to anti-microbial resistance (AMR)[4]. This is not a hypothetical threat. From the 1970s through the 1990s, malaria deaths in Africa, and globally in children under the age of five, rose sharply due to resistance to the affordable drug chloroquine[5]. The compounding effect of increasing AMR and a slowdown of new antibiotics discovery has created new challenges for treating infectious diseases.

To counter the lack of a commercial incentive, governments and foundations are increasingly

partnering with industry to convert important scientific research into needed products. Clearly, innovations are vital to overcome the global burden of infectious diseases that primarily affect the poor.

In the realm of GHPD, a pivotal role is played by Product Development Partnerships (PDPs). These entities, numbering over 16, are independent non-governmental organizations with a specific focus on managing extensive portfolios of products designed to combat a range of diseases and health interventions.[6] Their key function lies in their role as intermediaries or catalysts. PDPs adeptly aggregate and consolidate funding, chiefly from national governments and philanthropic sources, after which they establish partnerships with academic researchers and private sector entities.

PDPs offer several distinct advantages, notably their capacity to comprehend and operate across the entire spectrum of pharmaceutical discovery, development, and delivery. They are characterized by their agility, capable of promptly addressing gaps and forming partnerships with minimal bureaucratic constraints. Furthermore, they exhibit a unique ability to access funding from multiple sources, enhancing their financial sustainability.

The areas of focus for most PDPs typically revolve around single diseases or specific groups of diseases. PDPs channel the financial support they receive from governments and foundations into a diverse array of projects situated at various stages of development. Operating under a nonprofit status, PDPs facilitate the pooling of funds from donors for meticulously selected projects, often in collaboration with industry stakeholders. This approach results in the creation of comprehensive pipelines encompassing both current and next-generation products. The underlying rationale is that such a model enables investments and research to yield more substantial impacts compared to individual projects funded by single donors.

In practice, most PDPs predominantly engage in project management and allocate R&D funding through partnerships, including pharmaceutical companies and academic research institutions. These organizations heavily rely on donor contributions and grant funding to sustain their operations.

While several reports have been published offering methodologies for evaluating individual PDPs[7,8], the development of standardized metrics for assessing success or cost-effectiveness across all PDPs remains relatively underdeveloped and inadequately documented. Variations in scope, methodologies, and donor-specific reporting requirements among different PDPs have led to the argument that devising a universal set of metrics applicable to all may not be practical. However, the existence of lingering ambiguity concerning the inner workings and success of PDPs in delivering promised goods persists among external observers and donors alike. Misunderstandings often center on portfolio management strategies and the unique scientific complexities associated with innovation for neglected diseases.

These examinations suggest that while there are identifiable factors crucial to evaluating the efficiency and effectiveness of PDPs, substantial challenges remain. These include complexities in assessing long-term outcomes and uncertainties surrounding determining the true measure of health impact. Consequently, a comprehensive study is warranted to shed light on the assessment of PDPs and its practical applicability within the contemporary landscape of global health R&D.

1.3 Study aim and design

Study aim:

The aim of this study was to analyze how to measure the success of PDP models in a

comprehensive manner in order to inform strategies for various stakeholders to accelerate product development efforts and overcome the global burden of infectious diseases.

Several reports have documented methods for assessing individual PDPs; however, common metrics to measure success or cost-effectiveness across all PDPs are not well developed or documented. This study aimed to address this gap by analyzing potential ways to measure success criteria of PDPs, and implications of such criteria for actual usage by stakeholders in policy-making/strategic guidelines. The study involved both qualitative and quantitative methods, and combined a detailed description of current bottlenecks and potential ways to measure the success of PDPs with an in-depth analysis of methods, tools, and metrics (both existing and new).

Study design:

Success criteria for and the validity of PDPs were investigated with a mixed methods approach by conducting both qualitative and quantitative analyses[9]. The mixed methods approach was used to integrate key aspects of both analyses and allow for the development of actionable policy recommendations based on the combined results. Specifically, in-depth interviews were conducted to collect input from various stakeholders on the key research question, and quantitative analysis was also conducted sequentially to address and further bolster findings from the qualitative analysis of interview contents. The two phases (qualitative and quantitative) were conducted sequentially so there was an overlap between them. Qualitative and quantitative analyses therefore enhanced each other via an iterative process and culminated in an actionable policy recommendation. As such, this study consisted of the following objectives:

Objective 1 "Qualitative Analysis" – Examine current bottlenecks and potential ways to measure success criteria of PDPs by conducting in-depth interviews with relevant stakeholders.

This objective helped explore and identify considerations to be further investigated in the quantitative analysis (Objective 2). Qualitative data were also used to triangulate with quantitative data gained from Objective 2 to provide an in-depth understanding of metrics as well as their practical feasibility.

Objective 2 "Quantitative Analysis" – Examine relevant data and information pertaining to metrics and considerations identified from Objective 1. Objectives 1 and 2 took place sequentially to triangulate with and enhance the results of each other.

Objective 3 "Additional interviews as part of Mixed Methods Approach" – Examine further key questions and considerations that were identified through an iterative process of both qualitative and quantitative analyses (Objectives 1 and 2) to investigate the PDPs business model and its validity.

Objective 4 "Policy Synthesis" – Combine results obtained from the mixed methods approach in Objectives 1, 2 and 3, and develop policy recommendations for various stakeholders such as decision-makers and funders to help them develop strategies for PDP-related work.

1.4 Significance of study

Several reports have previously assessed the operations of PDPs. However, to gain a comprehensive understanding of the viability of the PDP business model, it is imperative to employ an inclusive approach. This entails conducting both qualitative and quantitative analyses using a Mixed Methods Approach. This study endeavors to deliver an exhaustive comprehension of the PDP mechanism, spotlighting its advantages and persisting challenges from the inception of these entities. Importantly, this study harnesses insights from multiple stakeholders intricately linked to PDP activities through a semi-structured interview process,

bolstered by pertinent quantitative data and information. This holistic approach holds the potential to furnish invaluable insights for various stakeholders and policymakers, facilitating the formulation of pragmatic strategies in the domain of global health R&D. Noteworthy beneficiaries encompass PDPs themselves, national governments, private sector enterprises, academic institutions, funders, and international organizations.

In summary, this study's outcomes are poised to enhance the existing knowledge base by forging actionable strategies for pertinent entities, including PDPs, funding bodies invested in PDPs, and other global agencies. Furthermore, it seeks to elucidate success criteria and pivotal considerations that possess applicability across the spectrum of PDPs, transcending individual instances.

1.5 Scope of the study

This study adhered to a well-structured sequential and explanatory mixed methods approach, conducting both qualitative and quantitative analyses concurrently in an iterative fashion. This methodological strategy facilitated a process where data and findings from the qualitative and quantitative arms of the study converged synergistically, elevating the overall analytical depth.

As elucidated earlier, extant literature comprises several publications that have analyzed the operations of specific PDPs and have explored potential determinants of their successes and, on occasion, failures. Nonetheless, these examinations have often been confined to individual PDPs, with a limited cross-PDP perspective. The pre-existing findings from these publications, along with the established frameworks, played a pivotal role in shaping the foundation of this study.

In its initial stages, this study reviewed the prevailing literature, identifying metrics that have

already gained recognition within the relevant communities and those that remain unexplored. Subsequently, the study embarked on a twofold mission: firstly, to delve into the existing discourse surrounding these acknowledged metrics and, secondly, to shed light on the validity of both established and novel metrics.

For instance, the development of interview questions pertaining to Objective 1 was carefully orchestrated. Questions were structured to align with pre-existing metrics, with the primary objective of soliciting stakeholders' invaluable insights on these established metrics. Simultaneously, an open-ended approach was adopted to encourage the exploration of novel metrics and points of discussion.

Throughout the qualitative and quantitative analyses conducted within this study, a continuous dialogue was maintained with the available literature. This iterative process included constant data analysis and literature reviews, bolstering the qualitative and quantitative analytical outcomes.

In essence, the mixed methods approach embraced within this study serves as a comprehensive and dynamic framework, integrating well-established metrics with innovative perspectives, thereby fortifying the research's rigor and capacity to unveil a nuanced understanding of the multifaceted aspects of PDPs.

1.6 Outline of the study

This study consists of eight chapters. The following provides an overview of the chapters' content.

Chapter	Overview of chapter content
Chapter 1	Overview of the study

Introduction	
Chapter 2 Literature Review	Section 2.1 provided an overview of key actors in global health R&D and its ecosystem. Section 2.2 identified the historical funding trends for these actors. 2.3 focused on PDPs and provided the overview of PDP mechanism, and existing framework/approaches to gauge the efficacy and impact of PDPs.
Chapter 3 Methods	Provided details regarding the process of conducting semi-structured interviews with multiple stakeholders, quantitative analyses with a mixed methods approach, and of the additional interviews conducted with experts to amplify the content of the preceding study process.
Chapter 4 Results	Presented the results of semi-structure interviews regarding the validity of PDPs mechanism (To address Objective 1)
Chapter 5 Results	Presented the results of quantitative analyses conducted concurrently with the semi-structured interviews as a Mixed-Methods Approach (To address Objective 2)
Chapter 6 Results	Presented the results of additional interviews conducted after the first batch interviews along with associated quantitative analyses were conducted (To address Objective 3)
Chapter 7 Discussion	Provided key considerations regarding the PDPs model, its pros and cons, and other important aspects based on the iterative process of Mixed Methods Approach, and presented actionable/tangible recommendations to relevant stakeholders in global health R&D (To revisit Objectives 1-3, and to address Objective 4)
Chapter 8 Conclusion	Summary of key points from the study

1.7 Conclusion

This chapter provided an overview of this study that intended to investigate the mechanism of PDPs in the space of global health R&D. The aim and objectives were delineated after providing a description of the significance and scope of the study. To enhance clarity, a summary table of the overall outline of the study (for each chapter, respectively) was also presented, which paved the way for a more detailed exploration of research activities, as elucidated commencing from Chapter 2.

2. Chapter 2 Literature Review

The literature review was conducted as a scoping review with the objective of identifying and analyzing knowledge gaps in the field of PDPs and global health R&D for neglected diseases. A scoping review was chosen due to its appropriateness for mapping broad and complex areas of

research where many types of studies and evidence are available. The review aimed to capture key studies, reports, and other relevant information across various sources, allowing for a comprehensive understanding of the landscape while identifying gaps in the existing knowledge.

For the identification of literature, PubMed was used as a primary database for academic peer-reviewed articles. Search terms included a combination of keywords such as "Product Development Partnerships," "neglected diseases," "global health R&D," "funding," and "collaboration." Additionally, grey literature were also included from annual reports and websites of relevant organizations, including PDPs, international health organizations, and philanthropic organizations. These sources were particularly important to capture recent developments that may not be available in traditional databases but are highly relevant for understanding the PDP landscape.

2.1. Overview: Global Health R&D Ecosystem – *Who are the actors?*

As recently as the late 1990s, the R&D ecosystem dedicated to new products for diseases that disproportionately impact the poorest was limited to publicly funded government and academic research, a limited numbers of low priority pharmaceutical company programmes, and a few poorly (or only opportunistically) funded, isolated non-profits and multilateral organizations like the Special Programme for Research and Training in Tropical Diseases or TDR at WHO and PATH (a Seattle-based non-profit global health organization).

Fuelled by 20 years of growing and significant amounts of R&D funding,[10] the number and the diversity of types of organizations participating and working together in the R&D ecosystem has grown. Non-profits and select for-profit businesses (e.g. contract research organizations, consulting firms) have thrived.

One way to organize the actors and their interactions in the ecosystem is according to how they contribute to R&D along the value chain.[11] (Figure 1) While there are important differences in the product development process between diagnostics, drugs, and vaccines, they follow a similar pathway from basic research, to translational research and pre-clinical testing, clinical development, registration, to product introduction, scale up, and post-introduction surveillance.

Within each phase, there are organizations that primarily do or facilitate the R&D, and others that fund it. This separation between those who *do* and those who *fund* is an important distinguishing feature of global health when compared with the traditional pharmaceutical R&D process. In a highly simplified version of the traditional process, early stage basic research is primarily funded and conducted by public and academic researchers, while for-profit biotech and pharmaceutical companies and their investors pay for and do most of the rest, although it is not the case for NTDs due to the lack of profitability.[12]

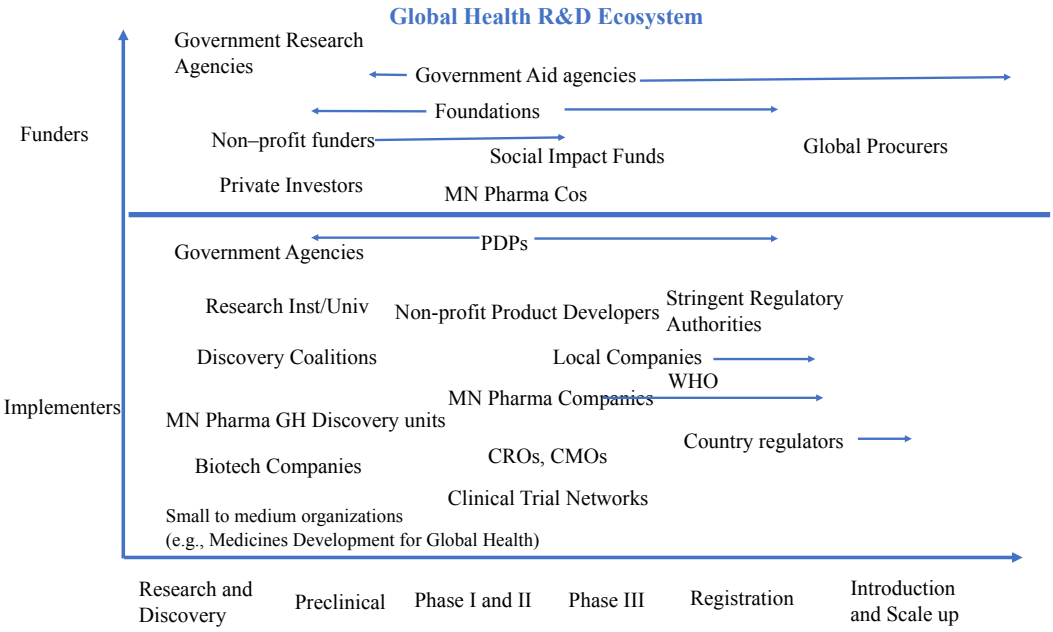


Figure 1: Global Health R&D Ecosystem

2.1.1. Basic Research and Discovery

Government research agencies, such as the US NIH, NIAID, and BARDA, are the primary funders and the implementers (e.g. Walter Reed Army Institute of Research), along with academic researchers in the case of the United States. Philanthropic organizations, such as the Wellcome Trust in the UK and the Bill & Melinda Gates Foundation in the U.S., and non-profit funders like GHIT (The Global Health Innovative Technology Fund, Japan)[13] and CEPI (Coalition for Epidemic Preparedness Innovations, Norway)[14], have also put resources into global health-specific discovery.[15]

To foster and accelerate innovation in disease areas that have historically been neglected, the Gates Foundation, Wellcome Trust and others have invested in coalitions of public and private organizations, such as the Collaboration for AIDS Vaccine Discovery,[16] the TB Drug Accelerator, and the Grand Challenges and Grand Challenge Explorations.[17] These funders have also invested in dedicated global heath discovery capacity in organizations such as the Broad Institute, Scripps, and Calibr.[18]

Many of the Product Development Partnerships (PDPs—the group of non-profit global health product development organizations established in response to the persistent gap between the need for new innovation for diseases that disproportionately impact the poorest in low- and middle-income countries; will be further discussed at the following sections), including IAVI (International AIDS Vaccine Initiative), MMV (Medicines for Malaria Venture), TB Alliance (Global Alliance for TB Drug Development), IVI (International Vaccine Institute), and PATH, have also built and managed discovery programs with funding from the Gates Foundation, GHIT, Wellcome Trust, and government donors. IAVI, unlike the other PDPs, has used donor funds to build state of the art research centres.[19] IVI in Korea has also done most of its own discovery work rather than use their funds to facilitate others.[20]

As for the private sector, a few pharmaceutical companies, namely GSK in Tres Cantos Spain[21] and Novartis in Singapore (until 2017) and Sienna, Italy, have created dedicated global health discovery teams/units that work in partnership with academic researchers and the PDPs. The companies contribute some financial resources, but the sustainability of the programmes depends upon their ability to raise external, philanthropic, or public funds.[22] GSK, for example, has supported a mini-portfolio at MMV to look for new leads that is co-sponsored with MMV resources.[23] Other pharmaceutical companies have made in-kind contributions, screening their compounds or making those compounds available to others to screen, and by supporting hit-to lead efforts and partnering with academic researchers that have PDP support to explore one of the companies' compounds. Eight companies screen compounds as members of the TB Drug Accelerator (TBDA) for example.[24] Additionally, through the GHIT Fund's Screening Platform, a number of Japanese companies have all received funding to support screening and hit-to lead programs in partnership with one or more PDP.[25]

There is still limited seed or early-stage venture capital investment in global health early research. Over the past 10 years, the Gates Foundation has made programme related investments (PRIs) through balance sheet funds, investing alongside traditional venture investors in early-stage biotech companies to secure access to their platforms for global health indications. Anacor and Atreca are two examples.[26]

2.1.2. Translational research

The lines between discovery, translational, and pre-clinical research are blurry, especially as products often go back for additional discovery research if they run into challenges in translational research. PDPs, in partnership with academics and pharmaceutical and biotech companies, have, at least until very recently, conducted most of the translational work with funding from Gates Foundation, Wellcome Trust, and government aid funders like USAID and

UK AID—agencies that traditionally only funded health systems and product procurement. Credit goes to the PDPs and Gates Foundation for successful advocacy efforts that have brought in hundreds of millions of aid dollars into global health R&D. In cases where a product does not have a lead company partner, PDPs have also contracted with university research centers like RTI and for-profit CROs to advance the translational and pre-clinical work.[27] National governments (e.g., India and Brazil) have also added to translational research through setting up their own institutes.

In 2018, the Gates Foundation disrupted the translation research space with the establishment of their own dedicated translational research subsidiary.[28] With the mission to bring the best of translational research methods and technologies to global health, the Gates Medical Research Institute (GMRI) has picked up portfolios (and their associated resources) from PDPs, such as TB Alliance and PATH's Center for Vaccine Innovation and Access. While its original scope was advertised as up to proof of concept, they recently licensed in a Phase III TB vaccine candidate from GSK, leaving open the possibility for additional programmes (and funding) diverted to the GMRI as they advance through the clinic.[29]

2.1.3. Clinical Development

Many of the same partners lead and fund the early clinical trials work as the translational research work. Government research agencies, such as the NIH, MRC in the UK, and an EU supported initiative called EDCTP (European & Developing Countries Clinical Trials Partnership),[30] have made significant investments into the in-country clinical trial infrastructure, networks and trials. PEPFAR in the U.S. has also supported HIV prevention trials (some of IPM's microbicide ring studies). Non-profits also play an important role, alongside CROs, managing the clinical trials in country. Larger PDPs, like PATH, have some capacity in the countries. Others rely on local government, WHO, and NGO partners.[31]

Within the companies, products that advance to clinical development tend to move from the discovery to the development team. As commercial and revenue criteria factor higher into investment decisions in the development business, the hurdle to invest in global health work also gets higher.

J&J has a dedicated Global Health unit with a protected, albeit limited, budget to conduct development work. J&J is also one of the few companies that has advanced its own global health drug candidate, for TB in this case, through to licensure without a non-profit partner.[32] Other companies like GSK (malaria drugs, TB drugs, malaria vaccines), Sanofi (malaria drugs, human African trypanosomiasis (HAT) drugs), Novartis (malaria drugs, leishmaniasis drugs, Chagas drugs), and Eisai (Chagas drugs) have stuck with the products as they advance within PDP portfolios. Another group of companies has transferred the technology to the PDP (J&J's antiviral to IPM for their microbicide ring). In the cases where a PDP product does not have a commercial partner – this includes products that never had one in the discovery phase – the PDP will oversee the clinical work and continue to look for a partner. In many cases, the PDP has brought in a non-Multinational Corporation (MNC) partner, often a local manufacturer. This list includes the Serum Institute of India (PATH's Meningitis vaccine Project), Bharat Biotech (PATH rotavirus program), Shing Poong (MMV), Shantha (IVI Cholera vaccine), and Mundo Sano (DNDi Chagas drug).[33]

In addition to moving products through the GMRI, the Gates Foundation has also made a few of bilateral company deals, funding the companies to lead the pre-clinical and clinical work (Pfizer and Group B strep vaccine, Novovax and RSV vaccine).[34, 35]

A new policy incentive, the Priority Review Voucher (PRV), introduced into law in the U.S. in

2008, has also helped pull forward a few global health products through development. Under the PRV program, in exchange for securing FDA regulatory approval for a new chemical entity, an organization (a company or a non-profit) is granted a PRV that it can apply to one of their products or sell to another company.[36] As the name suggests, a priority review speeds up the review process and can help a company gain market advantage by getting a product onto the market ahead of a competitor. As of now, 11 PRVs have been granted for NTD products (and many more for a separate PRV program for rare pediatric drugs). The average selling price is about $100m. While not enough to cover the costs of drug discovery through development, in combination with PDP or other grant support, the prospect of winning a PRV has helped motivate a number of the companies mentioned above to remain as the commercialization partner through development (GSK/malaria drug, Sanofi/HAT drug).[36]

The PRV has also helped bring in some venture capital investment to global health R&D. Most notably, the Global Health Investment Fund, established with investments from Gates, JP Morgan, Pfizer, and others,[37] used returns from the sale of a PRV to return capital to its investors. The PRV in this case was earned by a small non-profit Australian biotechnology company called the Medicines Development for Global Health for a drug to treat river blindness (onchocerciasis).[38] On the other hand, it is also noteworthy that the PRV system encompasses possible issues and risks as is clear from the case of miltefosine – the oral drug for leishmaniasis. A PRV (equivalent of US$125M) was awarded at the time of registering miltefosine in 2014; however, there is no apparent impact on drug access to date.[39] This incidence is interpreted as a major abuse of the PRV system itself as the company involved (and benefited from the system) neither discovered, developed or delivered miltefosine. It illustrates the fact that PRV is not a perfect solution for addressing the burden of neglected diseases.

2.1.4. Regulatory Approval

The majority of products first seek approval through a stringent regulatory authority such as the

FDA or European Medical Agency (EMA). The EMA has a specific regulatory track – Article 58 – for products to be used exclusively in the developing world. Most countries require prequalification (PQ) by the WHO and, often, their own regulatory authority. The Gates Foundation has invested significant resources to streamline, speed up, and make transparent the regulatory pathways for products including grants to the Critical Path Institute to accelerate TB drug development[40] and to WHO to build their pre-qualification capacity.[41] It also supported regional harmonization efforts in Africa to reduce the number of dossiers that companies need to apply for – the East African countries are furthest along in the development of a harmonized regulatory authority[42] – as well as the Chinese regulatory authority.[43]

The PDP and commercial partner work together to submit the regulatory dossiers and engage with regulators along the way including the WHO. Many products loose time at the WHO and even more so at the point in the process where the company needs to file dossiers in multiple countries. Lack of experience, excessive bureaucracy, and costs – including additional clinical trials in cases – serve as significant post-regulatory hurdles. Many product development funders are focused on regulatory approval as their end goal and have not adequately funded the PDPs – or provided alternative funding streams to the companies – to support all the post-regulatory approval work.[44,45]

2.1.5. Product introduction and scale-up

The R&D ecosystem of partners involved in product introduction, delivery and scale up is complex and voluminous. As per above, PDPs were originally set up and funded with an eye on the regulatory finish line. As products advance, often times without a major commercial partner, PDPs find themselves in a position of having to build up and try and fundraise for post-approval access work to help ensure that the products reach the patients.[46,47,48,49] There are Phase IV demonstration trials, country regulatory processes, complex supply chains, and health care

systems that all need to be managed for products to ultimately realize health impact.

The global health R&D ecosystem has transformed over the past decades. Especially in the upstream phases, many of the competency and capacity gaps have been filled by a combination of better funded academic research programs, PDPs, and continued targeted contributions by the pharmaceutical industry.[50] That said, the system remains largely dependent on philanthropic and donor funding as even with much of the costs subsidized, the return expectations remain too low to attract significant private sector investment.[51] The MNC's contributions are largely limited to support of specific projects as opposed to investments in broader programs. To attract and harness the best science, technologies, and processes that the life science industries can offer for global health, the ecosystem may need more push funding and the products need the pull of substantive, secure, and predictable markets.

2.2. Funding Trend for Global Health R&D

As discussed, there is no one entity in the public or philanthropic sector that manages the innovation pipeline for infectious diseases. The coordination of activities and the sharing of knowledge are largely bilateral rather than global, and agreements are non-binding. Early stage innovation can be driven by an individual funder or a partnership of organizations, investors, and countries. In addition to the criticality of new product development, some would also argue that a more robust delivery or distribution of existing products is urgently needed, hence new product development may not be sufficient enough to lift people out of poverty. However, given that this study is focused primarily on the assessment as well as strategies to advance product development forward, the discussion will be mostly centered around the product development element to be specific. Below is an outline of the various sectors and entities that are investing in and developing new GHPD.

Today, over 80% of GHPD efforts are funded by governments and foundations[15] (Figure 2), with the vast majority of funding coming from the world's high-income countries (HICs).

Figure 2 shows that there was an increase in total R&D funding by sector. Most of the increase came from HIC governments and multilaterals, but there was also an increase in funding from LMIC governments. While industry investment also increased, this was mainly due to the fact that there were new survey participants.

In 2017, the United States government was the largest funder of global health R&D – investing more than ten times the United Kingdom, the second largest funder (Figure 3). The growth in UK government funding was driven by the Department for International Development and the Department of Health and Social Care.

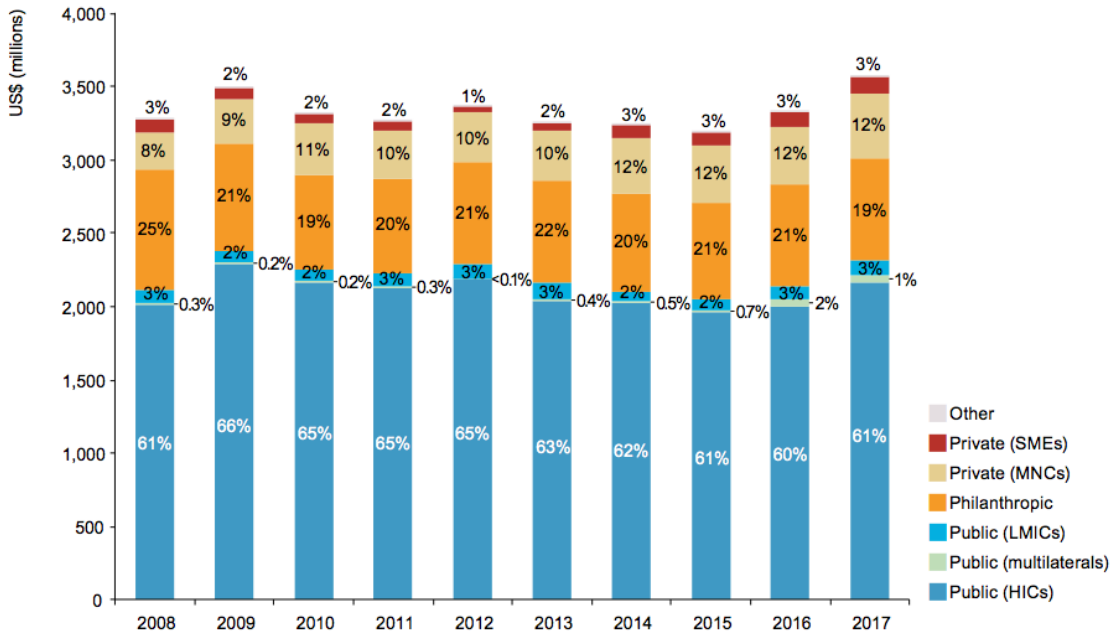


Figure 2. Total R&D funding by sector (2008 - 2017) (Cited from G-FINDER 2018 Report)

Country	US$ (millions)										2017 % of total
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	
United States of America	1,522	1,756	1,666	1,633	1,728	1,537	1,546	1,490	1,572	1,595	69
United Kingdom	88	123	135	109	77	105	109	90	98	186	8.0
EC	126	116	91	108	93	110	109	132	80	119	5.2
India	42	28	43	48	48	57	43	48	55	76	3.3
Germany	3.7	33	36	31	53	43	47	53	47	65	2.8
France	28	46	38	58	52	76	62	62	48	47	2.0
Netherlands	26	26	18	23	15	23	17	5.1	24	24	1.0
Australia	29	26	29	36	46	24	36	21	23	23	1.0
Switzerland	4.7	8.5	15	15	17	17	19	21	18	18	0.8
Japan	7.1	6.0	9.1	3.4	2.6	11	11	13	17	18	0.8
South Africa	4.8	6.9	7.4	6.7	5.4	12	4.1	6.6	11	14	0.6
Canada	26	18	9.3	9.3	18	19	13	9.9	6.9	13	0.6
Subtotal of top 12^	1,982	2,256	2,117	2,103	2,183	2,041	2,023	1,958	2,013	2,198	95
Total public funding	**2,118**	**2,376**	**2,255**	**2,225**	**2,286**	**2,159**	**2,106**	**2,052**	**2,137**	**2,318**	**100**

Figure 3. Top Public R&D Funders (2017) (Cited from G-FINDER 2018 Report)

2.2.1. National Governments

The bulk of government funding is often directed to the early development phases of pharmaceuticals, with less money being devoted to later-stage clinical trials. In the U.S. and other HICs, global health R&D spending is spread across multiple agencies, which can lead to cumbersome and inefficient processes. Advocacy groups have called for a "whole-of-government approach for global health R&D" to reduce silos, and increase transparency and information-sharing across agencies. In addition to providing financial support, governments can also create policy initiatives, such as the Orphan Drug Legislation (ODL) and the Priority Review Voucher (PRV), as discussed in the previous section.

2.2.2. Philanthropy

Philanthropic investments in global health R&D comprise a little less than one-fifth of the total funding. Just two foundations – the Wellcome Trust and the Bill & Melinda Gates

Foundation— account for nearly all of this contribution[15]. Both organizations have broad global views of the product development pipeline for the diseases they fund, conduct considerable due diligence prior to funding, and continue to influence product decisions for funded projects.

At the Gates Foundation, grant making decisions are usually made internally by Foundation staff, although some funding decisions may be outsourced to PDPs or organizations such as the Foundation for NIH, which manages the Grand Challenges program. The Wellcome Trust has an internal staff structure that is similar to the Gates Foundation but many of their funding decisions are reviewed through committees that include external expertise.

2.2.3. Industry

Biotechnology and pharmaceutical companies are integral to product development and innovation. Prior to the 1980s, these companies played a major role in developing life-saving treatments for infectious diseases, but the epidemiological transition to non-communicable diseases and the push for profits changed their positioning. Citing high research costs, poor returns, and onerous regulations, drug makers have lagged in developing needed treatments for the infectious diseases plaguing dozens of poor countries. In the late 1990s, the public sector emerged as a strong partner to industry, a move that dramatically sparked engagement and activity. In 2017, pharmaceutical companies spent $554 million on global health R&D and that number has continued to increase through expanding research initiatives[15].

2.2.4. Product Development Partnerships (PDPs)

Product Development Partnerships (PDPs) are independent, nongovernmental organizations that manage large product portfolios for a number of diseases and interventions. Over 16 PDPs[52] cover the focus areas of HIV, malaria, tuberculosis, and NTDs. PDPs have been termed intermediaries/catalysts as they collect and consolidate funding, primarily from national

governments and philanthropies, and then partner with academic researchers and private companies. The primary advantages of PDPs are 1) understanding and working across the pharmaceutical discovery, development, and delivery continuum, and 2) the speed and flexibility to fill gaps and partner with minimal bureaucracy, and 3) their ability to take funding from multiple sources. About 14% of total funding ($508 million) from charities and governments was programmed through PDPs in 2017[15].

2.2.5. Purchase Funds

Purchase funds play an important role in shaping the product market for needed drugs, vaccines, and diagnostics as they provide a vital procurement link that has been missing from other efforts. The creation of entities such as the Global Alliance for Vaccines and Immunization (GAVI) and the Global Fund for AIDS, Tuberculosis, and Malaria in the early 2000s brought billions of dollars of financing to the improvement of health delivery systems and purchasing power to poor countries for lifesaving drugs, vaccines, and diagnostics.

Over 500 million children have received DPT-HIB, hepatitis B, measles, rotavirus, and pneumococcal vaccines thanks to GAVI, saving 7 million lives. GAVI follows the Advanced Market Commitment (AMC) process that provides an assured market to pharmaceutical companies that will create and mass produce pneumococcal vaccines to meet the needs of low- and middle-income countries.

2.2.6. Other Models

The GHIT Fund is a unique collaboration between the Government of Japan, five of Japan's largest pharmaceutical companies, the Bill & Melinda Gates Foundation, and the United Nations Development Program. Founded in 2013, the GHIT Fund has increased Japan's R&D contributions to infectious diseases by more than five-fold in one year, from US$2.4 million in

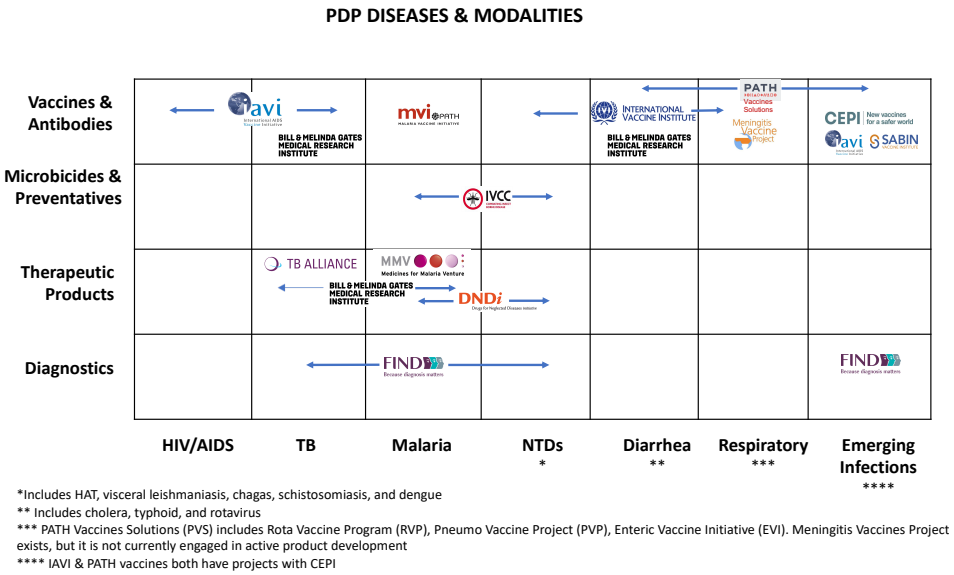
2012 to more than US$12 million in 2013.

Similar to GHIT, the Global Health Investment Fund (GHIF), headed by the Bill & Melinda Gates Foundation, aims to increase collaboration between investors and provide long-term funding for GHPD[53]. Launched in late 2013, GHIF finances late-stage clinical trials of high-impact drugs, vaccines, and diagnostic tools, specifically focused on reducing childhood death rates. Sponsors and partners include pharmaceutical companies, charities, investment banks, and governments. There has also been an increase in the number of GHIT-like business model organizations in recent years (e.g., the RIGHT Fund in South Korea and CEPI in Norway).

Medicines Development for Global Health (MDGH) is a non-profit pharmaceutical company dedicated to developing affordable and accessible medicines to address diseases that disproportionately affect low-income populations, often NTDs. The organization focuses on advancing drug development for conditions that have been overlooked by traditional pharmaceutical companies due to their limited commercial viability. MDGH operates with a mission to provide innovative health solutions, particularly for neglected and underserved communities around the world, contributing to global efforts in achieving health equity. One distinctive aspect of MDGH's approach to business sustainability is its utilization of the Priority Review Voucher (PRV) program. MDGH strategically employs PRVs as a financial incentive to support its ongoing research and development efforts. By leveraging the benefits of the PRV program, MDGH not only accelerates the regulatory process for its own projects but also has the potential to generate additional revenue by selling these vouchers to other pharmaceutical entities. This innovative approach helps MDGH sustain its mission-driven activities and contribute to the development of much-needed treatments for neglected diseases.[54]

2.3. PDPs: Preliminary survey of success and cost-effectiveness assessment approaches

PDPs have introduced innovative systems and processes for drug development outside the traditional pharmaceutical model, helping break down institutional barriers between partners who otherwise would not work together and thus catalyzing global health R&D initiatives that would not previously have been possible. While a consensus on the metrics of PDPs' success and cost-effectiveness does not yet exist, after several decades of operation under their belt, different assessments have emerged. Some PDPs are proving more effective and efficient than others. While government funding for PDPs has increased in recent years, the establishment of the Gates Medical Research Institute calls into question the faith of the biggest global health and PDP funder in the existing PDP model.



*Includes HAT, visceral leishmaniasis, chagas, schistosomiasis, and dengue
** Includes cholera, typhoid, and rotavirus
*** PATH Vaccines Solutions (PVS) includes Rota Vaccine Program (RVP), Pneumo Vaccine Project (PVP), Enteric Vaccine Initiative (EVI). Meningitis Vaccines Project exists, but it is not currently engaged in active product development
**** IAVI & PATH vaccines both have projects with CEPI

Figure 4. Product Development Partnerships (PDPs)

2.3.1. How PDPs work

Most PDPs focus on a single disease, or a specific group of diseases (Figure 4). PDPs channel

the funding they receive from governments and foundations into a number of different projects in various stages of development. PDPs' nonprofit status enables donors to pool funding for portfolios of carefully selected projects in collaboration with industry partners, thereby creating full pipelines of current and next-generation products. The rationale is that this model allows investments and research to achieve greater impact than individual, sole-donor projects.

Most PDPs focus primarily on project management and channel funding for R&D through partners, such as pharmaceutical companies or academic research institutions. PDPs are entirely reliant on restricted donor and grant funding to support their work.

According to the 2018 G-Finder Report, $508m (19%) of global external funding for neglected disease R&D was channeled through PDPs in 2017, up by $52m (or 11%) after a historic low in 2016, driven by increased funding from U.K. and U.S. government agencies.[15] In fact, 2017 marked the first time that PDPs received more funding (57%) from governments than from philanthropic organizations. Although the Gates Foundation is still the largest individual funder of PDPs (providing 39% of all PDP funding in 2017), this was the third consecutive annual decrease in funding and the lowest investment in PDPs by the Gates Foundation in the history of the G-Finder Report.[15]

2.3.2. PDP Organizational Update

There has been attrition in the PDP field over the past few years. Five of the original group[52] have been incorporated into others: AERAS into IAVI, Institute for One World Health into PATH, Sabin Human Hookworm Vaccine to Texas Children Hospital Center for Vaccine Development, Pediatric Dengue Vaccine Initiative from IVI into a newly establish coalition called Global Dengue and Aedes transmitted disease control. The Meningitis Vaccine Project succeeded in getting its vaccine to market and is no longer focused on R&D. The remaining 10,

plus the Bill & Melinda Gates Medical Research Institute (GMRI) and CEPI, are included in the table associated with this overview.

While each of the PDPs have their own operating models, they share some common features:

1. They focus on driving innovation to prevent, diagnose, or treat diseases that disproportionately impact the poorest in low- and middle-income countries.
2. They serve as an intermediary between global funders and the public and private actors in the R&D ecosystem that undertake the product development.
    - While most were originally set up as portfolio management and "virtual" organizations, facilitating, rather than doing, the product development in-house, over the years they have all built some human resource in-house capacity to adapt to gaps in the ecosystem. For instance, IAVI has built their own labs and clinical trial networks, essentially transitioning from an enabler to a doer.
3. Beyond funding, they mitigate the risks of global health R&D through in-house expertise about the disease, how to operate in low- and middle-income countries, and how to work with global regulatory, procurement and other partners.
    - The newly launched GMRI, and to a lesser extent the others, also offer partners innovative approaches to conduct translational and development research that proport to shorten timelines, lower costs, and/or accelerate update.
    - CEPI, also included in the table, is, like GHIT, primarily a funder and offers little "in-kind" disease or product development support to the partners beyond money and issue advocacy.
    - DNDi has also established innovative clinical networks to strengthen clinical research capacity (e.g., Leishmaniasis East Africa Platform, or LEAP).
4. While they are focused on solving for the R&D and innovation challenges, all the PDPs' missions focus on health impact and saving lives. Beyond the donor-requisite

negotiated global access agreements that all groups have with their partners, the PDPs are committed – and fund in varying degrees – product implementation and uptake.

2.3.3. Overview:

The specifics of each of the PDPs are summarized in Table 1. In summary, 10 of the 12 have been in operation for 15-25 years. CEPI and GMRI are the two exceptions – established in 2017 and 2018 respectively. All are relatively small (25-100 FTEs) non-profit organizations, with MVI and GMRI as subsidiaries of other organizations (PATH and the Bill & Melinda Gates Foundation, respectively).

[Scope of work] All their websites promote work across the value chain, from discovery through to support of product access.

1. In practice, at the discovery end, IAVI and CEPI are investing in the most innovative new technologies.
2. At the access end, it is the organizations with products on the market - MMV, TB Alliance, MVI, DNDi, and IVI – that are the most vested in turning access "theory" into practice through concrete actions and investments that they are well positioned to make. For several years, "access" was considered out of the PDP's scope by major donors and, as a result, their teams and programs are under-resourced.

[Funding/donors] While 9 of the 12 have successfully diversified their funding base from the standpoint of the number of donors listed on their website, from the percentages that are publicly available, the story is still one of a group of organizations highly dependent on the Gates Foundation and a few other bilateral donors (UK, USAID).

1. Almost 60% of MMV's funds come from the Gates Foundation. Even DNDi, which has intentionally sought to sustain a diversified funding base relies heavily on 4 contributors (UK-DFID (now FCDO), Gates Foundation, MSF, the Netherlands).
2. The HIV PDPs are the greater beneficiaries than the others of US funding, securing NIH, USAID, and PEPFAR funds.
3. MMV, DNDi, TB Alliance, PATH MVI, and FIND are GHIT Fund recipients.

[Products] A total of 7 of the 12 PDPs have supported products through registration.

1 Of the approved products listed on their websites, the majority are approvals of existing products on which PDPs worked with partners to improve/modify/formulate to improve uptake and access.

2 The novel molecular entities include: MVI-GSK's malaria vaccine, RTSS, MMV-GSK's new malaria drug for *P. vivax* malaria, tafenoquine, DNDi-Sanofi's new oral HAT drug, fexinidazole and TB Alliance's pretomanid, a new TB drug, developed for use in combination with bedaquiline and linezolid for adults with XDR, with a caveat that these novel molecules were discovered by other entities.

PDP	Website	Year Established	Disease(s)	Product Type(s)	General Accomplishments	CEO	Staff Size	Governance	Scope (Value chain)	Research + Translational (Projects and Mini Portfolios, e.g. GHIT screening)	Clinical Development (includes new combinations, new formulations)	Approved products (FDA, EMA, EUA, and/or WHO PQ)	Reference for approved products	Select Private Sector Partners	Select Public/Academic/Research Inst Partners	Donors (some list current and some list "all" donors from the time they were established). Bolded = primary funders.
Bill and Melinda Gates Medical Research Institute (GMRI)	https://www.gatesmri.org/	2018	TB, Malaria, Diarrheal diseases	Drugs, Vaccines	N/A	Penny Heaton	at scale, target 80-120	Non-profit biotech organization; subsidiary of BMGF	Translational research, Clinical trials; integrated organization, doing the work in-house	N/A	1 (TB Vaccine)	0		N/A	N/A	BMGF
Center for Epidemic Preprednss Innovation (CEPI)	https://cepi.net/	2017	Chikungunya, Lassa virus, Marburg virus, MERS coronavirus, Nipah virus, Rift Valley Fever, 2019-nCoV	Vaccines	In three years, raised 3/4B, issued three RFPs, funded 20+ projects including five for 2019-nCoV	Richard Hatchett	N/A	Norwegian Association governed by a Board, Investors Council, Scientific Advisory Committee, and Joint Coordination Group https://cepi.net/about/governance/	R&D for vaccine candidates and rapid response vaccine platforms	13 PC vaccine candidates and committed up to $54 million to fund the development of a vaccine printer, molecular clamp platform, and a self-amplifying RNA vaccine platform.	7 (includes 1 Ph III)	0		Emergent Biosolutions, Janssen Vaccines & Prevention B.V. CureVac, IDT Biologika, Inovio, Profectus Biosciences, Themis Bioscience, Public Health Vaccines, Valneva SE, Wageningen Bioveterinary Research, Inovio, Moderna, GSK	Imperial College London, IAVI, Colorado State University, PATH, U Tokyo, U Queensland, U Oxford	**Norway**, Germany, Japan, Australia and Canada, **BMGF**, **Wellcome Trust**, Belgium and the UK, EC
Drugs for Neglected Disases Initiative (DNDI)	http://dndi.org	2003	HAT, VL, Chagas, HCV, Pediatric HIV, Mycetoma, Filarial Diseases	Drugs	Approval of new first ever oral treatment for sleeping sickness; 7 new treatments (modifications, new formulations) from existing molecules; launched new not-for-profit from antibiotics, Global Antibiotic R&D Partnership (GARDP) (https://www.dndi.org/wp-content/uploads/2019/07/DNDi_2018_AnnualReport.pdf)	Bernard Pecoul	56	Independent Swiss Foundation governed by a Board of Directors, Expert Scientific Advisory Committee, Access & Product Mgmt Advisory Committee, and Global Safety Board https://www.mmv.org/about-us/people-governance	Discovery through Access	20	19	7 new treatments from existing molecules and recombining drugs 1. (Malaria) Artesunate + mefloquine (ASMQ) to treat malaria (EML, EMLc, WHO PQ) - handed over to MMV 2. (Malaria) Artesunate + amodiaquine (ASAQ) to treat malaria (WHO PQ) - handed over to MMV 3. (Chagas disease) Paediatric benznidazole 4. (Leishmaniasis) single-dose liposomal amphotericin B as a first option and paromomycin & miltefosine as a second option (WHO recommended) 5. (Leishmaniasis) sodium stibogluconate and paramomycin (SSG&PM) (WHO recommended) 6. (Paediatric HIV) Super-booster ritonavir therapy 7. (Sleeping Sickness) Fexinidazole (NCE) first all-oral cure for all stages	https://www.dndi.org/achievements/	Abbvie, Astalles, Astra Zeneca, Avista Pharma, Bayer, BMS, BI, Cipla, Daiichi Sankyo, Eisai, Gilead, GSK, Novartis, J&J, Sanofi, Takeda, Shinogi	Institut Pasteur, Broad, Sudan, Addis Ababa U, Chainag Mai U, Brazil, Imperial, Liverpool School for Tropical Med, LSHTM, Stellenbosch, Antwerp, Auckland, UCSF, Glasgow	Australia, Brazil, Canada, Columbia, EDCTP, EU, France, Germany, Global Fund, **UNITAID**, TDR, GHIT, Norway, Switzerland, **Netherlands**, UK Aid, USAID, **BMGF**, **Wellcome Trust**, Takeda, **MSF** (multiple countries and HQ), NIH
Foundation for Innovative New Diagnostics (FIND)	https://finddx.org	2003	AMR, HIV, HCV, NTDs, Malaria and Fever, Pandemic Preparedness, TB	Diagnostics	24 new diagnostics introduced	Catharina Boehme	120	Global non-profit governed by a Board of Directors and Scientific Advisory Committee https://www.finddx.org/ops-gov/	Development (Concept, Feasibilty, Development) through Guide Use and Policy (Evaluation, Demonstration) (https://www.finddx.org/wp-content/uploads/2019/10/FIND_RD-pipeline.pdf)	31 (Development)	23 (GU&P)	1. Xpert HIV-1 Qual 2. Xpert HIV-VL 3. Xpert HCV-VL 4. Xpert Ebola 5. Malaria highly sensitive RDT	24 WHO recommended products in all, including the 5 in column M that have received EMA approval or WHO PQ. https://www.finddx.org/dx-developed/	Otsuka, Abbott, Standard Diagnostics, Cepheid (Danaher), Omnione Inc., Fujifilm, Mologic, Molbio, Hain Life Sciences GmBH (Bruker), Inflammatix Inc. SD Biosensor, Eiken Chemical Co, Kalon Biological Ltd.	ASU, Tufts, Cornel, Stanford, Walter and Eliza Hall Institute, Institut Pasteur, Harvard	Australia, ASLM, **BMGF**, Elma Foundation, Fnd Botnar, CDC, EDCTP, Anesuad, GAVI, GHIT, Germany, EU, CEPI, **UK AID**, USAID, UNITAID, WHO, Switzerland, South Africa MRC, Stop TB Partnership, KNCV TB Foundation, Netherlands, Probitas Foundation,
International Aids Vaccine Initiative (IAVI)	http://iavi.org	1996	HIV vaccines and antibodies, TB vaccines, vaccines for emerging infectious diseases, monoclonal antibodies	Vaccines	Advancing biomedical vaccine and antibody breakthroughs including 1st immunogen vaccine in humans, access strategy for monoclonal antibodies, building capacity through laboratories and clinical research centers	Mark Feinberg	N/A	Non-profit scientific research organization governed by a Board of Directors	Discovery, Development; have their own Research and Development laboratories	17	5	0		GSK, Batavia, Janssen, Serum Institute of India, ViiV, Statens Serum Institute	IAVI Clinical Research Center Partners (Kenya, South Africa, Uganda, India, Zambia), Rockefeller University, Cornell, Duke, GWU, Scripps Research, Fred Hutch, UW, Kenya AIDs Vaccine Institute, World Bank, Imperial College London, MIT, Harvard, Seattle Children Hospital, U of Kansas, Kenya MRI, LSTHM, Oxford U, Beth Isreal Medical Center, South Africa TB Vaccine Institute	**USAID**, EU, PEPFAR, World Bank, **BMGF**, DOD, CEPI, UK Aid, EDCTP, Norway, Netherlands, Japan, Wellcome Trust, India, Ireland, NIH, NIAID
International Parntership for Microbicides (IPM)	https://www.ipmglobal.org/	2002	HIV, other STIs, multipurpose technologies	HIV prevention products for women	Dapivirine Ring under EMA review (Phase III show 30%-50% risk reduction)	Zeda Rosenberg	N/A	Non-profit product developer governed by a Board of Directors, Finance, Audit and Compensation Committee, Scientific Advisory Board, and Access Advisory Committee https://www.ipmglobal.org/about-ipm/ipm-governance	Development, Support Access	N/A	8 products have undergone some clinical testing, most are on pause due to insufficient funding	0 (one under EMA review)		ARV In-licencees - Janssen, BMS, Viiv, Gilead, Merck; Q Pharma (CMO)	Queens U Belfast, NIH,	PEPFAR, **USAID**, BMGF, World Bank, Sweden, Norway, Franc, EDCTP, Canada, Rockefeller Foundation, Ireland, OPEC Fund

International Vaccine Institute (IVI)	https://www.ivi.int/	1997	Typhoid, Cholera, HPV, Dengue (separate new entity - Global Dengue and Aedes-transmitted Diseases Consortium - in 2016), MERs-cov, emerging infectious diseases	Vaccines	2 WHO PQd oral cholera vaccines	Jerome Kim	N/A	Non-profit international organization as an initiative of UNDP and governed by a Board of Trustees and Scientific Advisory Group https://www.ivi.int/who-we-are/leadership/board-of-trustees/	Discovery through implementation	Has its own labs and does own discovery (oral cholera and conjugate typhoid)	3	Euvichol / Euvichol-Plus: bivalent inactivated oral cholera vaccine	https://www.ivi.int/what-we-do/overview/ Also worked to get two different company suppliers PQ'd - Shantha in India and Eubiologics in Korea. The vaccine is an reformulated version of a vaccine that at Vietnamese company, VaBiotech, had developed and licensed for the Vietnamese domestic market. IVI's contribution was the reformulation, technology transfer, working with the companies on the requirements for PQ etc. https://www.ivi.int/what-we-do/disease-areas/cholera/	Sanofi (Shantha is a subsidiary), SK, Incepta Vaccines, Eubiologics, PT Bio Farma, VaBiotech, Merck, Pfizer, GSK, CelTrion	Leiden, Maryland, ICDDRB	**Governments of the Republic of Korea**, Sweden, India, **the Bill & Melinda Gates Foundation**, LG Electronics, Kia Motors, the Yanghyun Foundation, the Export Import Bank of Korea, Rotary International, and Kim & Chang, Samsung, UK AID, EU, CEPI, Wellcome, Fleming Fund, CDC
International Vector Control Consortium (IVCC)	https://www.ivcc.com	2005	malaria, other insect borne diseases	Vector control tools - new insecticides for bednets and indoor residual spray	Supported the launch of two new long lasting IRS formulations, Sumitomo's SumiShield® 50WG and Bayer's Fludora® Fusion.	Nick Hamon	34	Not for profit company registered as UK Charity and governed by a Board of Trustees and Advisory Committees https://www.ivcc.com/about/	Active ingredient development, product portfolio development, formulation chemistry, entomology and field trials.	8	3	2 IRS formulations that expand the range of vector control tools for malarial insecticide resistance: 1. Fludora® Fusion 2. SumiShield® 50WG	https://www.ivcc.com/about/	Bayer, BASF, Syngenta, Mitsui, Sumitomo, Westham		**BMGF, UK AID**, USAID, UNITAID, Global Fund Australia, Switzerland
Medicines for Malaria Venture (MMV)	https://www.mmv.org/	1999	Malaria	Drugs	11 medicines approved (13 inc. stewardship of two from DNDi); 10 in development; estimates 2.2 m lives saved	David Reddy	111	Independent Swiss Foundation governed by a Board of Directors, Expert Scientific Advisory Committee, Access & Product Mgmt Advisory Committee, and Global Safety Board https://www.mmv.org/about-us/people-governance	Discovery through Access	24	9	1. Artesun®: Fosun Pharma's injectable artesunate for treatment of severe malaria 2. ASAQ Winthrop®: (artesunateamodiaquine) 3. ASMQ: (artesunate-mefloquine) 4. Coartem® Dispersible (artemetherlumefantrine), child-friendly formulation for uncomplicated malaria 5. Eurartesim® (dihydroartemisininpiperaquine) for uncomplicated malaria 6. Krintafel/Kozenis®: (tafenoquine), single-dose cure for relapsing malaria 7. Larinate: Injectable artesunate for severe malaria 8. Pyramax® granules, child-friendly formulation of Pyramax 9. Pyramax® tablets, (pyronaridine-artesunate) for uncomplicated malaria 10. Rectal Artesunate: products for prereferral management of severe malaria in children 11. SP+AQ: sulfadoxinepyrimethamine + amodiaquine for seasonal malaria chemoprevention in two different age groups	https://www.mmv.org/sites/default/files/MMVtimeline/mmvtimeline.html	GSK, Novartis, Cipla, Sanofi, Janssen, Merck KGAA, Takeda, Eisai, Shin Poong, Fosun Pharma, IPCA	UW, U Sydney, Dundee, Broad, UCB, Calibr, Kentucky	Australia, **BMGF**, EDCTP, Exxon Mobil, GHIT, Monaco, Ireland, New Crest Mining, Netherlands, RIGHT fund, Switzerland, Germany, **UK AID**, UNITAID, USAID, WHO
PATH - Malaria Vaccine Initiative (MVI)	https://www.malariavaccine.org/	1999	Malaria vaccines	Vaccines	1st malaria vaccine EMA approved in 2015 and WHO approved for pilots	Ashley Birkett	N/A	Program within PATH, nonprofit organization	Discovery through implementation	5	6	RTS,S the world's first malaria vaccine shown to provide partial protection against malaria in young children	https://www.malariavaccine.org/malaria-and-vaccines/rtss	GSK, Atreca, ExpreS2ion	Walter Reed Army Institute, Navel Research Institute, Oxford, NIAID, Johns Hopkins, Center for Infectious Disease Research, Institute for Molecular Medicine Lisbon, WHO	**BMGF**, Exxon Mobil, Germany, GHIT
Sabin Vaccine Institute	https://www.sabin.org/	1993	Ebola and Marburg	Vaccines	N/A	Amy Finan	N/A	Non profit organization governed by a Board of Trustees https://www.sabin.org/board-trustees	R&D, Advocacy, Access update (only 4% of current budget is R&D)	0	3 (all same vaccine applied to different diseases)	0		GSK	VRC, NIAID,	NIH, BARDA
TB Alliance for Drug Development (TB Alliance)	https://www.tballiance.org	2000	TB	Drugs	Partnered on three pediatric formulations and a new combination, BPaL for XDR TB (FDA approved with new drug, Pretominid earning TB Alliance a Priority Review Voucher); 3 new drug combinations in late-stage trials	Mel Spigelman	51	Not-for-profit organization governed by a Board of Directors, Scientific Advisory Committee, Access Advisors, and Pediatric Advisors https://www.tballiance.org/about/advisory-boards/scientific	Discovery through Access	15	7	1. Pretomanid, in combination regimen with bedaquiline and linezolid for people with XDR-TB or treatment-intolerant/non-responsive MDR-TB	1. https://www.tballiance.org/news/fda-approves-new-treatment-highly-drug-resistant-forms-tuberculosis 2. Also worked on pediatric formulations through STEP-TB: https://www.tballiance.org/sites/default/files/child-resources/New_Pathways_for_Childhood_TB_Treatment.pdf	AbbVie, Astallas, Chugai, Daiichi Sankyo, Eli Lilly, Fujifilm, GSK, Hongqu Pharmaceutical, HyphaGenesis, Macleods, Mylan, Panacea, Schrodinger, Takeda	GMRI, CETR, FIND, GH DDI, Harvard, IMPAACT, Institute of Materia Medica, JHU, MSF, MRC, NIH, Stellbosch U, TBDA, UCL, U Ackland, U Illinois, Weill Cornel Medical, Yonsei U	Australia, **BMGF**, EDCTP, Cystic Fibrosis Foundation, Germany, GHIT, Indonesia Health Fund, Ireland, MRC, NIAID, Rockefeller Foundation, UK AID, USAID

Table 1: Product Development Partnerships Overview

2.3.4. Assessing success

Since the formation of the first PDPs around 25 years ago, an impressive portfolio of drugs, vaccines, diagnostics, and vector control products has been established. PDPs have built important networks of academics, clinical research centers, sample libraries, screening facilities, and more. They have helped raise global health R&D significantly on the global agenda and offered compelling ways for pharmaceutical companies to engage in global health R&D. However, despite the growing number of technologies in the pipeline, relatively few products are successfully crossed the finish line to reach health practitioners and patients. Some question whether products have just quick wins that result from re-purposing existing drugs or developing combinations. Additionally, while some organizations such as The Global Fund, Unitaid, and GAVI have transformed access to medicines, the path from development to uptake remains complex.

Increasingly, donors are evaluating organizations not only on individual achievements but also on how well they collaborate and share their experiences with other grantees and engage the end user communities for these new products. It will be of stakeholders' interest to see that their funding is creating synergies and that efforts are not being duplicated unnecessarily.

PDPs have not traditionally prioritized information-sharing and collaboration between one another until recently, creating a perception that they compete for visibility and funding, with funder dollars going unnecessarily to these activities when they should be devoted to R&D itself. This very perception propelled PDPs to join forces on many fronts, leading to a much more prominent and credible international presence.[55]

Because each PDP differs in scope and methodology used, and since different donors have

different reporting requirements, some have argued that it is not useful to develop a common set of metrics across PDPs. However, ambiguity exists for many outsiders and donors alike as to how PDPs truly function and progress.[56] Some of the key issues – or misunderstandings – center around management of the portfolio approach and the unique scientific challenges of innovating for neglected diseases.

For example, donors may view project failures as being representative of organizational failures. Consequently, PDPs may keep unpromising projects on board for longer than is optimal. Assessing PDPs like a classic for-profit pharmaceutical company is not appropriate, given that unlike in the pharmaceutical sector, PDPs are not in competition with one another in the traditional sense and often work where basic structures for things like clinical trials do not exist. In fact, they often need to help create that infrastructure. Additionally, major scientific challenges that slow R&D or raise the likelihood of failure, which may form part of the reason no appropriate products yet exist against a specific disease, should not penalize the PDP working on high-risk projects to overcome them. Finally, others argue that consensus within the global health community on how to calculate the value of future products of PDPs will be crucial for any common metrics to be seen as anything more than process indicators.[56] There are also individual case studies from PDPs available, like DNDi's 15 years of lessons learned and opportunities report.[57] PDPs and other partners convened for a meeting in July 2019 to discuss bottlenecks related to the GAP and the WHO R&D accelerator (the meeting was jointly hosted by The Global Fund, WHO, and global health PDPs).

2.3.5. Measuring cost-effectiveness

Some published papers have assessed the cost-effectiveness of individual PDPs by specific funders, but those assessments are difficult to apply across all the PDPs. Two relatively recent reports, however, help illustrate existing approaches, while also outlining the challenges to

assessing PDP cost-effectiveness.

The first is a 2017 Tideline and Product Development Partnerships Innovative Financing Initiative (PDP IFI) working paper funded by the Gates Foundation, which offers clarity and practical guidance to the prospect of impact investment as a funding source for PDPs to complement ongoing financial support from public and philanthropic donors, using FIND, IAVI, and PATH as case studies. The paper categorizes the prototypical investor assessment into three elements to evaluate each case study's strengths and weaknesses as they relate to the potential for designing an investable opportunity:

- Clarity: Is there certainty about the market opportunity, and what is the nature of the underlying economics?
- Effectiveness: Does the concept deliver on global health impact objectives?
- Feasibility: What is the experience of the PDP in commercial environments, are the time and cost to implement likely to be reasonable, and do the PDP's core stakeholders support the approach?

The insights and implications generated from the case study assessments helped formulate a set of strategic recommendations for PDPs and their funders. The goal is to determine more definitively whether a PDP can attract impact investment capital. In most cases, the recommendations may require extensive collaboration to be implemented, with the goal of creating more diverse, sustainable, and additive sources of funding for PDPs and the market more broadly.[7]

Second, a DfID and German Ministry of Education and Research (BMBF) evaluation of PDP funding activities examined the value of their investments in FIND, DNDi, and EVI over the period spanning 2009-2013, using the "three Es" (as defined by the UK National Audit Office)[8]:

- Economy: getting the best value
- Efficiency: maximizing the outputs for a given level of inputs
- Effectiveness: ensuring that the outputs deliver the desired outcome

(The report acknowledges that the OECD identified a fourth E: Equity, though only the first three were used in the report).

The conclusion one could derive from these examinations may be that there appears to be a set of factors to be considered in assessing the efficiency and effectiveness of PDPs, but that many challenges still remain (e.g., difficulties around assessing long-term outcomes, uncertainty as to who to measure the health impact). Thus, a comprehensive study to elucidate the assessment of PDPs as well as its practical applicability in current global health R&D settings is needed.

3 Chapter 3 Methods

3.1. Introduction

This study aims to analyze how to measure the success of PDP models and how to apply them practically in a comprehensive manner in order to inform strategies for various stakeholders to accelerate product development efforts and overcome the global burden of infectious diseases. Several reports have documented methods for assessing individual PDPs; however, common metrics to measure success or cost-effectiveness across all PDPs are not well developed or documented. This study aims to employ both qualitative and quantitative methods to combine a detailed description of bottlenecks and ways to measure the success of PDPs with an in-depth analysis of methods, tools and metrics.

This chapter elucidates the comprehensive design and methodologies employed in the pursuit of scrutinizing the pivotal success criteria for PDPs and the viability of their business model in the

realm of global health R&D. The ensuing sections expound on the intricacies of the study's design, which seamlessly amalgamates qualitative analysis facilitated through a rigorous semi-structured interview process, orchestrated with an array of eminent stakeholders within the global health R&D landscape. This qualitative component is accompanied by a quantitative analysis that focuses on the salient points and critical components that emerged from the interviews, forming a harmonious and comprehensive "Mixed Methods Approach."

Moreover, this chapter furnishes an account of additional interviews conducted after the initial interview and quantitative analyses, emphasizing the study's iterative and inclusive nature. A detailed exposition of the research methods is provided, shedding light on the process of data collection and analysis.

This chapter also extends its purview to encompass the blueprint for data analysis, ensuring the study's reliability and validity, and delves into the ethical dimensions by articulating the obtained ethical approvals, thus ensuring adherence to research standards and ethical considerations.

It is expected that the findings from this study will add to existing knowledge by developing tangible, actionable strategies for relevant parties such as PDPs themselves, funders that invest in PDPs, and other international agencies, by elucidating success criteria that could be applied across all PDPs.

3.2. Study design

Success criteria and the validity of PDPs along with other relevant considerations were investigated with a mixed methods approach by conducting both qualitative and quantitative analyses[58]. The mixed methods approach was used to integrate key aspects of both analyses and

allow for the development of actionable policy recommendations based on the combined results. Specifically, in-depth interviews were conducted to collect input from various stakeholders on the key research questions, and quantitative analysis were conducted sequentially to address and further bolster findings from the qualitative analysis of interview contents. The two phases (qualitative and quantitative) were conducted sequentially so there would be some overlap between them. Qualitative and quantitative analyses therefore were expected to enhance each other via an iterative process and culminate in an actionable policy recommendation. In addition, additional semi-structured interviews were conducted to examine further key considerations that were identified through the iterative process of preceding qualitative and quantitative analyses.

In summary, the study design used in this research can be described as follows:

Objective 1 "Qualitative Analysis" – Examine current bottlenecks and potential ways to measure success criteria of PDPs by conducting in-depth interviews with relevant stakeholders. This objective helped explore and identify considerations to be further investigated in the quantitative analysis (Objective 2). Qualitative data were also used to triangulate with quantitative data gained from Objective 2 to provide an in-depth understanding of metrics as well as their practical feasibility.

Objective 2 "Quantitative Analysis" – Examine relevant data and information pertaining to metrics and considerations identified from Objective 1 such as the timeline, cost, and public health impact for global health products. Objectives 1 and 2 took place sequentially to triangulate with and enhance the results of each other.

Objective 3 "Additional interviews as part of Mixed Methods Approach" – Examine further key

questions and considerations that were identified through an iterative process of both qualitative and quantitative analyses (Objectives 1 and 2) to investigate the PDPs business model and its validity.

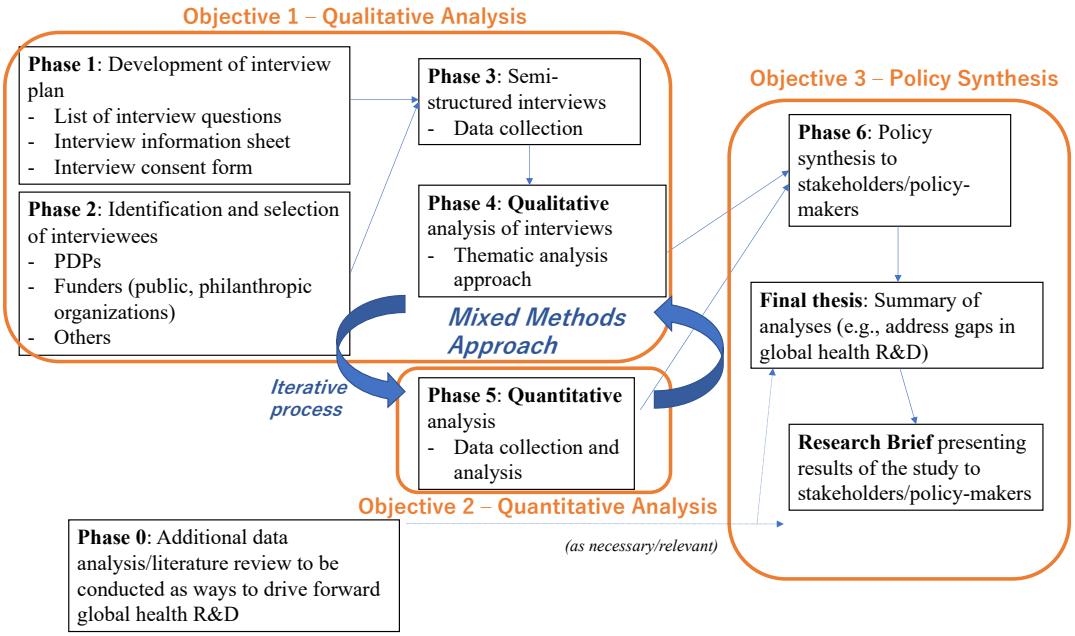


Figure 5. Project phase matrix

The project flow is shown in Figure 5. Details of each study design are described in the following sections. As delineated in the above sections, this study followed a sequential and explanatory mixed methods approach with qualitative and quantitative analyses taking place concurrently through an iterative process. This process was selected as an overarching framework and design of the study since it is a commonly used, well-known tool that would allow data and findings from qualitative and quantitative analyses to triangulate with and enhance each other.[58]

3.3. Research methods

3.3.1 Qualitative analysis with semi-structured interviews

Perspective

In light of the reality that infectious diseases will undoubtedly continue to present major obstacles to economic growth, health security, and human development in poor countries, it is critical to develop strategies and policies that will help foster and accelerate the innovation of global health products. PDPs have played, and are expected to continue playing, major roles in bringing forward innovations for global health R&D. Yet, it remains uncertain how success (and failure) of the PDP model should be measured, and how this could lead to the creation of strategies for PDPs as well as stakeholders such as funders. To this end, in-depth interviews were conducted to elucidate current obstacles to measuring PDP success, and potential ways to address them.

Key research question

What are the success criteria of PDPs? And what have we learned from the failures? How could we utilize them to develop strategies to drive forward innovations in the global health R&D space?

Data collection

In-depth interviews with questions regarding key research topics were conducted with interviewees, who included world leaders in the global health arena. Originally, the study had aimed to conduct in-person interviews if and where possible. Given the COVID-19 pandemic, however, all interviews were conducted via videoconference or teleconference for an indefinite period of time. Semi-structured interviews were used as this approach is appropriate for capturing perspectives, insight, and practices of stakeholders with various backgrounds and expertise.[59] Qualitative analysis of the interview contents helped explore and identify potential metrics and other considerations to be further investigated and expanded in the quantitative analysis (Objective 2). Qualitative data were also used to triangulate with quantitative data

gained from Objective 2 to provide an in-depth understanding of the metrics and their validity for application across all PDPs.

This study aimed to include respondents representing various sectors and expertise in order to capture balanced perspectives from different/diverse angles. Interviewees were carefully identified and selected in close consultation with supervisors. Specifically, it was aimed to identify and recruit relatively equal/similar number of respondents for each sector such as PDP, funder, international organizations, private sector companies, academia, and NGOs. It was also expected to select different entities for the same sector (e.g., different entities for PDPs) to allow for diverse perspectives. For each entity, those who were considered to possess and/or be in a position to have in-depth knowledge and experience regarding their organizational strategy were identified and recruited in close consultation with supervisors and advisors.

In-depth interview

The interviewer explained the following to the interviewee before the interview took place. Interviewee consent, both verbal and in an official consent form, were required before proceeding with an interview (Appendix 1):

This semi-structured interview is aimed at learning more about your organization's strategy and decision-making process for the discovery, development, and delivery of global health innovation. The information from the interview will be used solely for the purpose of a study focused on drug discovery and development for infectious diseases. No presentation or discussion of an individual organization's strategy and decision-making process will be shared outside the study. A report summarizing aggregate observations is expected to be drafted. Do you consent to be interviewed?

After the interviewee agreed with the above, a semi-structured interview was conducted. All interviews were recorded with the interviewee's consent in order to allow for smooth and evidence-based analyses.

Several publications have documented analyses of specific PDPs and discussed possible determinants of success (and failure), albeit not across all PDPs.[7,8] As explained above, keywords for possible determinants of PDP success discussed in these publications include: clarity, effectiveness, feasibility, economy, and efficiency.

With these 'a priori' themes in mind, interview questions regarding Objective 1 were developed with an aim to obtain stakeholders' feedback on them and explore new metrics or points for further discussion in an open question manner. Interview questions included both general and PDP-specific topics to elucidate key determinants of PDP success from both macro- and micro-level perspectives. Provided below is the list of questions for in-depth interviews:

- The PDP model has existed for the past couple of decades in the global health R&D space. Has this particular model been successful/valid, and why?
- Aside from PDPs or a traditional pharmaceutical company model, what organizations and/or systems have played, or are expected to play, complementary roles in product development for global health? Any change in terms of context/architecture for global health R&D expected in the near future?
- In comparison to other models (e.g., pharmaceutical company), what are the advantages and disadvantages of PDPs?
- What are the key elements to determine success and failure of the PDP model from the perspective of each entity?
    - For instance, there are some reports that identified the following metrics for

success and failure of PDPs[7,8] – what are your views on them?

- Clarity: Is there certainty about the market opportunity, and what is the nature of the underlying economics?
- Effectiveness: Does the concept deliver on global health impact objectives?
- Feasibility: What is the experience of the PDP in commercial environments, are the time and cost to implement likely to be reasonable, and do the PDP's core stakeholders support the approach?
- Economy: Getting the best value.
- Efficiency: Maximizing the outputs for a given level of inputs.

  - Aside from the above, what other parameters/determinants exist to measure success and failure of PDPs, and why are they important?

- PDP-specific question (to be asked when interviewing that PDP and its stakeholders): Looking back at the past track record of PDP "A," what are the major achievements and failures? What metrics could be used to measure such outcomes?
- If we are to develop guidelines for determining the success of PDPs, what are the benefits and pitfalls that we need to be aware of in utilizing them in the global health community?
- Who are the exact stakeholders that such criteria should be communicated with, and how? PDPs, funders (governments and philanthropical organizations), and others?
- What approaches does each entity use to develop organizational strategies? Will success criteria of PDPs help, and how/why?

The interview method was consistent with the widely accepted approach utilized in a qualitative study, such as raising open-ended questions instead of leading questions, and starting with broader questions before asking specific ones.[60] The prompts were included in the interview

if/when needed to clarify and/or probe the interviewees' responses.

Study subjects

Study subjects intentionally included respondents representing various sectors and expertise to allow for capturing balanced perspectives from different/diverse angles.

PDPs:

PDPs working in the field of neglected diseases primarily affecting low- and middle-income countries were identified, and interviews were conducted.

Funders:

The top ten public funders in the global health R&D area were identified using 2018 G-Finder data, and interviews were conducted with some of them in decreasing order of funding amount.

In a similar manner, the top ten philanthropic funders in the global health R&D space were identified using G-Finder data. Interviews were conducted with each funder in decreasing order of funding amount.

Various other organizations (academic organizations, pharma companies, etc.):

Other stakeholders in the field of product development such as international organizations (e.g., WHO, Global Fund), pharmaceutical companies, universities, and global health professionals that are working directly with and for PDPs were also identified for interviews.

With regard to who were interviewed, individuals who possess in-depth knowledge and experience regarding their organization's strategy and are in a high-level management position were identified and interviewed. With respect to the sample size, approximately thirty

interviews were expected to be conducted, in order to maintain the validity of analysis[61] and to make the analysis pragmatically feasible. Interviewees were carefully identified and selected in close consultation with supervisors. Data collection was discontinued once saturation was achieved (i.e., same themes recurring, and no new insights are obtained from additional interviews) for each category.

3.3.2 Quantitative analysis with mixed methods approach

Perspective

It was expected that the qualitative analysis with key stakeholders (Objective 1) would result in the identification of determinants for the success and failure of the PDP model. As noted in previous sections, several organizations have analyzed the quantitative aspect of the PDP model and its effects, but not yet in a holistic manner to cover all, or a majority, of PDP type organizations. For instance, then-DfID and German Ministry of Education and Research (BMBF)'s evaluation of PDP funding activities use the "three Es" (economy, efficiency, and effectiveness),[62] but it only examined the value of their investments in the three PDPs: FIND, DNDi.

Building on results gained from the preceding qualitative analysis, this study aimed to conduct relevant quantitative analyses to further bolster the results and pave the way to the ensuing discussion concerning the development of policy recommendations to the global health community. Objectives 1 and 2 took place sequentially via an iterative process to triangulate with and enhance the results of each other.

The linkage from the preceding qualitative analysis

The preceding qualitative analysis with semi-structured interviews identified the roles of PDPs

in advancing global health R&D to a great extent; some argue that most or many of the products developed by the work of, and/or in collaboration with, PDPs may not be novel or innovative, but rather just a combination/repurposing of other existing therapeutics.

In order to determine how PDPs have helped advance innovations in the global health space, it would be informative to consider the impact brought about by investing in PDPs and understand how innovative products have been developed. To this end, an input-output analysis was performed. Specifically, the amount of investment for each PDP was investigated, which was then compared by the number of new chemical entities (NCEs) developed by the corresponding PDPs as well as that of products using a combination/repurposing of technologies. These data were compared with similar parameters from pharmaceutical companies, if and where possible, in order to examine the efficiency of PDPs.

The qualitative study with semi-structured interviews also revealed various important factors for the PDP business model as described in the later chapter of results. It was noteworthy that many interviewees identified the successful inclusion and engagement of LMICs, to be one of key contributions that the creation of PDPs has made. Some emphasized that continuous engagement of LMICs in global health R&D activities would be critical. Others also stressed that the pharmaceutical industry continues to be the key to achieving goals of each PDP.

As most interviewees noted, PDPs cannot achieve their goals on their own. Rather, the majority of their work depends on the capacity and capability of other entities through their partnership model with LMICs particularly regarding clinical studies. Sustaining sufficient levels of engagement and contribution from LMICs is thus concluded to be one of the most critical components of PDPs as a whole.

With these points in mind, the trend in terms of the partnerships with LMICs was investigated as part of a subsequent quantitative study. Quantitative data on the trend in the number of partnerships with LMICs were bolstered with additional key stakeholder interviews (i.e., Objective 3: additional interviews as part of "Mixed Methods Approach") to identify factors that enable such partnership creation.

Key Research Question

How can the success and failure of PDPs be measured quantitatively? How is each PDP doing in accordance with the key determinants such as the metrics described above in Perspective?

After completing the initial interview process

Based on the considerations derived from the semi-structured interviews conducted as part of the qualitative study as described above, the following components were further examined as part of Objective 2.

- Input-output analysis on PDPs (Objective 2-1)
- Comparison of efficiency between PDPs and multinational pharmaceutical companies (Objective 2-2)
- PDP partnerships in LMICs (Objective 2-3)

Objective 2-1: Input-output analysis

With regard to the funding amount received by each PDP, G-Finder 2012 was used for years 2007-2008.[63] For years 2009-2018, G-Finder 2019 was used.[64] For years 2006 and prior, and 2019-2020, individual annual reports of PDPs were used. The number of products developed by each PDP was extracted from a relevant article.[65] The funding amount required to develop a product and take it to market was then calculated by dividing the total amount of funding by the

number of products developed.

Objective 2-2: Comparison of efficiency between PDPs and multinational pharmaceutical companies

The top 10 multinational pharma companies with the greatest revenue in 2020 were identified (pharma segments only)[66] and each company's website was searched for activities related to global health; the search was limited to medicines and vaccines as anti-infectives. PDP websites were also reviewed to catch products that may not have been highlighted on company websites. The literature and review articles we targeted in our search for recently approved products or products in late-stage development were related to neglected diseases. HIV/AIDS products were not included as they attract an inordinate amount of R&D relative to other global health products.

Objective 2-3: PDP partnerships in LMICs

The data pertinent to PDPs' partnerships with and in LMICs were collected from various resources such as the websites, annual reports of PDPs, and other publicly available information. The obtained data were then categorized into the following segments: the number of regional offices in LMICs, training and laboratory strengthening for LMICs, influencing national decision-making in LMICs, and connecting and mobilizing local stakeholders in LMICs.

3.3.3 Additional semi-structured interviews as part of Mixed Methods Approach

Perspectives

Based on the results of Objective 1-2 (described in the Results chapters later), it was revealed that there are several areas for further consideration with regard to PDP's business model and its efficiency. Specifically, the following points warranted careful deliberation. As previously

discussed in the Phase Matrix and Methodology sections, several interviewees have been asked these points/questions—again—as part of the iterative process between the qualitative and quantitative analyses ("Mixed methods approach").

- Judging by the funding amount and the number of products developed quantitatively, the amount of funding required for each PDP seems to be lower than the traditional cost of R&D to develop one drug. However, one could counter argue that the majority of products may be considered "not so innovative," as only 4.6% of products developed by PDPs are focused on innovative mechanisms (i.e., NCEs). How could PDPs defend themselves against such an argument? What could have happened if PDPs had not been involved in the development of innovative global health products such as acoziborole, LXE-408, fexinidazole, tafenoquine, RTS,S, and pretomanid?

- Based on publicly available data and information, it seems difficult to make a head-to-head comparison between PDPs and pharmaceutical companies in developing a new product for global health, as most pharma companies actually work with PDPs (over 80% in the case of therapeutics) for such activities. What are the reasons that necessitate pharmaceutical companies to partner with PDPs in developing a global health product? Drawing on this, what would it take to further enhance/expedite global health R&D—any roles expected from PDPs and/or other stakeholders?

- While many PDPs provide statements that emphasize the importance of partnerships with LMICs, upon closer inspection, only a limited amount of data/information seems to be available with respect to the impact and level of engagement/involvement in and with LMICs. From a long-term perspective, would this be something that should be considered/addressed further?

Based on the contents of potential questions to be asked, the list of potential candidates to be interviewed were created in a close consultation with supervisors.

Data Collection

A total of six interviews were conducted as part of the qualitative study ("second-batch"). Below is a summary of these interviews.

- Period: June 2022 – September 2022
- Mode: All interviews were conducted via video conference.

Interviewees: A total of seven candidates were selected in consultation with both supervisors. These candidates represent various types of entities such as PDPs, pharmaceutical companies, bio-venture companies whose expertise was expected to address the above additional key questions arising from the preceding qualitative analyses from the 'first-batch' of interviews along with the quantitative analyses. Seven candidates were contacted via email, of whom six agreed to participate in the interview; one did not respond.

3.4. Data analysis process

Data analysis for semi-structured interviews (Objectives 1 and 3)

After completing the interviews with key stakeholders as delineated above, interview contents were immediately transcribed. A deductive and inductive approach was taken in analyzing the qualitative data in order to examine 'a priori' themes and identify emerging themes in the interviews. For the deductive analysis, thematic analysis served as the guiding framework, particularly in identifying ana applying pre-determined themes that were informed by existing literature on PDPs and global health R&D. The interview content was analyzed using NVivo (NVivo 12.6.0). A thematic analysis approach was used to analyze the data, which were

expected to represent both a priori and emerging themes. Interviews were transcribed and analyzed simultaneously with thematic headings; therefore, it allowed for identification of emerging themes to be further explored in subsequent interviews. Interview questions described above were continuously updated.

A common analytic framework was developed in order to identify common themes across all PDPs, as well as those that are specific to individual PDPs[67]. The analytic framework of interviews was critically reviewed by supervisors and advisors of the study in order to maintain and enhance the validity of findings.

Data analysis for quantitative study

According to the key determinants identified, the relevant data from existing resources such as literature and other publicly available information were gathered. Specifically, data and information on the products and pipeline of each PDP were explored. Financial aspects of PDPs were collected on their websites. Data pertaining to funding for each PDP from donors were available in many cases from G-FINDER, which were also used to analyze aspects relating to various funding routes for each PDP.[15] If there was limited data available and further clarification was required on top of the publicly available information, relevant questions were posed during the in-depth interview processes in Objective 3 (i.e., "second-batch interviews"), if/where appropriate. Analysis was conducted based on the collected data and information to elucidate quantitative characteristics of PDPs in their entirety, as well as those of individual PDPs against each of the key metrics.

3.6. Study bias and mitigation measures

The rigorous methodology employed in this study, comprising qualitative and quantitative

analyses using a mixed methods approach, demands careful consideration of potential biases. Qualitative research, by its nature, involves various challenges that may influence the quality and interpretation of the findings. To address these challenges, the study has incorporated measures to minimize potential sources of bias.

Researcher Characteristics

As a researcher, my background as a medical doctor and my role as a director in a funding organization may introduce certain biases. To mitigate these biases, particular attention was given to maintain a neutral and unbiased stance throughout the research process. This involved transparent communication with interviewees, emphasizing the study's non-partisan nature, and the genuine aim to comprehend their perspectives. Furthermore, ongoing self-reflection and awareness of my dual role were integral in preserving impartiality and objectivity during the research. It was also made clear periodically during the interview process, when deemed necessary, that I was "wearing a graduate student hat, not a GHIT (i.e., funder) hat for the interview," so that both the interviewee and I were aware of this throughout the interview process.

Potential Responder and Researcher Biases

Responder and researcher biases are recognized challenges in qualitative research[68]. These biases could be compounded when the researcher is an outsider, in this case, a foreign investigator conducting interviews with stakeholders intricately involved in global health R&D. To counteract this, it was imperative to assure interview participants of the study's independence from any financial or political affiliations. Emphasis was placed repeatedly on understanding the participants' viewpoints on issues related to the research, fostering an environment for candid and honest responses.

Cultural Awareness and Bias

While conducting interviews with a diverse range of stakeholders involved in global health R&D, it is essential to remain vigilant regarding potential cultural awareness and bias issues. Although no significant cultural bias was readily apparent during the interview process, it's important to acknowledge that nuances and cultural factors may influence the responses and perspectives of interviewees.

To address this, several measures were in place to ensure a respectful and culturally sensitive approach. These included, but were not limited to, an initial familiarization with the cultural contexts relevant to the interviewees/interviewer and a commitment to approach discussions with openness and sensitivity. The aim was to foster an environment where participants felt comfortable sharing their insights and opinions.

Furthermore, the interview process followed a well-structured, semi-structured format that allowed interviewees to express themselves freely. Open-ended questions and a flexible conversational style were employed to accommodate different communication preferences and ensure that interviewees felt at ease.

This proactive approach, combined with the reflective stance of the researcher, aimed to minimize the potential for any cultural awareness or bias-related issues and to create a space where authentic insights could be shared. It's important to emphasize that these measures were implemented to uphold the quality and reliability of the study findings, fostering an environment of mutual respect and understanding during the interview process.

Interview Technique and Biases

To reduce acquiescence and social desirability biases, which can manifest when participants

provide answers to please or align with the researcher, specific measures were taken, as partially described above. Specifically, interviews commenced with broad, non-controversial questions before delving into more sensitive topics. Indirect and multifaceted questions approached topics from various angles, diminishing the risk of participants providing expected or favorable answers. Additionally, the researcher's body language was deliberately remained neutral, even via videoconference, refraining from implying right or wrong answers.

3.6. Reflexivity and positionality

This research is underpinned by the background and experiences that I bring as a medical doctor with a transition into a role within an international funding organization that actively collaborates with PDPs. The journey leading to this study was catalyzed by the interactions and observations made while navigating the complex landscape of global health R&D.

My transition from a medical practitioner to a leadership role in a funding organization has equipped me with a unique vantage point. On one hand, my medical background has nurtured a profound understanding of the clinical aspects and patient needs within the healthcare system, particularly in the context of neglected diseases. On the other hand, my role within the funding organization has provided insights into the intricate dynamics of global health financing, research, and innovation.

It is essential to recognize that my positionality as a medical doctor and a professional within a funding organization inevitably influences the research process. The motivations for this study are deeply rooted in the aspiration to advance the mechanisms of PDPs, subsequently enhancing product development for neglected diseases. These motivations stem from a genuine interest in the global health landscape, driven by a commitment to finding avenues for improving healthcare delivery and making a meaningful contribution to the eradication of neglected

diseases.

In this context, the research inherently reflects my enthusiasm for driving change and fostering innovation within the global health arena. While this enthusiasm is a driving force, it is critical to acknowledge the potential for bias, stemming from a certain degree of optimism regarding the potential of PDPs in addressing the health needs of marginalized populations. However, this optimism is complemented by a scholarly obligation to critically evaluate the effectiveness and efficiency of PDPs, addressing not only their successes but also the challenges and ambiguities that may exist.

Furthermore, my position as a funding organization representative who interacts with PDPs frequently positions me as an "insider" to some extent. This may influence the response dynamics during interviews. While I have strived to maintain objectivity, the interviewees may perceive me as having a vested interest in the success of PDPs. Hence, this study has embraced meticulous efforts to mitigate potential bias by maintaining a reflexive and open stance, adhering to ethical research principles, and allowing interviewees to express their unfiltered views.

In essence, this study is a product of my journey, motivated by a holistic approach to improving the mechanisms of PDPs, informed by medical insights and operational experiences within a funding organization. The research process is marked by a commitment to ensuring rigor, objectivity, and a nuanced understanding of PDPs in the context of neglected disease research and development.

3.7. Ethics considerations

Approval was obtained from the ethical committee of Nagasaki University with respect to the

plan to conduct interviews with global health stakeholders (Appendix 3).

Informed consent

As described in the previous section, the interviewer explained the following to the interviewee before the interview took place. Interviewee consent, both verbal and in an official consent form, were required before proceeding with an interview (Appendix 1):

This semi-structured interview is aimed at learning more about your organization's strategy and decision-making process for the discovery, development, and delivery of global health innovation. The information from the interview will be used solely for the purpose of a study focused on drug discovery and development for infectious diseases. No presentation or discussion of an individual organization's strategy and decision-making process will be shared outside the study. A report summarizing aggregate observations is expected to be drafted. Do you consent to be interviewed?

After the interviewee agreed with the above, a semi-structured interview was conducted.

Data management procedures

This study handled both qualitative and quantitative data. Qualitative data included those from semi-structured interviews with stakeholders; quantitative data was those analyzed based on publicly available information and data pertaining to PDPs. Most data were analyzed in Microsoft Excel and Word. NVivo were also used to organize and analyze qualitative data obtained from interviews. The data management plan was duly approved by Nagasaki University's Ethical Committee in July 2020 (reference no. NU-TMGH_2020_070_4; Appendix 3).

All the datasets including recorded voice memo as well as transcripts that were generated thereafter were stored confidentially in the interviewer's Nagasaki University computer that was securely password-locked. The interviewer's computer was also protected using a security software.

All the data obtained from interviews will be securely stored for five years after the completions of the applicant's PhD programme. Thereafter, all dataset pertaining to these interviews will be discarded.

All the raw data pertaining to interviews as well as associated data (e.g., transcripts) will be discarded from the applicant's computer five years after the completion of applicant's PhD programme.

No sensitive or personal information will be collected during this project.

3.8. Conclusion

In this chapter, the methodology employed for this study, which seeks to elucidate the success criteria and mechanisms of PDPs in the context of neglected disease R&D was provided.

The study design was framed to facilitate a rigorous and holistic examination of PDPs, aligning with the mixed methods approach. The methodology seamlessly integrates qualitative analysis through semi-structured interviews with key stakeholders in the global health arena and quantitative analysis, informed by findings from these interviews. This mixed methods approach presents a robust strategy for examining the multifaceted dynamics of PDPs. Additionally, insights into the supplementary interviews conducted after the initial data analysis phase was also provided, further enriching the depth and breadth of the study.

A paramount focus has been placed on transparency and rigor throughout the data analysis process. The framework for data analysis has been structured with a commitment to revealing the nuances and challenges faced by PDPs, thus offering an authentic and comprehensive account of their operations.

However, it is important to acknowledge the limitations that exist within this study. The finite number of stakeholders interviewed, though considered sufficient, may not capture the full spectrum of perspectives. The potential for bias due to the relationship between the researcher and interviewees, as an official within a funding organization, is an inherent limitation that has been addressed with careful planning and mitigation measures.

The essence of reflexivity and positionality within the study has been openly discussed, recognizing the influence of the researcher's background as a medical doctor and as an individual operating within a funding organization. These personal attributes and experiences play a pivotal role in shaping the motivations and the overall direction of this research, emphasizing the need for a critical evaluation of PDPs.

Ethical considerations have remained at the forefront, with measures in place to protect the privacy and confidentiality of participants. The ethical approval obtained underscores the commitment to conducting this study with the utmost integrity and respect for the individuals involved.

These methodologies and considerations served as my compass, guiding me through the entire study process. The following chapters delve into the outcomes of the study, providing insights into the mechanics and efficacy of PDPs in global health R&D.

4 Chapter 4 Results of Semi-structured interviews

4.1 Introduction

This chapter marks the initiation of the triad of findings chapters within this thesis, delving into the intricate mechanism of PDPs within the global health R&D landscape. As elucidated in the preceding section, the findings presented here are the result of the first series of interviews with various global stakeholders in the field. These interviews followed the protocol outlined in the methodology section, and the subsequent data analysis was conducted accordingly.

This section embarks on a comprehensive journey through the details of these semi-structured interviews, unravelling the range of perspectives, viewpoints, and insights that collectively paint a portrait of the PDP business model's validity. The dialogues and discourses within these interviews provided multiple lenses through which the PDP landscape is observed and comprehended. These diverse viewpoints set the stage for ensuing discussions and the identification of key themes that warrant further exploration through subsequent quantitative analyses and additional rounds of interviews.

For the sake of clarity, the thematic revelations stemming from the semi-structured interviews have been thoughtfully organized into distinct components, ensuring an easily comprehensible format. This chapter thus serves as an initial exploration into the understanding of PDPs, revealing the first strokes of understanding while considering the path for future inquiries and analyses. The ensuing narrative allows for an immersive process of understanding the complexities and nuances of PDPs as articulated by those involved in global health R&D.

Data collection for semi-structured interviews

As a result of the above, a total of 26 interviews were conducted as part of the qualitative study. Below is a key summary for these interviews conducted.

- Period: May 2020 – June 2021
- Mode: All interviews were conducted in English via videoconference.
- Interviewees: A total of 30 candidates were selected in consultation with both supervisors. These candidates represent various types of entities such as PDPs, funders, international organizations, private sector, academia, and NGOs. Potential interviewees were contacted with the aim of having a diverse, balanced representation from various types of entities. Careful consideration regarding diversity was also given such that interviewees represented diverse, balanced backgrounds (e.g., gender, ethnicity, regions). The majority of candidates responded and confirmed their willingness to join, and partook in the interview thereafter, whereas only a few had difficulty setting up a meeting, mostly due to the COVID-19 situation. In total, 26 interviews were conducted, out of which nine were female (35%) and six interviewees (23%) were from NTD-endemic countries. In terms of ethnicity, eight (31%) were Asian, two (8%) were Hispanic/Latino, four (15%) were black, and twelve (46%) were Caucasian. A breakdown by type of organization for these interviews is shown in Table 2.

Type of organization	Number of interviews
PDP	4
Funder	4
International organization	3
Private-sector company	3
Academic instituion	4
National Government	3
NGO	5

Table 2 Interviews by type of organization

An overview of the themes that have emerged from these semi-structured interviews is shown below (Figure 6).

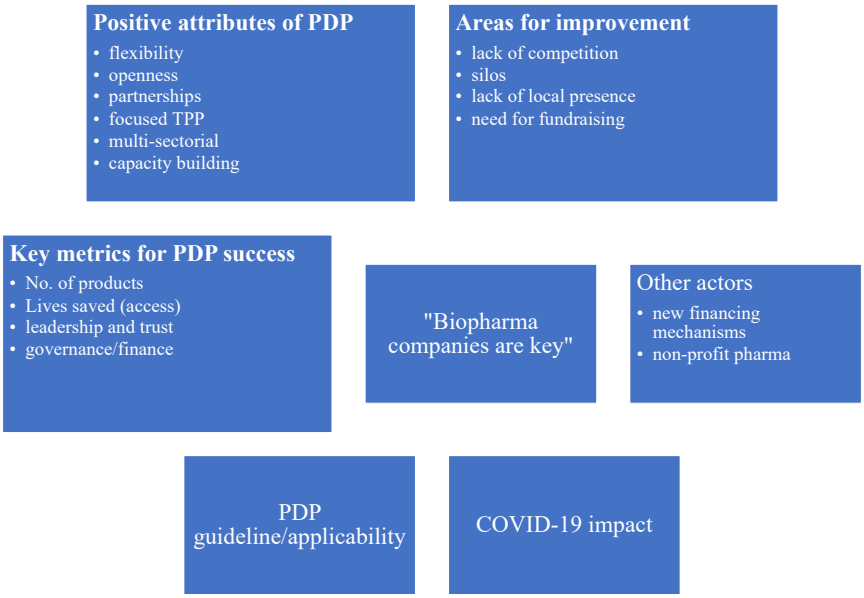


Figure 6. Overview of the themes emerging from semi-structured interviews

4.2 Positive attributes of PDP system – a wide range of advantages its business model can bring:

It was noteworthy that all interviewees responded that the PDP system, in general, has been successful and/or valid to address global health issues, while most added that there is room for further improvement. The interviews identified various advantages and benefits of the PDP model as shown below.

Flexibility

It was pointed out by many interviewees that the strength of the PDP system lies in its flexibility. In many cases, PDPs are smaller than pharmaceutical companies, which allows them to adapt to situations where "*markets are changing, focus is shifting*." Even within the same entity, different projects have different scopes, criteria, and arrangements. Therefore, "*being flexible about understanding the environment and what the issues are and adapting our*

[PDP's] approach and our [PDP's] model to that" becomes critical.

Openness – working 'together' with partnerships

By nature, PDPs focus on areas which have little or no commercial incentives. Therefore, it fosters an environment where people "*work together rather than compete.*" This is an advantage of the PDP model. In fact, many PDPs promote an open approach, share openly what they do, and publish freely – these elements help science and innovation work. These would be difficult for private sector companies due to intellectual property restrictions. MMV's example was presented in which many organizations proactively bring their projects from around the globe to work together to move them forward. One also commented that "*...there's much more an attitude and a flavor for sharing of information, sharing of knowledge, publishing results for the benefit of the entire community.*"

Partnership with various entities like academia

Many interviewees pointed out that PDPs have been successful in galvanizing and encouraging academia (research organizations, universities) and make an alignment between research and development. MMV's malaria box initiative was taken as an example to encourage the research community to help address the needs in drug discovery. It is noteworthy that many used the same word 'encourage' in describing the way PDPs have engaged the research community in the global health R&D space.

Focus area and Target Product Profile (TPP)

Having a specific focus (i.e., disease, intervention) also helps PDPs avoid "*becoming overcomplicated or overly big.*" In other words, it makes sense to have different PDP entities working on different missions while maintaining a relatively limited number of personnel and small size. It was also mentioned that the work of PDPs is important for providing clarity on

what it takes to eliminate their disease of focus. Hence, setting up the target product profile with this clear mindset and articulating it globally is critical "*so that anybody that wants to work in this field understands what the big problems are that need to be solved.*"

Multi-sectorial collaborations

Numerous interviewees emphasized that the distinct strength of PDPs lies in their ability to foster multisectoral collaborations from diverse perspectives. From a financial standpoint, PDPs are frequently recipients of funding from various sources. This characteristic allows the PDP system to capitalize on funding from a wide array of contributors, including governments, philanthropic organizations, and corporations. Interviewees, particularly representatives from PDPs, underscored that the diverse funding streams from various entities and sectors play a pivotal role in enabling PDPs and their collaborators to drive innovations in global health. Many interviewees also highlighted that, owing to their multisectoral nature and engagement with multiple stakeholders, PDPs are well-positioned to receive well-rounded feedback and insights regarding their strategies and other pertinent components. From an advocacy standpoint, for instance, it was noted that PDPs can effectively raise awareness of patient needs and encourage various stakeholders to engage in addressing the issue by leveraging their networks and collaborative frameworks with them.

Capacity building/field connections

Along with their clinical development work in endemic countries, some PDPs provide training at clinical trial sites. They could also help support local investigators, providing them with continuity rather than having personnel come and go frequently. DNDi, headquartered in Geneva, Switzerland, has a strong regional focus which allows them to be closely connected to patients and the field. Another example was shared in which a certain university in a disease-endemic area benefited from working with MMV – "*we didn't have the infrastructure because*

we didn't even know how to build it. But as we worked with MMV, it became clear what kind of infrastructure and technologies and skills that we needed to really bring on the ground to do this."

4.3 Area for improvement/further consideration

In contrast to the myriad advantages and merits intimately associated with the PDP business model, a substantial number of interviews have underscored the presence of several entrenched pitfalls, challenges, and dilemmas that are linked with the PDP mechanism, some of which intriguingly mirror aspects previously described as positive attributes.

Lack of competition / priority setting

Unlike the traditional pharmaceutical industry, where competition serves as a catalyst for innovation, PDPs operate in a unique landscape. The absence of direct competition might create a challenge – a risk of complacency. If a PDP perceives itself as already performing optimally, there may be a reluctance to seek further improvements. This lack of competitive pressure could inadvertently lead to the persistence of overlooked areas or "*blind spots*" within the PDP model. In relation to this, some interviewees also raised concerns around the need for prioritization. Several interviewees, from industry and academia, commented that there is an absence of a well-defined prioritization strategy within PDPs, signaling a call for more systematic project selection and emphasizing the urgent need for a structured approach to prioritize initiatives. The suggestion made by an interviewee from a pharmaceutical background was to embrace an 'early kill' stance, similar to practices in the pharmaceutical industry. This strategic approach involves directing resources toward the most promising projects, ensuring efficient allocation and maximizing impact, especially when resources are limited.

"Silos"

Although the PDP model makes sense in that each PDP has a different/separate focus, it was pointed out that there is much room for improvement in terms of sharing of knowledge and capabilities between different PDPs (e.g., PDPs working on the same disease but different interventions) or sharing development costs such as cheaper contracts with CROs with larger commitments. It was also stated that, with more coordinated work, PDPs could potentially reduce the amount of time/financial resources required for ethics and regulatory approval. Most of the interviewees mentioned a further need for better coordination among PDPs to reduce inefficiency and avoid duplication of work. Many interviewees also noted that PDPs should work on enhancing networks and connections with other PDPs to learn from their success in order to further advance innovations in the space of traditional interventions (i.e., therapeutics with small molecules, vaccines, and diagnostics), as well as technologies that have arisen in recent years (e.g., monoclonal antibodies[69], AI-based drug discovery) in order to transform global health R&D.

Lack of local presence/representation

It was mentioned that many PDPs do not have a local presence in the countries/areas where diseases are prevalent. "*….[PDPs] don't even have a local presence in the countries where the work is being done. And I think that's a disadvantage because the knowledge and the skills don't reside close to where the patient is.*" It was also pointed out that the boards of PDPs do not necessarily represent perspectives of the local people and hence are missing insight as to what is truly taking place on site. Some interviewees noted that they feel capacity building is not well embedded in the PDP strategy and that PDPs in general need to empower people (e.g., local scientists) in endemic regions to "*make a difference.*" One interviewee also stated that PDPs should be transparent about how much they spend in which country or region.

Constant need for fundraising

While the strength of PDPs is their ability to leverage multiple funding resources, it became clear that many see this from the opposite perspective, i.e., that PDPs by nature need to constantly raise money from various funders. Some seem to consider this to be a "*distraction*" instead of an opportunity as it could mean financial vulnerability. Some interviewees also stated that political instability (e.g., Brexit, US pulling out of WHO) could have a negative impact on funding for PDPs, and hence their sustainability. Some also commented that '*donor interference*' can sometimes be a challenge, especially if donors "*really want to be on the development part as well,*" to which they feel that clear roles and responsibilities between donors and partners including PDPs are required.

4.4 Key metrics for PDP success:

Several elements were raised as points of discussion for determining PDP success. Some interviewees indicated that the metrics have changed over time as the relevant organizations and PDPs have developed and the landscape has changed as presented and discussed in the earlier sections.

Number and quality of products / efficiency

The number of products is a straightforward way to measure success, as far as 'product development' goes. At the same time, however, one must be mindful of the danger of fixating too much on numbers, as the quality aspect might be dismissed or overlooked. One interviewee commented that "*I read just recently in a document that PDPs themselves had prepared that since 2010, developed more than 60 health technologies, and I think that's really a testament to the success of this model in such a short period of time.*" [PDPs – Keeping the Promise Report,

February 2021] In relation to this, the measurement of efficiency will be a key consideration. The PDP model employs pharmaceutical and academic expertise, without having any labs, infrastructure, or any fixed costs. Creating a collaborative framework with flexibility to outsource work where necessary could be an indicator of how efficient a PDP functions.

Access and delivery of product, "lives saved"

It was pointed out that what should be measured in the context of global health is "*lives saved*" for fatal diseases. For non-fatal diseases, the measure would be infections prevented or morbidity reduced. The success should be linked with "*delivering treatments to patients, seeing improvement in their health, saving lives and the socio-economic impact for those families and for the environments and the countries in which they live in.*" It is noteworthy that most of the interviewees considered the access and delivery component to be a critical indicator for PDP success. They stressed the importance of discussing access conditions for a product in the early (as early as possible) development stage.

Leadership and trust

Many identified leadership as an integral component of a PDP's success, since it also leads to building trust with relevant stakeholders. MMV was used as an example to illustrate how the interaction between academic researchers and MMV changed after MMV gained trust and respect by demonstrating a clarity of vision, and articulating that vision. Many also stated that the "*people element*" is strongly linked with the successful work of PDPs. One interviewee mentioned "*…so if you're talking about the key determinants is that you do good human resources management in the appointment of people*" and "*…the CEO or the president of a PDP must, him or herself engage because it is so critical that in the senior management, you really have people who work with head, heart and hand.*" Many interviewees also pointed out that PDPs require an independent, external body to review the progress of their work from both

strategic and scientific perspectives in order to ensure they deliver against their objectives – this will also ensure the "*scientific validity of PDPs*" as commented by interviewees (with pharmaceutical background).

Governance and finances

Interviewees with a pharmaceutical background noted that, similar to how executive leadership in companies is under tremendous pressure to deliver and reshape organizations, such pressure is also needed for the governance structure of PDPs. Many interviewees stressed the importance of PDP's being fully transparent about their strategy to engage relevant stakeholders. It was pointed out that financial aspects of the organization should be also handled properly – according to one interviewee, "*accountancy and reporting is [are] just absolutely sacred.*" It is also important for an entity to determine whether or not to work/continue working with a certain PDP – "*…so I don't want to see PDP bankrupt next year.*"

4.5 Biopharmaceutical companies are key

Interviewees highlighted the importance of biopharmaceutical industry—be it large-scale pharma companies or small-to-mid-size biotech companies— when discussing the work of PDPs and in the context of global health. One interviewee commented, "*...pharma is key obviously and will always be key. And in fact, I guess, the whole point of course is that pharma could do it all. And the only reason they don't is because there's no profit.*" Many pointed out that pharmaceutical companies can work on drug discovery and development in one place – allowing them to move quickly. The example of a certain pharma company which had one of their units become similar to a PDP was also mentioned: "*They closed down the therapy area, they made lots of people redundant, and they condensed down to just a few people who really*

knew it all here. And then all the work was outsourced with university partners and CRS. That's basically a PDP." Some interviewees expressed their concerns regarding pharma companies' continuous involvement in PDPs: "*I'm definitely concerned about our ability to retain the involvement of pharma going forward. I think it's very complex, but I think one of the key challenges we face is the lack of sort of market assurance that they see to make feel confident about investing as well as the opportunity costs.*"

4.6 Other actors

In the context of PDP work, there are multiple other actors one must be cognizant of such as universities, donors and funders, and public health stakeholders who play a major role in setting direction and strategy from the public sector perspective. The Bill and Melinda Gates Foundation and the aforementioned GMRI, a non-profit organization dedicated to the development and effective use of novel biomedical interventions addressing substantial global health concerns[70], were also raised in the interviews.

Novel, innovative financing mechanisms (e.g., GHIT, Unitaid)

In addition to the PDP business model, other financing mechanisms such as the GHIT Fund and Unitaid were mentioned during interviews as ways to supplement or bolster the work of PDPs.[71] CEPI was also taken as an example of a relatively new global health entity by some interviewees – "*....it's almost like a PDP hybrid with a GHIT Fund in some ways.*"

"Non-profit" pharmaceutical company model

A company called Medicines Development for Global Health was referred to multiple times during the interview process for its unique "non-profit" pharmaceutical company model. With funding from the Global Health Innovation Fund (GHIF), they developed the drug moxidectin

following the preceding development work by UNICEF, UNDP, World Bank, WHO TDR and Pfizer[72], and obtained a priority review voucher (PRV), which was then used to enable manufacturing and delivery of the drug. Some consider this business model to be self-sustaining, in particular as opposed to the traditional PDP model which requires constant fundraising.

4.7 PDP guidelines – its potential applicability and relevance

While some interviewees agreed with the idea of having guidelines for PDPs to create a vision for each disease and align with other PDPs as an integrated approach instead of working separately, many also identified the difficulty and risks (especially associated with generalization) of creating such guidelines, given the wide range of focus in terms of diseases and interventions across PDPs. One interviewee stated that "*...once you try to make guidelines, there is a risk of putting this[these] ideas inside a box and giving a cake recipe that everybody must follow and then after a while, you may lose some of these crazy ideas that are actually ideas of genius people. So, this is a downside I guess of developing a guideline.*" Many suggested that, if we are to have such guidelines, they need to be customized for each PDP to serve as a helpful tool for further improvement. Some also referenced the Access to Medicine Index (ATMI) for similar purposes, noting that "*creating such guidelines/tools usually require sufficient data/information, but without mandatory/obligatory procedures, it may be challenging to collect relevant data.*"

4.8 Impact of COVID-19

The impact of COVID-19 will be critical as there is uncertainty around funding going towards global health R&D. Funding for the PDP/global health R&D space could increase or decrease, so in essence there could be opposite scenarios. In February 2022, when this part of the work

was completed, it was reported that the global funding for poverty-related diseases remains virtually unchanged, with investment dropping only 4% in 2020[73]. The report states that the sustained investment in global health R&D is reassuring, but also warns that there could be potential impacts on funding in the future as it is still a preliminary stage after the pandemic started. Moving forward, in the worst-case scenario, one interviewee noted that, according to one paper, "*the number of cases and deaths are going back to what it was in the year 2000 approximately, we go back 20 years.*" Despite ongoing difficulties and challenges, it was noteworthy that a number of interviewees also see the current situation as a 'potential opportunity' for the global health R&D space since it has highlighted the significance of R&D and subsequent access to medicine, even for the general public. Some interviewees also mentioned that several PDPs have started to engage in the COVID-19 response while their original mandate was on different diseases.

4.9 Conclusion

The findings presented in this section are a reflection of the ideas and thoughts provided by a diverse spectrum of global stakeholders. The interviews followed a designated protocol, and the data analysis was conducted with precision.

The interviews, in this initial batch, expressed a general consensus that the PDP system has, to some extent, proven to be a successful and valid approach to address global health issues. However, it's worth noting that this affirmation is tempered by the acknowledgment that there is room for improvement. The discussions revealed a variety of advantages associated with PDPs, such as their adaptability, capacity for collaboration, encouragement of academic research, and their ability to define clear focus areas and target product profiles. They are also adept at leveraging funding from diverse sources. This collective sentiment underscores the role of PDPs

as influential entities shaping the landscape of global health R&D.

Yet, the interviews also unveiled several pressing challenges and concerns intrinsically linked to the PDP model. The absence of competition has the potential to lead to complacency, and prioritization issues need to be addressed. There are collaboration silos within and between PDPs that must be dismantled to promote more effective knowledge sharing and coordinated efforts.

Concerns were also raised about PDPs' limited local presence in endemic regions, prompting a call for more transparency and community engagement. While the constant quest for funding can be a strength, it's also seen as a vulnerability, particularly in times of political instability. Addressing these drawbacks is essential for the continued viability of PDPs in the evolving landscape of global health R&D.

These findings serve as the foundation for subsequent discussions and explorations, including additional interviews with key opinion leaders in the global health R&D sphere.

Additionally, the innovative financing mechanisms and 'non-profit' pharmaceutical company models discussed in the interviews hold potential for further transformation within this domain. The concept of PDP guidelines, while a subject of debate, offers potential for more holistic and integrated approaches.

In the context of an evolving global landscape due to COVID-19, the potential impacts on funding for global health R&D remain uncertain. The future is characterized by both challenges and opportunities, as the importance of R&D and access to medicine gains increased global attention. This chapter serves as a solid foundation upon which one could build a multifaceted

exploration of the PDP landscape, its impact, and means for further enhancements within the field of global health R&D.

5 Chapter 5 Results of Quantitative Analysis

5.1 Introduction

This chapter presents the quantitative analysis results, building upon the thematic groundwork laid out in the preceding semi-structured interviews. The insights garnered from those interviews have acted as the compass, directing our research towards three specific components: input-output analysis on PDPs, a comparative assessment of efficiency between PDPs and pharmaceutical companies, and an in-depth exploration of PDP partnerships within Low- and Middle-Income Countries (LMICs). The findings unveiled in this chapter are based on numerical data and statistical analyses, designed to provide a robust and impartial evaluation of the areas in focus.

Our exploration commences with an in-depth investigation of the intricate input-output relationships within the PDP realm. This component scrutinizes the resources poured into PDPs, the outputs generated, and the efficiency with which these partnerships operate. The ensuing sections delve into a direct comparison of PDPs with pharmaceutical companies, appraising their respective efficiency landscapes, which helps to delineate the niche PDPs occupy in the global health R&D space.

The chapter proceeds to shed light on the partnerships formed by PDPs within LMICs. Here, we dissect the nature and extent of these partnerships, with a particular emphasis on their economic and social dimensions. The objective lens of the quantitative analysis allows us to distill factual insights from the data, avoiding undue embellishment while providing a comprehensive

understanding of the quantitative aspects surrounding PDPs.

In this chapter, the overarching aim is to extend our understanding of PDPs, facilitating well-informed and pragmatic insights into their role within global health R&D. By examining the quantitative dimensions, we seek to enhance the empirical basis for future decision-making and discussions, paving the way for an objective evaluation of the strengths and limitations associated with the PDP model.

5.2 Input-output Analysis on PDPs

The results are shown in Table 3. The amount of funding required to develop a product and take it to market differed across PDPs. If focusing on PDPs working on the same or similar intervention, then the amount may be more similar. For instance, DNDi, MMV, and the TB Alliance primarily focus on new therapeutics, with 98.3, 88.3, and 112.1 million USD, respectively, required to take one product to be launched regardless of the development stage in which each PDP started investing. On the other hand, for FIND, whose primary focus is diagnostics, the amount of funding required for one product is much lower (15.0 million USD). This may reflect the relatively low cost required to develop a new diagnostic and/or absence of regulatory requirements as opposed to a therapeutic or vaccine.[74] The same rationale could be applied to IVCC (51.7 million USD), which focuses on vector control technologies.

While the above mentioned amount of funding calculated per one product seems to be somewhat lower than the average R&D cost traditionally required to develop a drug—1 billion to 2 billion[75]—there is also another component to consider. It is true that PDPs have taken multiple new products to market; however, only a few of these products are considered innovative. For instance, out of the 87 products developed by or in collaboration with PDPs, only five (5.7%) are based on new chemical entities (NCEs), i.e., fexinidazole, tafenoquine,

arterolane, RTS,S, and pretomanid. Using the same calculation above, the amount of funding required to develop an innovative product (e.g., NCE) and take it to market may be much higher for each PDP, bringing us back to the fundamental question of whether or not PDPs are truly efficient.

Table 3 Amount of funding and products for each Product Development Partnership

PDP (year established)	Funding received (USD millions)	Average annual funding received (USD millions)	# products in the R&D pipeline (as of Oct 2020)	# products registered (as of Oct 2020)	# products to market (as of Oct 2020)	# funding required for 1 product to market (USD millions)	# Truly innovative NCEs
Aeras (1997) [acquired by IAVI in 2018]	502.2 [2007-2018]	0.4	See IAVI	See IAVI	0	N/A	0
DNDi (2003)	786 [2003-2020] 2003-2008: https://dndi.org/wp-content/uploads/2009/03/ar2009.pdf 2019-2020: https://dndi.org/wp-content/uploads/2021/06/DNDi-FinancialPerformanceReport-2020.pdf	34.2	48	9	8	98.3	**1: Fexinidazole** - "Through an extensive compound mining exercise, DNDi screened more than 700 compounds from 15 different sources in academia and industry, in collaboration with the Swiss Tropical and Public Health Institute. These efforts led to the rediscovery of fexinidazole, which had been developed but abandoned for strategic reasons by Hoechst (now Sanofi) in the 1980s. Fexinidazole was funded for research on HAT at Glasgow University and in 2009, DNDi and Sanofi partnered to develop fexinidazole for HAT, with DNDi responsible for preclinical, clinical, and pharmaceutical development, and Sanofi responsible for industrial development, registration, and production." - Keeping the Promise Report, p. 34: https://static1.squarespace.com/static/5fa16fcb053b490d0db02488/t/601022f7aee2b960b2937c5d/1611670279200/KeepingThePromise-Report_2021.pdf
EVI (1998)	51 [2007-2018] Difficult to extract numbers in a consistent way with other organizations and in line with G-Finder methodology for 2019 & 2020, and prior to 2007	4.6	24	0	0	N/A	0

FIND (2003)	359.9 [2007-2019] 2019: https://www.finddx.org/wp-content/uploads/2020/12/Annual-Report-2019.pdf	27.7	47	27	24	15.0	N/A
IAVI (1996)	915.2 [2007-2020] 2019-2020: https://www.finddx.org/wp-content/uploads/2020/12/Annual-Report-2019.pdf]	65.4	29	0	0	N/A	0
IDRI (1993)	158.2 [2007-2019] 2019 #s from Form 990 https://apps.irs.gov/pub/epostcard/cor/911608978_201912_990_202104121792643.pdf]	12.2	16 [data from IDRI website]	0 [internet searches]	0 [internet searches]	N/A	0
IPM (2002)	506 [2002-2019] 2002-2006 (funding available as of Dec 31, 2006): https://www.ipmglobal.org/sites/default/files/attachments/IPM%20Annual%20Report_2006_FINAL_eng.pdf 2019: https://ipmglobal.org/report/2019/financi	28.1	13	0	0	N/A	0
IVCC (2005)	258.5 [2007-2020] #s reported in sterling, used exchange rate of 1USD=0.73£ on Sept 27, 2021. https://www.ivcc.com/wp-content/uploads/2020/12/IVCCOV96-Annual-Report-2020-v8.pdf	18.5	16	5	5	51.7	0

IVI (1997)	207.5 [2007-2020] https://www.ivi.int/wp-content/uploads/2021/05/IVI-Annual-Report-2020-vf.pdf	14.8	8 [data from IVI website]	2 [data from IVI website https://www.ivi.int/what-we-do/develop/]	2 [data from IVI website https://www.ivi.int/what-we-do/develop/]	103.8	0
MMV (1999)	1,147.4 [2002-2020] 2002-2006 extracted from "income" paragraph (p. 40) in 2006 Annual Report: https://www.mmv.org/sites/default/files/uploads/docs/publications/3_-_FINAL_FOR_WEB_mmvAR06_LowRez_3.pdf Note: numbers may be inflated due to difficulty calculating new income vs continued funding for 2019-2020. https://www.mmv.org/sites/default/files/uploads/docs/publications/annual_report_2017/annual_report_2020/9.%20Finance_chapter_2020.pdf	60.4	37	14	13	88.3	**2: Tafenoquine and arterolane** **Tafenoquine:** From a 2013 interview with Project Leader, Dr JP Kleim: "It was a unique and ground-breaking agreement and it set the tone for collaboration on many other projects, including tafenoquine. There is a lot of synergy between the partners; both bring very different skills to the table. It's really MMV that oversees the entire portfolio of investigational antimalarials. MMV has established governance and oversight committees of malaria and drug development experts that simply don't exist anywhere else. Our senior review committees at GSK always take ESAC advice into consideration. Additionally, the expertise and network at MMV, spanning the public and private sectors as well as malaria-endemic regions, has been crucial to the progress of our efforts to tackle malaria." - https://www.mmv.org/newsroom/interviews/mmv-project-year-award-2013-tafenoquine **Areterolane**: Arterolane was investigated for its antimalarial properties by Ranbaxy Laboratories, with support from MMV. It is a unique and novel endoperoxide with both an ozonide group and an adamantane substituent. Despite initial setbacks and the withdrawal of MMV's support in 2007 after a $20 million investment, Ranbaxy continued development independently. Ranbaxy received approval to market the arterolane/piperaquine combination drug in India in 2012 under the brand name Synriam, and in several African countries in 2014. https://www.business-standard.com/content/b2b-pharma/ranbaxy-receives-approval-for-malaria-drug-synriam-from-7-african-countries-114121700050_1.html

PATH (incl. MVI) (1977)	1,250.2 [2007-2018] Annual report available for 2019 & 2020 but revenue numbers in these and previous annual reports and 990s are so much higher than G-Finder levels I am not comfortable adding annual report #s, as the algorithms seem to be very	104	44	32	29 (7 have been discontinued)	43.1	**1: RTSS** "The RTS,S vaccine was conceived of and created in the late 1980s by scientists working at SmithKline Beecham Biologicals (now GSK Vaccines) laboratories in Belgium. The vaccine was further developed through a collaboration between GSK and the Walter Reed Army Institute of Research in the U.S. state of Maryland and has been funded in part by the PATH Malaria Vaccine Initiative and the Bill and Melinda Gates Foundation." - https://en.wikipedia.org/wiki/RTS,S
Sabin Vaccine Institute (1993)	31.3 [2007-2018] Audited statements available but difficult to match G-Finder algorithm]	2.6	3 (difficult to verify - looked at 2020 Annual Report https://yearly.report/from/#/sabin-	0 [internet searches]	0 [internet searches]	N/A	0
TB Alliance (2000)	672.3 [2007-2019] 2019: https://www.tballiance.org/sites/default/files/assets/TBAlliance_2019-Financial-Statement.pdf	51.7	32	6 (pediatric products are counted separately as they are manufactured and used separately)	6	112.1	**1: Pretomanid** - Pretomanid was first identified in 2000, in a series of 100 nitroimidazopyran derivatives synthesized and tested for antitubercular activity, by PathoGenesis (now a subsidiary of Novartis). - Stover CK, Warrener P, VanDevanter DR, Sherman DR, Arain TM, Langhorne MH, Anderson SW, Towell JA, Yuan Y, McMurray DN, Kreiswirth BN, Barry CE, Baker WR (2000). "A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis". Nature. 405 (6789): 962–6. - "TB Alliance initially in-licensed pretomanid in 2002, leading it through a full clinical development program; the FDA submission ultimately detailed data from a total of 19 clinical trials." - Keeping the Promise Report, p. 32: https://static1.squarespace.com/static/5fa16fcb053b490d0db02488/t/601022f7aee2b960b2937c5d/1611670279200/KeepingThePromise-Report_2021.pdf
TBVI (2008)	58.2 [2009-2020] #s reported in sterling, used exchange rate of 1USD=0.85€ on Sept 26, 2021. Note: 2019&2020 income in Annual Report representa sharp decline from G-Finder income reported in earlier years. https://www.tbvi.eu/wp-content/uploads/2021/06/Financial-	4.8	10	0	0	N/A	

5.3 Comparison of efficiency between PDPs and pharmaceutical companies

Analysis results are shown in Table 4. Of the 22 known global health products (16 therapeutics and 6 vaccines), for which the top 10 multinational pharma companies contributed to R&D, 4 have been approved by regulatory authorities and are currently available for the target indications: the first 2 Ebola vaccines, the first all-oral treatment for sleeping sickness, and the first dengue vaccine. Each pharmaceutical company has partnered with universities, research organizations, and/or PDPs to create nearly all of these products; pharmaceutical companies in particular have collaborated with PDPs to create 13 products out of a total of 16 therapeutics (81.3%). Notably, in a stark contrast, none of the 6 vaccine products have apparent partnerships with PDPs, although all of them have partnerships with universities or research organizations.

This suggests that multinational pharma companies do not seem to engage in global health R&D without partnership of PDPs, governments, research institutions, or donors, particularly when developing new therapeutics for global health. Therefore, evaluating the efficiency of these companies in producing truly innovative global health products against the efficiency of PDPs seems very challenging, as companies rarely engage in such R&D without partnering with PDPs or equivalent entities. This is to say nothing of the fact that little information is available on the costs associated with the development of the various agents. The opposite phenomenon we see for vaccine development may result from the profitability associated with the targeted viral diseases (e.g., dengue).

Table 4 Global health (anti-infective) products by top multinational pharmaceutical companies

Product	Type of Agent/Innovation Level	Target Disease	Stage/Outcome	Partners/PDP	Company's Role	On Market?
Abbvie						
-	Bumped kinase inhibitors (BKIs) Highly innovative; no BKIs yet approved	*Cryptosporidium*	At preclinical stage; working on identifying a potential clinical compound for further testing[76]	U. Washington	Supplying BKIs	No
DNDI-6174	Highly innovative: described as new mode of action	Visceral leishmaniasis	Preparing for pre-clinical studies[77]	DNDi	Collaborating with DNDi on preclinical studies	No
TylAMac (ABBV-4083)	Oral macrolide-based antibiotic Approach (targeting worms' *Wolbachia* endosymbiotes) is innovative; could lead to oral treatment regimen of a week or less	Filariasis (river blindness), onchocerciasis (elephantiasis)	Phase I studies showed TylAMac is safe, well tolerated; DNDi is preparing to launch a phase II proof-of concept study for river blindness, as well as a phase II study for elephantiasis. [78,79] The elephantiasis trial was registered with WHO in 2021.[80]	DNDi	Helped lead screen of anti-infective compounds	No
Amgen						
AMG 634	PDE4 inhibitor Moderately innovative: multiple PDE4 inhibitors are already approved to treat	Tuberculosis, leprosy	Phase 2 trials set to begin in 2021[81]	Medicines Development for Global Health (MDGH)	Licensed compound to MDGH, supplying drug and compound for phase 2 clinical trials	No

	inflammatory skin and lung diseases					
Bristol-Myers Squibb						
CC6166	Novel class Highly innovative	*Onchocerca guttura, Onchocerca lienalis*	Preclinical studies[82]	DNDi	Developed compound, turned project over to DNDi in late 2020	No
Johnson & Johnson						
Flubendazole	Benzimidazole Not so innovative; already used to treat human intestinal worms	Filariasis (river blindness), onchocerciasis (elephantiasis)	Abandoned. Parental route not compatible with field-based NTD indication; intramuscular injections caused inflammatory reactions at injection site; oral formulation had poor bioavailability; may be carcinogenic.[83]	DNDi	Discovered and developed agent; provided drug, scientific assistance, funding, and technical expertise	Yes, but not for this indication
Zabdeno + Mvabea	Monovalent + Multivalent filovirus vaccine combination Highly innovative, but 2 doses required (not suitable for emergency response)	Ebola	Approved by EMA, pre-qualified by WHO[84], not yet approved by FDA	Bavarian Nordic, NIH, others	Took lead in development alongside Bavarian Nordic	Yes
V180	Recombinant subunit vaccine Has potential to be very innovative if it can be used on its own, with an adjuvant, or as a	Dengue	Phase I trials complete[85,86]; no active clinical trial on clinicaltrials.gov, though, or updates since 2019	Various universities, NIH	Very active in development	No

	booster for a live attenuated tetravalent vaccine being developed by NIH (and if it has fewer safety concerns/restrictions than Dengvaxia)					
Ervebo (rVSV-ZEBOV)	Highly innovative, first Ebola vaccine, single dose	Ebola	Approved by EMA, FDA; pre-qualified by WHO	Various research partners	Very active in development	Yes
Also shares compound library with PDPs[87]						
Novartis						
Ganaplacide (KAF156)	Imidazolopiperazine Very innovative; new class of agents	Malaria	Novartis website reports phase II study in Africa, Asia[88]; WHO registry lists multiple phase 2 trials of KAF156 plus lumefantrine in pediatric and adult patients with uncomplicated *P. falciparum* malaria	Medicines for Malaria Venture, Swiss Tropical Public Health Institute	Has done much of the work to develop, along with partners	No
Cipargamin (KAE609)	Spiroindolone Very innovative; new class of agent	Malaria	Currently being investigated in phase II study in Africa[89]; results thus far are promising, if agent is used as part of combination therapy[90]	Medicines for Malaria Venture, Swiss Tropical Public Health Institute	Helped develop agent	No
KDU731/ED1048	PI4K inhibitor Very innovative; new class of agent	*Cryptosporidium*	Can't find any updates since 2018, at which time it was still undergoing preclinical testing. May have been abandoned.[91]	University of Georgia, Washington State University	Helped develop, test agent	No
LXE408	Kinetoplastid proteasome inhibitor	Visceral leishmaniasis	Phase I study began in 2020 but faced delays due to COVID-19; results expected in 2021. Phase II study to commence in India in 2022.[92,93]	University of York, University of Washington, University of Glasgow, DNDi	Led partnership that discovered agent	No

	Very innovative; represents optimized version of another agent (GNF6702) that Novartis has been developing for some time					
NITD-688	Tetrahydrothienopyridine Very innovative	Dengue fever	Have completed initial preclinical safety studies, expect to begin clinical trials in 2021.[94] Can't find any registered yet.	In a recent research article on this agent, the only external author listed was at Utah State University.[95]	Sounds like they are developing it	No
Pfizer						
Acoziborole	Benzoaxaborole Very innovative	*T.b. gambiense* (sleeping sickness)	Waiting for final study report for phase II/III clinical trial in Africa[96]	DNDi	Initial hit identified in Anacor's chemical library (Anacor was acquired by Pfizer in 2016)	No
DNDI-6148	Oxaborole Very innovative	Visceral, cutaneous leishmaniasis	Phase I study underway, another expected to start in 2022[97]	DNDi	These were from AnaCor which was bought out by Pfizer. Anacor, started by ex-Abbott staff developed a whole series of boroles.	No
		Chagas disease	Phase I studies planned[98]			No
Roche						
Couldn't find any involvement in R&D for global health medicines or vaccines, but Roche is active in developing diagnostics for diseases such as Zika, Ebola, etc.[99]						
Sanofi						
Dengvaxia	Live attenuated vaccine Very innovative (first Dengue	Dengue	Approved by FDA, EMA, many other countries	Ostensibly limited to local trial sites	Led development	Yes, with limitations

	vaccine), but also controversial, with many restrictions on its use for safety reasons[100]					
Fexinidazole	Nitroimidazole Innovative; first all-oral treatment for sleeping sickness	*T.b. gambiense* (sleeping sickness)	On WHO Essential Medicines List, approved by EMA, FDA[101]	DNDi	Involved in development, manufacturing, and distribution of agent while it was being studied	Yes
		Chagas disease	Phase II trial results expected in 2021[102]	DNDi	Involved in development, manufacturing and distribution of agent while it is being studied	Not for this indication
Takeda						
S07 lead chemical series	Unclear/not available Very innovative	Leishmaniasis	Have identified 2 promising candidates for pre-clinical study, are now characterizing them[103]	DNDi	Collaborating with DNDi on optimization, characterization	No
DENVax (TAK-003)	Live attenuated vaccine Has potential to be very innovative if it has fewer safety concerns than Dengvaxia and can be used in patients without previous dengue infection. Data promising so far.	Dengue	Phase I and II trials complete, phase III trial underway; Takeda has filed marketing authorization application with EMA[104]	Looks like no PDPs, Takeda took the lead	Takeda has taken the lead	No
DNDI-5561	Aminopyrazole	Leishmaniasis	Development stopped in 2019 due to unfavorable safety results in pre-clinical studies[105]	DNDi	Collaborated with DNDi; originally from Pfizer library	No

TAK-426	Inactivated, adjuvanted, whole Zika virus vaccine Very innovative	Zika	In a phase I trial, vaccine was well tolerated, had an acceptable safety profile, and was immunogenic.[106] It is slated for further development, but no new trials are currently registered.	US Department of Health & Human Services' Biomedical Advanced Research & Development Authority (BARDA)	Takeda appears to be taking the lead based on the publication describing the Phase I trial	No

5.4 PDP Partnerships in LMICs

The results are shown in Table 5. While several articles suggest that PDPs play an important role in health R&D capacity strengthening in LMICs,[107] which is critical to accelerating the development and dissemination of high-impact, cost-effective health technologies for use in disease-endemic countries,[108] it turned out that collective quantitative data do not consistently exist on the specific number of PDP partnerships with LMIC-based entities or how that number has evolved over time; the financial investment of PDPs (collectively or individually) in partnerships with and within LMICS; the percentage of PDP partnerships with entities in LMICs vs those in wealthy countries; or the impact of those partnerships on global health R&D progress or capacity.

Except for DNDi, which does provide data in some Annual Reports on percentage and number of partnerships with LMIC-based entities, most PDPs provide statements about the value of partnerships and broad descriptions that partnerships are plentiful, but rarely do they provide specific data about how and with whom they partner at a macro level. At a micro level, many PDPs offer limited data on numbers of people trained or laboratories strengthened on their websites or in annual reports, though this data is typically snapshot-based, not tracked over time, and not provided consistently from year to year.

Table 5 Product Development Partnership (PDP)'s partnerships with and in low- and middle-income countries

			Achievements & examples		
PDP	**# Partnerships in LIMICs**	**# Regional offices in LMICS**	**Training and laboratory strengthening for LMICS**	**Influencing national decision-making in LMICS**	**Connecting and mobilizing local stakeholders in LMICs**
DNDi[109] [110] [111]	200+ partners and service providers in 40+ countries; 51% of R&D partners are in LMICs 66% of all R&D partner FTEs are in Africa (as of 2020) 37% of DNDi R&D partners (as of 2020) are in LMICS	6 (Brazil, DRC, India, Kenya, Malaysia, South Africa)	6,700+ health personnel trained since 2010 The #2 imperative in DNDi's current Strategic Plan: Joining with public health leaders and R&D actors in LMICs to advance sustainable innovation ecosystems that address neglected patients' need	DNDi's experience and lessons learned are documented and disseminated to influence multiple policy processes – from WHO, G7/G20, and the UN to national and regional policy forums and funders – particularly around core principles and practices that enable needs-driven R&D (e.g., open sharing of research data and R&D costs, and pro-access management of IP and licensing).	4 clinical research networks created for target diseases in Africa and Latin America, bringing together 500+ researchers across institutions in dozens of LMICs to support and strengthen R&D capacity, promote scientific exchange, and facilitate access to new treatments Co-founded the COVID-19 Clinical Research Coalition of 800+ researchers, physicians, funders, and policymakers from 88 countries to fast-track research for tools adapted to the needs of patients and health systems in resource-limited settings Launched ANTICOV, an adaptive platform trial in 13 African countries testing multiple early treatment options for mild-to-moderate COVID-19.

FIND [112] [113]	200+ academic, industry, governmental, and civil society partners worldwide	4 (India, Kenya, South Africa, Vietnam)	Diagnostic capacity strengthened in nearly 650 laboratories or testing sites in 18 LMICSs; 2,245 health workers trained across 40 LMICs. A preferred supplier to the Global Fund for lab strengthening. FIND has been a WHO Collaborating Centre since 2014, acting in the areas of laboratory strengthening and diagnostic technology evaluation.	FIND's recommended network design for the Philippines allowed the national programme to make a US$21 million saving, which can be redirected to other case finding and management activities. FIND supported Uganda to be the first to submit a dossier to WHO evidencing the elimination of sleeping sickness (per WHO criteria).	"Private sector engagement is one of the key priorities of [India's] National TB Elimination Programme (NTEP). The efforts of FIND and other partners of the Joint Effort for Elimination of TB (JEET) consortium have been critical in mounting an effective intervention to engage the private sector efficiently and provide diagnostic and treatment adherence support to patients treated in the private sector." - *Dr K.S. Sachdeva, Deputy Director General, Central TB Division. National TB Elimination Program, Ministry of Health and Family Welfare, India*

MMV[114] [115]	Clear that many (and many types of) partnerships exist across sectors, but TOTAL number of partnerships not public. 165+ partnerships with clinical centers in LMICS	0	While building research capacity in endemic countries is not one of MMV's primary objectives (between 2005-2008, 2% of total R&D expenses were invested in capacity building), it is a natural outcome of MMV's R&D work. MMV provides training in good clinical practice and help to ensure that that trial sites meet stringent regulatory requirements.	Difficult to identify/isolate	Difficult to identify/isolate

TB Alliance[116] [117]	150+ active global partnerships, and an extensive network of over 400 partners in 50 countries since its inception in 1999. 32 trial sites & community engagement sites in 27 LMICs	1 (South Africa)	TB Alliance works with partners to develop tools, like its research literacy toolkit, and Good Participatory Practice for TB Drug Trials to train community members on key concepts in research and product development.	Difficult to identify/isolate	TB Alliance's Community Engagement (CE) initiatives prioritize capacity building of community leaders and staff at research sites on TB drug R&D, research literacy and education, and awareness-raising campaigns. TB Alliance pioneered and standardized CE as a critical component of TB drug clinical trials. In 2019, 32 CE programs held events in nine countries in support of TB awareness, screening and treatment. https://www.tballiance.org/annualreport2019/partners TB Alliance's network of Community Advisory Boards (CABs) is made up of local stakeholders who help shape how clinical research is implemented, build research literacy, and relay trial information to their constituents.

Case studies of Successful Partnerships with PDPs in Global Health R&D

While the quantitative analysis offered perspectives on cost, innovativeness, and partnership functionality, examining specific programs allows for a more holistic understanding of the product development for global health in partnership with PDPs. In other words, conducing these additional case studies are based on the recognition that while quantitative analysis provided valuable insights into various aspects of global health R&D partnerships, a deeper exploration of concrete examples will help unravel the multifactorial dynamics and contexts of the PDP mechanism.

The choice of the following three programs was with the aim to encompass a diverse range of neglected infectious diseases. By examining programs targeting different diseases, it was intended to capture the strategies employed in addressing each neglected disease. Additionally, programs involving multiple partner organizations, including industrial partners, academia, funders, and PDPs, were selected as they would allow for elucidating the intricate mechanisms of collaboration and delineate the roles and responsibilities of each entity involved. By examining concrete examples, it was aimed to offer insights, evidence and relevant data into the complexities of partnership dynamics and contribute to the discussions for both qualitative and quantitative analyses of the study.

Case Study 1: acoziborole - pioneering advances in HAT treatment

Introduction

Sleeping sickness, or human African trypanosomiasis (HAT), has long affected remote communities in West and Central Africa. Fatal if left untreated, the disease has been a historical challenge[118]. However, a certain hope has emerged with the development of acoziborole, a promising antiprotozoal compound that has been developed by a partnership between Anacor,

Drugs for Neglected Diseases initiative (DNDi), SCYNEXIS, and the Bill and Melinda Gates Foundation (BMGF)[119]. This case study aims to illustrate the landscape of acoziborole's development, from its inception to its promising Phase II/III results, contextualizing its potential to transform HAT treatment.

Background and Context

HAT - A Persistent Threat

HAT, transmitted by tsetse flies, unfolds in two stages. In the haemolymphatic stage, patients suffer headaches or fever. In the late stage, the parasite invades the central nervous system, leading to neuropsychiatric symptoms and eventual death. While reported cases have significantly reduced, the risk of outbreaks remains, demanding continuous innovation in treatment.[118]

Evolution of Treatment

Over the last decade, the collaborative efforts of Anacor, DNDi, SCYNEXIS, and BMGF have led to a transformative advancement in HAT treatment. Historically speaking, the successes of a partnership involving DNDi, Sanofi, national control programs, WHO, and Médecins Sans Frontières have markedly improved treatment options[120]. These background and relevant contexts set the stage for the development of acoziborole.

Development Plans and Partnerships

Acoziborole's discovery

Acoziborole's discovery and development commenced with Anacor's identification of the lead compound, leading to the formation of a partnership involving DNDi, SCYNEXIS, and BMGF. This partnership played a pivotal role in securing funding and advancing the compound to Investigational New Drug (IND) status[121]. Specifically, DNDi and SCYNEXIS played a critical

role in defending the project with budget and timelines, which led to funding approval from BMGF. SCYNEXIS then developed the compound to IND ready status, after which DNDi performed the clinical studies[122].

Strategic Collaborations

Collaborations between pharmaceutical entities, non-profit organizations, and philanthropic foundations have been instrumental to acoziborole's development. The orchestrated efforts between Anacor's chemistry, SCYNEXIS's discovery, DNDi's clinical expertise, SCYNEXIS's developmental expertise, and BMGF's financial support exemplify the synergy needed to tackle the burden of neglected diseases such as HAT.

Progress and Timeline

In late 2009, acoziborole was selected as a pre-clinical candidate to treat HAT, and in 2012, became the first new chemical entity to enter clinical development from DNDi's own lead optimization programme for HAT, followed by the Phase I study with acoziborole conducted and completed in 2015[123]. The Phase II/III study conducted by DNDi between 2016 and 2019 emerged as one of the most critical turning points throughout the development process of acoziborole. The trial, spanning the Democratic Republic of the Congo and Guinea, demonstrated significant success rates of up to 95% and Dr. Victor Kande, principal investigator, expressed optimism about a potential one-day treatment, a revolutionary prospect for remote communities[124]. Acoziborole's development timeline, from the Phase I study in 2015 to the Phase III trials, adheres to the proposed schedules[125]. According to the article published by Mary Moran, the typical development timeline for new drugs ranges from 7 to 12 years[126]. Acoziborole's timeline, initiated in 2012 and reaching Phase 3 by 2022, falls within this range, suggesting a timely advancement.

In relation to the above, it is noteworthy that a strategic approach was utilized for the development of acoziborole. Specifically, it involved a strategic approach blending pharmacokinetic-pharmacodynamic (PK-PD) measures with in vitro testing. Initially, compounds demonstrating favorable in vitro activity and selectivity against the target parasite were prioritized. Further evaluation included rigorous assays to assess metabolic stability, permeability, and tissue binding, crucial for ensuring therapeutic concentrations in target tissues. In vitro time-kill and reversibility kinetics were then employed to establish correlations between exposure levels and activity, helping identify predictive pharmacodynamic measures. These findings informed the design of dosing regimens for pivotal PK-PD studies using animal infection models, aiming to define the therapeutically relevant exposure required for efficacy in target tissues[127]. This comprehensive strategy not only facilitated the discovery of acoziborole itself but also underscored the importance of early establishment of PK-PD measures in the drug development paradigm, particularly for challenging diseases such as HAT – therefore suggesting its relevance to the timely advancement of acoziborole from discovery to clinical development.

Financial component

Funding Structure and costs

Financial support from diverse sources for the development of acoziborole delineates the commitment of stakeholders involved. Specifically, the following entities provide grants to support the development of acoziborole: BMGF; UK aid; the Federal Ministry of Education and Research (BMBF) through KfW, Germany; the Swiss Agency for Development and Cooperation (SDC); Médecins Sans Frontières (MSF); the Dutch Ministry of Foreign Affairs (DGIS); the Norwegian Agency for Development Cooperation (Norad), Norwegian Ministry of Foreign Affairs, as part of Norway's in-kind contribution to EDCTP2; Stavros Niarchos Foundation; the Spanish Agency for International Development Cooperation (AECID); and the

BBVA Foundation (through the 'Frontiers of Knowledge Award in Development Cooperation')[124]. These multiple organizations contributed to acoziborole's development – the allocation of these resources underscores the urgency and significance of developing a transformative drug for HAT[125]. The investments made by various stakeholders are a testament to the belief in acoziborole's transformative potential and its role in advancing global health goals.

By taking a closer look at the funding amount from the above entities, the total expenditure on the development of acoziborole was calculated from publicly available information, such as the annual reports published by DNDi[128].

	UK AID	The Netherlands, DGIS	Germany, BMBF through KfW	Switzerland, SDC	France, AFD	EDCTP, EU	Norwegian Government	US NIH	Bill & Melinda Gates Foundation	MSF	Programmer elated financing	Takeda Pharmaceutical Company Limited, Global CSR Program	Foundations and other	**Total Expenditure (EUR)**	**Total Expenditure (USD)**
2022 funding	6,958		28,417	107,995		514,789			4,323,891	30,929	74,611		88,296	5,175,887	5,641,717
2021 funding	51,863	128,751				342,668			2,462,626	333,022			63,137	3,382,066	3,686,452
2020 funding	202,831	120,219		400,483		44,567			2,349,176	3,674			642	3,121,592	3,402,535
2019 funding	1,166,276	106,555	233,212	642,389	5				2,082,433	1,663		3,509		4,236,042	4,617,286
2018 funding	433,323		229,777	6,051					3,319,522	157,303			145,278	4,291,253	4,677,466
2017 funding	83,529		78,859	27,537					2,696,684					2,886,609	3,146,404
2016 funding	93,599		201,169						1,762,423	29,267				2,086,459	2,274,240
2015 funding	3,586		252,921				199,851		799,973	2,458				1,258,789	1,372,080
2014 funding	295,026	210,333	398,717	100,976			228,690			2,869				1,236,612	1,347,907
2013 funding	164,777	251,053	601,270	91,930			337,364			362,433			123,714	1,932,540	2,106,469
2012 funding		70,514	284,840	113,349					281,089					749,792	817,273
2011 funding	152,695	103,520	10,351		1,523			735	935,166				60,867	1,264,857	1,378,694
2010 funding									873,837					873,837	952,482
Total	2,654,463	990,945	2,319,533	1,490,710	1,528	902,024	765,905	735	21,886,820	923,618	74,611	3,509	481,934	32,496,335	35,421,005

Table 6. Expenditure on acoziborole (2010-2022)

The total expenditure for acoziborole's development over the period of 2010 to 2022 was approximately $35.4 million. In Mary Moran's framework, the average cost for new drugs is in the low hundreds of millions spread over 7 to 12 years, equating to an annual cost of $15 million to $30 million[126]. Acoziborole's average annual cost over this period is approximately $2.6 million, which is notably lower than the upper limit suggested by Moran. This suggests that, relative to the average costs for new drugs in the broader pharmaceutical landscape, acoziborole has been developed with a more cost-effective approach.

Context of Global Funding for NTDs

Mary Moran's insights into the funding landscape for NTDs reveal a significant gap between what is needed and what is actually invested[126]. While the pharmaceutical industry averages hundreds of millions for each new drug, funding for NTDs, when available, may fall short. Therefore, while it is suggested that the discovery and development costs for acoziborole appear to have been much lower and more cost-effective than the traditional industry standard, it remains uncertain how this compares to the development costs (and efficiency) for other NTD drugs. Nevertheless, a similar case could be used as a benchmark for the development of NTD drugs such as fexinidazole. Fexinidazole, another drug for HAT, took about 13 years (2005-2018) and cost Euro55 million ($64 million)[129]. The average annual cost of fexinidazole is approximately $4.9 million, while the average annual cost of acoziborole is approximately $2.6 million, suggesting that the development of acoziborole has been relatively cost-effective compared to available benchmarks in the NTD field.

Impact and Delivery

Transforming Treatment Paradigms

It is important to note that acoziborole's potential as a single-dose treatment will challenge the traditional paradigms of HAT management. The shift towards a 'screen-and-treat' approach at the village level could be a game-changer in achieving the WHO's goal of eliminating *gambiense* strain HAT by 2030[124]. As the Phase II/III results present a potential breakthrough, the implications for public health are profound. The simplification of treatment, removal of the need for hospitalization, and the ease of administration can transform the landscape of HAT intervention, especially in remote and resource-constrained settings[124].

Prospects

The publication of Phase II/III trial results in November 2022 garnered significant attention.

Extensive media coverage and expert endorsements followed, creating a ripple of anticipation. Furthermore, the ongoing trials and the initiation of a paediatric clinical trial showcase the dynamic nature of acoziborole's continued developmental process[125]. The path to regulatory approval, particularly through the European Medicines Agency (EMA), also becomes crucial for acoziborole's integration into standard treatment protocols. Sanofi's commitment to donate acoziborole to WHO upon regulatory approval emphasizes their and other partners' commitment, positioning this effort as a collective effort toward global health equity[120].

Conclusion

Based on the cost analysis, it appears that the development of acoziborole was notably more efficient than the traditional industry standard and even within the context of NTD drug development. However, from a timeline perspective, whether it was faster than the industry standard remains debatable, as the timeline appears to fall within the typical range or possibly even longer. Nonetheless, the development of acoziborole was only feasible through a partnership involving multiple entities, each contributing their unique capabilities and expertise. Specifically, the partnership between Anacor, DNDi, SCYNEXIS, BMGF and many other collaborators/funders enabled the development of a promising new antiprotozoal drug for neglected tropical diseases, which otherwise would have been difficult to achieve[130]. Taking into consideration the complexities of neglected diseases and the difficulty in advancing R&D associated with these diseases, acoziborole can be considered as a successful case, embodying the potential of science, partnerships, and commitment across multiple sectors/parties in addressing health disparities.

Case Study 2: LXE-408 – a new treatment of visceral leishmaniasis

Context and History

Leishmaniasis, a neglected tropical disease caused by a parasitic infection via sandflies, affects people living in low and middle income countries and manifests in multiple forms: visceral (VL), and cutaneous (CL) as main forms; and mucocutaneous (MCL), diffuse cutaneous (DCL) and post-kala-azar dermal (PKDL) as minor forms, with VL being the most severe form[131,132]. The estimated annual cases of VL range from 0.2 to 0.4 million, while the estimated annual cases of cutaneous leishmaniasis (CL) range from 0.7 to 1.2 million globally[133]. Specifically, more than 90% of global VL cases occur in six countries: India, Bangladesh, Sudan, South Sudan, Ethiopia, and Brazil. Cutaneous leishmaniasis is more widely distributed, with approximately one-third of cases occurring in each of three epidemiological regions: the Americas, the Mediterranean basin, and western Asia from the Middle East to Central Asia[133].

The ten countries with the highest estimated case counts for CL are Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica, and Peru. Together, they account for 70 to 75% of the global estimated CL incidence[133].

In the pursuit of improved treatments, Novartis started its discovery work in 2011, which then formed a collaboration between Novartis, the Drugs for Neglected Diseases initiative (DNDi), and the Wellcome Trust in 2020 – this collaboration aimed to develop LXE-408, a first-in-class compound discovered at Novartis, as a potential oral treatment for VL[134]. Novartis, with a long-standing commitment to neglected tropical diseases, and DNDi, a not-for-profit research and development organization, combined forces to address the shortcomings of existing VL treatments. The goal was to create an affordable, safe, and effective drug accessible to the populations most affected by this devastating disease[134].

Novartis's Global Approach to Tropical Disease Research

The Novartis Institute for Tropical Diseases (NITD) was initially established in Singapore in

2003 as part of Novartis's commitment to addressing neglected tropical diseases, including malaria and dengue. However, in 2015, Novartis announced the closure of its Singapore-based NITD operations as part of a strategic restructuring[135].

Following the closure of NITD in Singapore, Novartis shifted its focus on tropical disease research to its Global Discovery Chemistry site in Emeryville, California, and its Genomics Institute of the Novartis Research Foundation (GNF) in San Diego, California[136]. LXE408, the potential treatment for VL was developed at GNF. The decision to develop LXE408 at GNF was likely influenced by the expertise and capabilities available at the institute, as well as the strategic alignment of research priorities within Novartis's global research network. GNF has a strong track record in drug discovery and has been actively involved in research efforts targeting various diseases, including neglected tropical diseases. Therefore, it was a natural fit for the development of LXE408 within the Novartis research ecosystem, particularly after the closure of NITD in Singapore. LXE-408 specifically targets visceral leishmaniasis, prevalent in regions like Brazil, East Africa, and India, where the Phase 2 study is currently underway[137].

Development Plans and Partnerships from Discovery to Delivery

The work of LXE-408 required a strategic collaboration between Novartis and DNDi. Novartis, responsible for completing Phase I clinical trials, utilized its expertise in drug discovery. DNDi, with a focus on neglected diseases, played a crucial role in providing scientific and strategic guidance, managing clinical trials, and ensuring the drug's accessibility[134]. The compound LXE-408 itself was originally discovered in the drug discovery programme at the Genomics Institute of the Novartis Research Foundation (GNF) which is partially supported by grants from the Wellcome (091038/Z/09/Z to R.J.G. and F.S.)[138].

The collaboration extended further with the Wellcome Trust awarding a €5.7 million grant to

DNDi, emphasizing the significance of partnerships in addressing neglected diseases[139]. The broader program involved a consortium of partners, including the University of Dundee, GSK, Pfizer, TB Alliance, and Takeda Pharmaceutical, working towards developing new treatments for leishmaniasis[134].

Progress So Far

The collaboration's progress materialized with the initiation of the first Phase 2 proof-of-concept study for LXE-408 in India in December 2022. This study aims to evaluate the safety and efficacy of LXE-408 in VL patients, determining the optimal dosage and treatment regimen. DNDi plans to expand these trials to Ethiopia by Q3 2023[140].

The Wellcome Trust's grant further underscores the commitment to advancing LXE-408's development. Its renewal builds on the successful project, '21st-century treatments for sustainable elimination of leishmaniasis,' initiated in 2018, and is stemming from the reality that leishmaniasis, being a deeply neglected disease affecting the poorest communities, requires innovative, oral, and well-tolerated treatments[139].

Timelines

In 2020, despite facing delays in the Phase I multiple ascending dose study due to the COVID-19 pandemic, planning for Phase II studies in India and Ethiopia persisted. By 2021, Phase I results supported the continuation to Phase II, and preparations were underway for the Phase II study in India according to the publicly available information[140]. The reality of navigating clinical trials during a global pandemic seems to have showcased the resilience of the collaboration consisting of multiple sectors and entities.

As of 2022, the Phase I clinical study report was completed, regulatory approvals for the Phase

II study in India were secured, and the first patient was enrolled. Simultaneously, preparations for a separate Phase II clinical trial in Ethiopia were ongoing[140]. The timelines, while influenced by unforeseen challenges such as the COVID-19 pandemic are in alignment with the partnership's commitment to advancing the development of LXE-408. The collaboration's experience in overcoming pandemic-related delays could also offer valuable insights into the adaptive strategies required for the timely execution of clinical trials in times of various difficulties.

The development timeline of LXE-408, from its initiation of discovery work in 2011 to the current Phase II status, has been approximately 12 years. While exact figures may vary, the relevant article suggests that the average development time for a pharmaceutical drug is 7–12 years[126]. Although the detail may be lacking, the timeline for LXE-408 appears to be in line with the industry standard.

Costs

The costs associated with the development of LXE-408 are multifaceted and involve financial support from the Wellcome Trust, grants from various entities, and the strategic allocation of resources by Novartis[134, 137, 139]. In particular, the grant from the Wellcome Trust grant seems to have played an instrumental role in advancing the compound from discovery (with Wellcome financially supporting the discovery programme at GNF) to Phase II trials.

The commitment of the partnership to affordability and accessibility also aligns with sector norms for neglected diseases[134]. The collaboration's emphasis on maximizing access in endemic countries reflects a broader understanding of the economic challenges associated with neglected diseases by and large and the need for sustainable solutions to address them. An in-depth examination of costs would involve considering the broader economic impact of leishmaniasis

on affected communities. By addressing these financial aspects comprehensively, the collaboration will be able to ensure that the ultimate delivery of LXE-408 aligns with global health equity goals.

Although the information was limited to Year 2020 and beyond along with the fact that it includes other compounds that are currently in the development phase, the total expenditure data was captured from the publicly available information[128]. Below is the table showing the cumulative expenditure for LXE-408 and multiple other compounds for visceral leishmaniasis over three years at DNDi.

	UK AID	The Netherlands, DGIS	Germany, BMBF through KfW	Japan, GHIT	Switzerland, SDC	MSF	Programmer elated financing	Wellcome	Foundations and other	**Total Expenditure (EUR)**	**Total Expenditure (USD)**
2022 funding	71,004		335,255	1,734,331	11,197	4,937	27,071	3,203,096	88,673	5,475,564	5,968,365
2021 funding	41,366	24,392	65,182	1,374,947		2,118		3,569,274		5,077,278	5,534,233
2020 funding	93,513	55,826	282,125		45,487	43,319		3,716,408		4,236,678	4,617,979
Total	205,883	80,218	682,562	3,109,278	56,684	50,374	27,071	10,488,778	88,673	14,789,520	16,120,577

Table 7. Expenditure on leishmaniasis candidates: DNDi-0690 + DNDi-6148 + DNDi-6174 + Novartis LXE408 + GSK compounds (2020-2022)

In general, it is known that each new drug is likely to cost in the low hundreds of millions spread over 7–12 years, averaging $15 million to $30 million per drug per year[126]. The cumulative cost of $16 million for multiple compounds, including LXE-408, over three years (hence the average of $5.3 million), therefore, is clearly lower than the standard, suggesting a reasonable and cost-effective investment in line with the sector norm. The comparative analysis indicates that the cumulative cost for the development of LXE-408 and other compounds for leishmaniasis is consistent with, or even more cost-efficient than, the financial parameters associated with a traditional pharmaceutical drug development. Furthermore, similar to the analysis in Case Study 1, one could use the comparator of fexinidazole in the NTD drug development space. The average annual cost of fexinidazole is approximately $4.9 million[129], while the average annual cost of LXE-408 (and other compounds) over the same period is in a

similar range of approximately $5.3 million. This cost comparison suggests that the development of LXE-408 has been relatively (or even more, as the calculated costs include not only LXE-408 but also several other compounds in development) cost effective, which is in line with the costs associated with the development of other NTD drugs such as fexinidazole.

It is also worth noting that the collaborative efforts in the development of "multiple" compounds for leishmaniasis may potentially optimise costs through shared resources and knowledge. Further insight into the specific cost distribution between different compounds would provide a more detailed understanding of the financial landscape.

Delivery and Impact within the Public Health Context

The impact of LXE-408 in the public health context is profound, considering the urgent need for improved VL treatments. If successful, LXE-408 could offer a new, first-in-class treatment to this infectious disease.

The focus on sustainability and elimination efforts, especially in regions like India and East Africa, demonstrates a commitment to addressing the broader public health challenges associated with leishmaniasis. The collaboration's efforts align with the World Health Organization Roadmap for Neglected Tropical Diseases, emphasizing user-friendly, safe, and efficacious treatments[139].

In conclusion, the collaborative efforts of Novartis, DNDi, and the Wellcome Trust in developing LXE-408 exemplify a strategic approach to neglected diseases. The cost analysis revealed that the development of LXE408 was indeed in line with, or even more efficient than, the industry standard or NTD drug development. In terms of the timeline, it is debatable whether it is faster than the industry standard considering the duration from its discovery phase

to the current Phase 2. Further investigation is required to explore potential approaches for expediting and advancing the process from discovery to development. Nonetheless, the process from discovery to ongoing clinical trials reflects the commitment of all parties involved to addressing the persisting global burden of leishmaniasis. The collaboration's effort to navigate challenges during ongoing clinical trials will continue, serving as another example for future neglected disease R&D.

Case Study 3: Fosravuconazole for the Treatment of Mycetoma

Context and History

Mycetoma - A Silent Affliction

Mycetoma is a rare infection caused by several different types of microorganisms (fungal and bacterial), resulting in progressively debilitating yet painless subcutaneous tumor-like lesions, usually on the extremities. Low-income populations in tropical regions are primarily affected, particularly in regions collectively known as the Mycetoma Belt, which includes Venezuela, Chad, Ethiopia, India, Mauritania, Mexico, Senegal, Somalia, Sudan, and Yemen. Fungal mycetoma (eumycetoma) predominates in Africa, while bacterial mycetoma (actinomycetoma) causes the majority of cases in South and Central America and some Asian countries[141,142]. The most common causative agents are the fungus *Madurella mycetomatis* and the actinomycetes *Nocardia brasiliensis, Actinomadura madurae, Streptomyces somaliensis*, and *Actinomadura pelletieri*[143]. Little is known about the global burden of mycetoma, transmission modes, risk factors, or pathogenesis. In 2016, the World Health Organization added mycetoma to the list of 18 priority neglected tropical diseases, marking an important step toward better epidemiologic characterization of the disease and concerted efforts to improve diagnostics, treatment, and prevention recommendations[144].

Mycetoma is characterized by chronic granulomatous disease with a progressive inflammatory

reaction. Over years, it progresses from small nodules to large, bone-invasive mutilating lesions. Mycetoma typically occurs when the skin is repetitively broken and exposed to soil or water containing the causal bacteria or fungi. It presents as a triad of painless, firm subcutaneous masses, formation of multiple sinuses within the mass, and a discharge containing sand-like particles called "grains," which can vary in color. Lesions are usually painless and slowly progressive, leading to varying times from initial infection to care initiation. Actinomycetomas progress to bone invasion more rapidly than eumycetomas and occur more frequently on the chest, abdomen, and head, while eumycetomas primarily affect the extremities. Secondary bacterial infection may further complicate treatment[142].

An Unseen Menace

The disease, first reported in Madurai, India, in the mid-19th century and initially termed Madura foot, typically manifests as a chronic condition affecting young adults, particularly males aged 15 to 30, in low- and middle-income countries. Those of low socioeconomic status and manual workers, such as agriculturalists, laborers, and herdsmen, are most commonly affected. Accurate data on incidence and prevalence are elusive, but mycetoma's adverse medical, health, and socioeconomic impacts are profound, necessitating early detection and treatment[141].

Fosravuconazole's Promise

Addressing a Critical Gap

Recognizing the urgency of a solution for mycetoma, DNDi and Eisai worked together to identify and develop fosravuconazole, a novel triazole antifungal agent, as an accessible, effective treatment for eumycetoma[145]. Fosravuconazole is a prodrug of ravuconazole, an antifungal agent originally developed by Bristol-Myers Squibb (BMS). Ravuconazole was initially investigated by BMS as a potential treatment for systemic fungal infections, including

aspergillosis and candidiasis. The development of ravuconazole was based on its potent antifungal activity against a wide range of fungal pathogens, along with favorable pharmacokinetic properties[146]. As ravuconazole demonstrated promising efficacy and safety profiles in preclinical and early clinical studies, efforts were made to optimize its pharmacokinetic properties further. This led to the development of fosravuconazole, a prodrug of ravuconazole designed to improve oral bioavailability and systemic exposure.

Fosravuconazole, belonging to the class of triazole antifungals, exhibits robust antifungal properties. Triazoles are renowned for their efficacy against a spectrum of fungal infections by inhibiting the synthesis of ergosterol, a vital component of fungal cell membranes. One of fosravuconazole's distinguishing features is its broad-spectrum activity. It demonstrates effectiveness against various fungi, showcasing versatility in combating different strains and species responsible for mycetoma. This attribute enhances its potential utility in diverse clinical scenarios[145,147].

Fosravuconazole boasts favorable pharmacokinetic properties, including good oral bioavailability. This is a critical factor for its consideration as a treatment option, as oral administration facilitates ease of use and potentially enhances patient compliance, especially in resource-limited settings. Another area of particular interest is the potential of fosravuconazole to contribute to shorter treatment durations (better than itraconazole). This is a critical factor in improving patient compliance, reducing the burden on healthcare systems, and addressing the challenging aspects of mycetoma, especially in resource-constrained regions[145].

The Global Burden Unveiled

The World Health Organization (WHO) outlines mycetoma's key facts, underscoring its chronic, destructive nature and its prevalence in tropical and subtropical regions[141]. More than

70 bacteria and fungi can cause mycetoma, with transmission likely occurring through traumatic inoculation. The chronicity, painless progression, and lack of awareness contribute to late-stage presentations, often necessitating amputation as the only viable treatment[141].

Development Plans and Partnerships

DNDi's medium-term goal materialized into a Phase II Proof of Concept study, a critical milestone in fosravuconazole's journey. The study, conducted in Sudan, engaged 138 adult patients, aiming to demonstrate fosravuconazole's superiority over itraconazole in a 12-month period. Surgical removal of lesions at 6 months, followed by antifungal treatment, formed the robust protocol[145].

An Unseen Barrier

As the project proceeded, the unforeseen COVID-19 pandemic introduced unprecedented challenges. Country-wide lockdowns disrupted patient follow-ups, prompting a strategic protocol review in 2021. Despite these challenges, the project showcased resilience, adapting timelines and strategies to navigate the complex landscape of global health challenges. For instance, the decision was made to register fosravuconazole in Sudan, initially on a compassionate or conditional basis in advance of full registration in 2021[145].

Timeline and Progress So Far

For the development of fosravuconazole, the Global Health Innovative Technology Fund (GHIT Fund)'s injection of $5 million propelled the trials forward[147]. Despite recruitment challenges and the pandemic effect ensued, the commitment of the partner organizations along with the financial support of these funders has had significant impact in terms of sustaining the continued effort to advance the development of this new drug. The Phase II clinical trial outcomes, presented at the European Congress on Tropical Medicine and International Health in

2023, echoed positive notes. Fosravuconazole's safety and efficacy, coupled with cost-effectiveness, marked significant strides[145].

Fosravuconazole, in its developmental journey for mycetoma treatment, spans from 2016 to now, where the completion of Phase II trial is envisioned[145]. The development phase over this period has been approximately six years and, comparing this timeline with Mary Moran's insights, which indicate that the average development time for new drugs is 7–12 years[126], fosravuconazole appears to be progressing efficiently within the industry standard.

Incorporating WHO's Call for Action – with leadership of Professor Fahal

WHO's call for action on mycetoma, highlighted in the 'Khartoum Call for Action,' emphasizes the need for specific public-health and policy measures. Fosravuconazole's development aligns with these global strategies, placing it at the forefront of the battle against a disease that transcends borders[145]. Recognizing the importance of regional collaboration, the Government of Sudan and WHO organized the First International Training Workshop on Mycetoma in 2019. The workshop, drawing expertise from the Mycetoma Research Centre in Khartoum, facilitated knowledge exchange among approximately 70 health staff from mycetoma-endemic countries[141,145]. The founder and director of the Mycetoma Research Centre is Professor Ahmed Hassan Fahal, a prominent figure in the field of mycetoma research, known for his significant contributions to understanding and addressing the challenges associated with this particular disease. Professor Fahal's leadership at the Mycetoma Research Centre has been instrumental in advancing research, diagnosis, and treatment options for mycetoma. His efforts have not only contributed to expanding the scientific understanding of the disease but have also fostered collaboration and knowledge exchange among healthcare professionals and researchers globally[148].

The abovementioned workshop reflects Professor Fahal's commitment to facilitating knowledge exchange and capacity building in mycetoma-endemic countries. Professor Fahal's leadership exemplifies the principles outlined in the World Health Organization (WHO) Neglected Tropical Diseases (NTD) Roadmap, particularly Pillar 3, which emphasizes the importance of changing operating models and culture to facilitate country ownership[149]. By empowering healthcare professionals and institutions in mycetoma-endemic countries, Professor Fahal's leadership aligns with WHO's vision of strengthening local capacity and ownership in addressing neglected tropical diseases like mycetoma.

Cost Overview

Delving into the financial components of the fosravuconazole project, it is estimated that the collective contribution from funding agencies, including BMGF, UK-(then) DFID, Dutch Ministry of Foreign Affairs (NL-DGIS), GHIT, Canton de Geneve, and MSF, amounts to approximately 9 million USD[150]. These funds play a pivotal role in advancing the research and development necessary to address mycetoma. One notable aspect of the funding dynamics is the participation of Eisai, the Japanese pharmaceutical collaborator, which provides in-kind contributions, highlighting their commitment to advancing research and development for neglected tropical diseases, including mycetoma.

Looking into the detailed breakdown of costs in the development of fosravuconazole from publicly available resources, the total expenditure for fosravuconazole's development from 2016 to 2022 is approximately 5.6 million USD[128].

	UK AID	The Netherlands, DGIS	Japan, GHIT	Switzerland, SDC	MSF	Programmer elated financing	Foundations and other	**Total Expenditure (EUR)**	**Total Expenditure (USD)**
2022 funding	18,485		136,848	154,043	323,841	440	4,294	637,950	695,366
2021 funding	74,987	86,907		160,317	152,356			474,567	517,278
2020 funding	499,819	57,725	293,261	163,703	87,353		1,394	1,103,255	1,202,548
2019 funding	24,433		573,523	121,717				719,674	784,445
2018 funding	113,189		631,158	1,259				745,605	812,709
2017 funding	180,431	489,512	222,677	9,236	18,340			920,196	1,003,014
2016 funding	184,549	382,354						566,903	617,924
Total	1,095,893	1,016,498	1,857,467	610,275	581,890	440	5,688	5,168,150	5,633,284

Table 8. Expenditure on fosravuconazole (2016-2022)

Comparing the estimated expenditure for fosravuconazole's development (with the range of 5.6 to 9 million USD as described above) with Mary Moran's indications that new drug development typically costs in the low hundreds of millions spread over 7–12 years[126], fosravuconazole's cost appears notably more cost-effective. In both timeline and cost aspects, fosravuconazole's development seems favorable when compared with the benchmark of fexinidazole, which incurred a development cost of EUR 55 million over the years from 2005 to 2018[129], specifically in the context of NTD drug development. However, it's crucial to acknowledge that a straightforward comparison of costs across different products is challenging due to the diverse considerations inherent in each disease and product. Furthermore, in comparison to the number and diversity of funders in the other preceding case studies, the number of funders for the development of fosravuconazole is much lower. The limited number of funders for fosravuconazole, primarily GHIT from Japan, underscores the challenging nature of mycetoma as a truly neglected disease. This scarcity of funding may reflect mycetoma's (relatively) recent inclusion in the NTD category in 2016[151].

Addressing the Unknowns

Mycetoma's unknown global burden emphasizes the need for a robust global surveillance system. The absence of control programs, except in Sudan, underscores the complexity of prevention. Fosravuconazole's success offers a glimpse into addressing the unknowns,

positioning it not only as a treatment but as a great potential for future prevention and control strategies for similar neglected diseases. It also underscores opportunities for a comprehensive public health strategy. It stresses the importance of epidemiological data collection, research investment, and the development of cost-effective prevention and treatment measures. Active case-finding, early diagnosis, and accessible tools become crucial in the fight against mycetoma.

Prospect

As fosravuconazole advances, the project's success lies not just in clinical outcomes but in its ability to address global health disparities by involving multiple stakeholders. The adoption of results from the trials can potentially transform mycetoma's treatment landscape, offering hope to the most vulnerable populations in remote regions.

The anticipated outcome from the current development of fosravuconazole is an improvement in clinical results and the swift availability of safe and effective drugs, extending beyond the borders of Sudan. Appropriate treatment, supported by accurate diagnosis, has the potential to expedite recovery, a crucial factor for children and adolescents to remain integrated into their peer groups and maintain positive prospects for education and employment. Swift recovery can act as a deterrent against the severe psychological stress commonly experienced by mycetoma patients, contributing significantly to the reduction of stigmatization associated with the disease. This forward-looking strategy aims not only to advance the clinical landscape but also to address the broader socio-psychological dimensions associated with mycetoma, envisioning a future where individuals affected by this condition can lead fulfilling lives without the burden of prolonged suffering and societal prejudice[147].

Conclusion

In the context of global health challenges, mycetoma often occupies a lesser-known narrative.

The significance of the current development of fosravuconazole is not merely a development of a pharmaceutical agent; it also represents a continuing effort to unravel the unknowns of mycetoma and to foster global collaboration to confront this infectious disease.

Despite the progress made so far, it is imperative to acknowledge the persisting challenges and contemplate the potential hurdles that may emerge in the path forward. Considering the complex landscape of mycetoma, questions linger about the scalability and accessibility of the developed interventions. The translation of promising drug candidate from clinical trials to real-world settings demands meticulous consideration of logistical, economic, and infrastructural factors, warranting a cautious approach among all the relevant stakeholders. The complexed nature of mycetoma necessitates a holistic understanding of its socio-economic impacts, epidemiological dynamics, and healthcare delivery systems. While fosravuconazole holds promise, sustained efforts are required to address the challenges associated with mycetoma, including but not limited to diagnostic accessibility, treatment affordability, and community awareness.

Moving forward, the development of fosravuconazole will require a comprehensive exploration of the ethical considerations linked with neglected disease research. Sustaining a balance between scientific advancement, ethical imperatives, and the imperative to meet the immediate needs of affected communities requires continuous vigilance and ethical scrutiny.

In conclusion, while the fosravuconazole project represents a great potential to the pursuit of mycetoma treatment and management, the ongoing and possible future challenges need to be continuously considered. It is not merely a testament to a drug's potential but a call for sustained dedication and collaborative endeavors to transform the landscape of mycetoma management on a global scale.

5.5 Conclusion

The comprehensive quantitative analyses of PDPs have elucidated several critical aspects of their operations within the global health R&D landscape. These insights will help drive the subsequent additional interviews, providing a well-rounded understanding of PDPs' multifaceted roles in global health R&D.

The funding requirements for developing and bringing products to market within PDPs exhibit notable diversity. While some focus on similar interventions, like therapeutics, showing consistent funding needs, others concentrating on diagnostics or vector control technologies reflect substantially lower costs. This discrepancy prompts reflection on the level of innovation. With only a small fraction of products classified as innovative based on new chemical entities (NCEs), questions regarding PDP efficiency, especially for such groundbreaking products, remain critical. Furthermore, while the analysis in this section was focused on the costs associated with product development, it is essential to examine the development timeline to determine if accelerated development of new global health products is indeed feasible through collaborations with PDPs.

Directly comparing PDPs with multinational pharmaceutical companies reveals an intriguing contrast. Multinational pharma companies appear to seldom engage in global health R&D without PDPs, government, research institution, or donor partnerships when developing new therapeutics. This interdependence makes evaluating the efficiency of these companies in producing innovative global health products complex. In contrast, the development of vaccines for targeted viral diseases occurs with no apparent PDP involvement, potentially attributed to the profitability of these endeavors.

Despite the belief in PDPs playing a pivotal role in strengthening health R&D capacity in

LMICs, quantitative data on the specifics of these partnerships and their impact remain scarce. While some PDPs provide broad statements about the value of partnerships and training, concrete data about the scope, financial investment, or evolution of these partnerships are often elusive. Furthermore, detailed information on the number of people trained or laboratories strengthened tends to be sporadic and snapshot-based, rather than systematically tracked over time.

These quantitative analyses will lead to the additional interviews, an integral component of this research, as they will delve into the qualitative dimensions again ("Mixed Methods Approach"), providing a more comprehensive understanding of PDPs' intricate roles in global health R&D. The knowledge generated through these interviews will enhance the preceding analyses and contribute to informed discussions about the future of PDPs and their impact on global health.

6 Chapter 6 Results of integrated insights: Merging qualitative and quantitative analyses (Mixed-methods approach)

6.1 Introduction

This chapter aims to investigate the multilayered landscape of global health R&D and PDPs, building upon the insights collected from preceding semi-structured interviews and quantitative analyses. The perspectives uncovered in the initial interview phase and the quantitative findings form the background based on which additional interviews with key stakeholders were conducted.

The first series of interviews provided a foundational understanding of the various lenses through which PDPs are perceived, shedding light on their advantages, challenges, and their impact on global health. The subsequent quantitative analyses added quantitative components,

looking into funding dynamics, efficiency, and partnerships.

Subsequently, this chapter focuses on three key themes that emerged from integrating the qualitative and quantitative findings. The first theme addresses considerations on the innovativeness of PDP products, emphasizing the extent to which these initiatives foster novel solutions to unmet health needs and the obstacles to driving innovation in global health. The second theme explores collaboration and challenges within PDPs, specifically their relationships with pharmaceutical companies, shedding light on how these partnerships operate, the benefits each sector derives, and the difficulties they face. Lastly, the third theme investigates the role of LMICs in global health R&D, underscoring the importance of including LMIC perspectives and capacities in global health efforts and assessing how PDPs contribute to this goal.

In this section, it was aimed to unravel further details and bring additional qualitative depth to the preceding findings by conducting additional interviews. By engaging with individuals who are related to PDPs in many ways, it was hoped to capture the complexities of their operations, challenges faced, and the perceived outcomes of their endeavors. The synthesis and integration of these additional interviews with the preceding qualitative and quantitative phases aims to provide a more comprehensive narrative. By collecting additional voices and perspectives of those who are closely linked with the work of PDPs, the intention is to refine our understanding of the complex dynamics in the current global health R&D space. This chapter serves not only as an endpoint for this phase of the study but also as a starting point for the ensuing discussions and recommendations.

6.2 Considerations on the “innovativeness” of PDP products

The interviewees have provided various perspectives on the role and impact of PDPs in

developing global health products. They agree that PDPs have been successful in making affordable medicines available to low-income countries. One common theme is the focus of PDPs on clinical development rather than new chemical entities, which reduces the cost of development. Here is the relevant comment from one interviewee: "*I think the advantage…is that the PDP approach had in the early days was that what was coming to them were products that were relatively 'low hanging fruit' that were pretty guaranteed to make it most, if not all the way, in development.*" Some interviewees emphasize the importance of collaboration in drug development, while others highlight the value of innovation in making drugs more usable and cost-efficient for the public.

The interviewees, especially those with industry/pharmaceutical background, also highlight the challenges and unpredictability of drug discovery and development, and some suggest that PDPs have filled the gap left by pharmaceutical companies that have moved away from anti-parasitic research to focus on '*billion-dollar compounds*.'

In terms of defending themselves against the argument that they develop few truly innovative products, many interviewees highlighted the importance of considering the unique challenges faced by PDPs and the populations they serve when it comes to neglected infectious diseases. As a matter of fact, they emphasized the need to focus on impact and the value of meeting unmet needs, rather than just developing NCEs. One interviewee commented as follows, which clearly depicts these points well: "*I think for the patients, it is not relevant what mechanism of actions of how innovative the medicine are. The real important thing is the access and the availability of these medicines, that is key for the patients. And in that context, the PDPs, certainly MMV and DNDi for sure, have been extremely successful of making medicines available to the patients, which were significantly less toxic or overcame resistance when they worked on the artemisinin for instance, which is really important for the patient. So actually, for*

the patient, that's innovation. I mean, having a medicine that solves the problem, which they did not have before."

Regarding the products developed by PDPs, all interviewees agreed that they have played a critical role in addressing neglected diseases and improving global health. Many interviewees suggest that, without PDPs, it is possible that these products may not have been developed or made accessible to those who need them.

It was also noteworthy that some emphasized the cost advantages of PDPs focusing on developing drugs with existing assets, whereas another emphasized the importance of innovation, not just in discovering new molecules, but also in making drugs more usable and cost-efficient for the public.

In summarizing the insights gathered from the interviews, several key themes emerged, shedding light on the role and impact of PDPs in the field:

Firstly, the significance of PDPs was underscored in the context of drug development for neglected diseases and low-income regions. Traditional pharmaceutical companies, constrained by profit-centric motives, have often refrained from investing in these areas. PDPs, however, have assumed a pivotal role in bridging this gap, addressing medical needs that might otherwise be overlooked.

A notable theme highlighted the cost advantages associated with PDPs' strategic focus on developing existing assets rather than venturing into the creation of new chemical entities. This pragmatic approach aligns with the specific requirements of neglected diseases, optimizing available resources for maximum impact.

Collaboration emerged as a recurrent theme, emphasizing the value of partnerships in the drug development landscape. PDPs were found to be adept at leveraging the collective expertise of individuals with clinical, manufacturing, and regulatory experience, often drawing from the reservoir of knowledge present in larger pharmaceutical enterprises. This collaborative model was seen as instrumental in navigating the complexities of drug development.

Finally, the success of PDPs was noted in their contribution to making medicines more accessible and affordable. This was particularly crucial for patient populations that would otherwise face challenges in obtaining essential medications. The role of PDPs in enhancing accessibility and affordability emerged as a critical aspect of their overarching mission to address global health disparities.

6.3 Navigating collaboration and challenges: Insights into the symbiotic relationship between pharmaceutical companies and PDPs

All the interviewees stated that collaboration between pharmaceutical companies and PDPs is essential for the development of global health products. Pharmaceutical companies require expertise in clinical research organizations, regulatory compliance, manufacturing, and CMC, which is readily available in the pharma industry. PDPs often lack the infrastructure to conduct drug discovery, development, and production on their own and rely on global partnerships with universities, research institutions, and pharmaceutical companies – indeed, this is the essence of the PDP mechanism. One interviewee addressed these points, using the metaphor of 'orchestra' – *"The great thing about the PDPs is they avoid all of that elaborate infrastructure…… It's not an organization in that sense, [but] virtual, I suppose….So, the key element for the PDP is, have you got a small team as it was initially, of people that can 'orchestrate' what is happening….an*

orchestra interested in music, there is a conductor, the PDP is the conductor, multiple conductors, [but]not a huge number of people."

One common issue mentioned in the interviews is the insufficiency of funding for early-stage research, including screening, medicinal chemistry, and PK. One interviewee suggests funding companies with knowledge of infectious diseases to develop new chemical entities. Another suggests that PDPs could establish incubators in low-income countries or high-income countries to identify early-stage technology and transition it into applied science to deliver new chemical entities. This could be done at a relatively low cost and would enable pharma to identify innovative research that could be validated by people with expertise in R&D in pharma.

Again, the importance of public-private partnerships for neglected diseases is highlighted. Pharmaceutical companies have a mission to develop medicines for people, and public health projects, which often partner with large pharmaceutical companies, show that they can contribute to solving global health problems beyond generating profits. These partnerships often bring know-how and in-kind contributions to PDPs, which are extremely valuable because PDPs do not have access to the same tools as pharmaceutical companies, as commented by one interviewee "*... pharmaceutical companies— this is where everything reside in terms of expertise…..So having access to the right clinical resource organization that can conduct that work, having access to the right regulatory people that can have access to the whole process and manufacturing expertise, and the CMC, and so on."* This interviewee, with a significant industry background also added, *"….this is pharma side of the industry where everything that you have is there. And obviously they can expedite the development of these compounds. I think that will remain necessary, to participate with these PDPs in order to advance with technology as quickly as possible.*"

Some also say that intellectual property is an essential tool for these collaborations. It can be used to promote innovation, but it can also be abused. It was noteworthy that some interviewees stated many PDPs are insisting on having IP on the things they contribute, so they have the freedom to give it away, and others cannot prevent PDPs from using it.

Finally, the importance of the CEO's vision (both for PDPs and pharmaceutical companies) is highlighted as it can have a significant impact on the collaborations with PDPs, pharmaceutical companies and other entities, and their foci. One commented that "*…it really depends on the vision of the CEO and we do see quite big swings when, quite often when the CEO changes. In some cases, a new CEO comes in and wipes out neglected diseases."* Some say that family-owned companies are said to be more passionate about their work, and stakeholder commitment is also mentioned, with some respondents noting that European organizations have more time to think about these things compared to their American counterparts.

In summary, the interviewees agreed on the importance of collaboration between pharmaceutical companies and PDPs in developing global health products. The scarcity of funding for early-stage research seems to be a common issue, and suggestions for addressing this include funding companies with knowledge of infectious diseases and establishing incubators to identify early-stage technologies. The importance of public-private partnerships for neglected diseases is emphasized, as is the need to make the best use of intellectual property for society. Finally, the importance of the CEO's vision and stakeholder engagement is highlighted, with family-owned companies being noted for their passion about their work in many cases.

6.4 Enhancing global health R&D: Insights on the involvement of LMICs

Throughout the interviews, the experts discussed various aspects of product development partnerships (PDPs) and their collaboration with pharmaceutical companies in developing global health products. The experts shared their perspectives on the challenges and opportunities associated with global health research and development.

One common theme among the experts was the importance of involving LMICs in research and development activities. However, they also emphasized the need to do so carefully and strategically to ensure that resources are used effectively. Some experts, from both academic and industrial backgrounds, suggested that involving LMICs in areas where they already have expertise, such as clinical development or manufacturing, could be more effective. Others stressed the importance of providing training and support to build expertise in areas where it is lacking. The following comment of one interviewee, representing a certain PDP, illustrates these points well, "*...of course, I'm more in favour to include these countries in the research and working with the PDPs, but we need to be sure, because the resources are so limited and the cash is so limited that either we go with an idea of training and getting the level of expertise for these people in order later to be able to conduct this research, or we have to rely on people that have that expertise and have proven on a track record that they can do it, in order for us to have them involved."* This interviewee added and warned that one should be cautious about the fact that, in the areas that are different from the appropriate level of expertise, the appropriate amount and quality of training/support may not be guaranteed.

Another common theme was the importance of local partnerships and community involvement in addressing neglected diseases. The experts emphasized the need to conduct clinical trials in countries where patients are located, as this increases the likelihood of success. They also suggested that creating organizations or offices in endemic countries and involving local people in clinical trials and drug development efforts can lead to more effective solutions.

The experts also discussed the role of PDPs in global health research and development. While some experts expressed uncertainty about measuring impact quantitatively, others emphasized the important role that PDPs play in advancing research and development activities. They noted that PDPs have a unique ability to bring together stakeholders from different sectors and regions to collaborate on global health challenges. For instance, as opposed to the aforementioned idea of having office(s) in endemic countries, some suggested that there are many other ways to involve people in LMICs 'without' having local offices such as engaging them in various committees, pointing out that it is a reasonable, economical solution. "*They [PDPs] do have a lot of involvement with the people from the lower income countries, but by and large, they do that [in] a number of ways… one [way of] getting their involvement on the various committees [is] that MMV has the expert scientific advisory committee, the product development committees, the committees that look to see when applications come in. And they expect those committee member—and they do—to open up the opportunities. So, you can do an awful lot on a one on basis. You don't need to have a congregation of half a dozen or more people in half a dozen different countries."* This interviewee also added that the job of "*the people in Geneva* [where many PDPs are headquartered]" is to make sure that they are in touch with all the people that are really starting to make contributions in the global health R&D space and encourage them.

Finally, the experts discussed the challenges associated with global health research and development, including the lack of infrastructure and the need for training and development to help empower people. One emphasized, "*All of these things [product development for neglected diseases] where you can involve those communities with the whole process of making the medicine and making it accessible, is, from my opinion, going in the right direction. Because one important aspect, these modern medicines, it's not just a pill, it's a whole sophisticated*

information package of what this thing is doing to the disease, and needs some understanding of the mechanism of action of what it does for the best use. And the only way you can learn about this thing is participating in doing it. And that's why all of these projects should be always joint projects with people in the endemic regions." Some interviewees, both with PDPs and pharmaceutical backgrounds, also highlighted the importance of addressing racism and other biases in the field to ensure that everyone is treated equally and that research and development activities are conducted in an ethical and inclusive manner.

In conclusion, diverse perspectives among the experts resulted in an overall agreement on critical aspects, particularly underlining the strategic importance of local partnerships, judicious engagement of LMICs, and the pivotal role of PDPs in advancing global health R&D. This collective insight, derived from nuanced discussions, emphasizes the need for a careful, context-specific, and inclusive approach to navigate the complexities of global health initiatives. The acknowledgment of the strategic integration of LMICs into research and development activities reflects a consensus on the imperative to bridge gaps in healthcare accessibility and address neglected diseases effectively.

6.5 Conclusion

In synthesizing the wealth of insights drawn from the additional interviews, a comprehensive understanding emerges regarding the critical considerations on the "innovativeness" of PDP products and their symbiotic relationship with pharmaceutical companies. Each section of the inquiry, spanning the innovativeness of PDP products, collaboration dynamics between pharmaceutical companies and PDPs, and the involvement of LMCIs in global health R&D, offers distinct yet interrelated perspectives.

Innovativeness of PDP Products:

The discussion surrounding the innovativeness of PDP products looked into the fundamental question of whether these entities, despite being cost-efficient, contribute to genuinely innovative solutions. While quantitative metrics, such as the proportion of New Chemical Entities (NCEs), might suggest a modest percentage, the interviews elucidate more contexts to be considered. Interviewees emphasize that the focus on clinical development over NCEs aligns with the specific challenges posed by neglected infectious diseases. The success of PDPs, as articulated by interviewees, is measured not solely by the novelty of mechanisms but by the tangible impact on patients. The emphasis on addressing unmet needs and making medicines accessible is considered a form of innovation crucial for patients in underserved regions.

Collaboration Dynamics with Pharmaceutical Companies:

The exploration of collaboration dynamics underscores the indispensable partnership between pharmaceutical companies and PDPs. Interviews reveal a consensus on the crucial role of these collaborations in the development of global health products. The metaphorical depiction of PDPs as conductors orchestrating a virtual ensemble of expertise highlights their pivotal role in leveraging the infrastructure, regulatory knowledge, and manufacturing capabilities of pharmaceutical companies. The interviews reflect a shared recognition of the financial challenges faced by PDPs, particularly in early-stage research. Proposed solutions include funding companies with infectious disease expertise and establishing cost-effective incubators for early-stage technology. The significance of public-private partnerships, coupled with insights on intellectual property, further emphasizes the multifaceted nature of these collaborations.

Involvement of LMICs in Global Health R&D:

The discussions addressing the involvement of LMICs accentuates the importance of inclusivity

and strategic engagement. Experts concur on the need to involve LMICs in research and development activities while acknowledging resource limitations. Suggestions range from focusing on areas where LMICs possess expertise to providing targeted training and support. The interviews underscore the value of local partnerships, community involvement, and conducting clinical trials in the countries where patients reside. While acknowledging the challenges, such as infrastructure deficits and the imperative for training, experts express a commitment to inclusive and ethical research and development. Importantly, the narrative urges a shift beyond physical offices in LMICs, proposing committee engagements as a pragmatic and economical means of involving stakeholders.

These collected insight underscores a collective agreement on the pivotal role of PDPs in global health R&D. The narrative consistently highlights the unique challenges faced by PDPs in addressing neglected diseases and the essential nature of their contributions. The interviews illuminate a pragmatic approach to innovation, emphasizing impact and value in meeting unmet needs. Collaboration is depicted as a key driver, drawing on the strengths of both PDPs and pharmaceutical companies. Moreover, the inclusion of LMICs is not just advocated for ethical reasons but is strategically considered essential for effective and impactful global health initiatives.

In conclusion, the comprehensive synthesis of expert opinions leads to a clear need for an inclusive, collaborative, and context-sensitive approach in navigating the intricate landscape of global health research and development. The themes of innovation, collaboration, and strategic engagement with LMICs emerge as pillars guiding the prospect of future endeavors in the quest for improved global health outcomes.

7 Chapter 7 Discussion

7.1 Introduction

Global health R&D is critical for advancing scientific understanding of diseases and developing new treatments to improve public health. However, the challenges faced by LMICs, including limited resources, infrastructure, and expertise, have made it difficult to address their health needs. To overcome these challenges, PDPs have emerged as a critical mechanism for advancing global health R&D.

As discussed in the previous sections, PDPs are multi-stakeholder partnerships that bring together public and private sector actors to develop new health products, including drugs, vaccines, and diagnostics, for neglected diseases that primarily affect LMICs.[55] PDPs have been successful in developing new products and increasing access to existing treatments, but they also face several challenges, including financing, governance, and quality control.[56]

To assess the success of PDPs and address the challenges, both qualitative and quantitative studies were conducted to evaluate PDPs in global health R&D as described and discussed in the preceding sections. The research employed a qualitative approach, consisting of semi-structured interviews with various stakeholders, and a quantitative approach, including an input-output analysis and a comparison of efficiency versus pharmaceutical companies. It also employed an iterative process between qualitative and quantitative analyses as part of a mixed-methods approach.

This chapter provides a comprehensive overview of key findings from a blended methodology and offers pragmatic policy recommendations. The insights derived not only contribute to the current understanding of neglected infectious diseases but also present actionable strategies to

enhance the impact of global health R&D. This work aims to guide the endeavors of PDPs and stakeholders, fostering a collective response to the challenges posed by neglected infectious diseases on a global scale.

7.2 Policy analysis with Policy Triangle Framework

Analyzing the results of both Objective 1 and 2, and in accordance with the qualitative analysis methodology adopted in Objective 1, actionable recommendations were created to be deployed in global health R&D space. Additional literature review was conducted to bolster the outcomes and to increase the potential to impact the global health community more strongly. The policy methodology also draws on several sources such as the World Health Organization (WHO) guidelines on good governance for medicines.[152]

Furthermore, the policy triangle framework (figure 7) [153] was used in this policy analysis to identify key actors, context, and process—the components that are often overlooked in health policy research—in addition to the content of each policy recommendation. The selection of the policy triangle framework as the analytical framework for this study is based on its relevance and applicability to health policy research in developing countries. The policy triangle framework has been widely recognized and utilized in the field of health policy analysis, offering a comprehensive and systematic approach to understanding the intricate dynamics of policy formulation and implementation.

The decision to adopt this particular framework stems from several factors. Firstly, the policy triangle framework's strength lies in its ability to consider multiple dimensions within the policy process, including actors, context, and process. By incorporating these dimensions, the framework enables the identification of various stakeholders involved in policy-making, their

respective roles, interests, and power dynamics. Additionally, it allows for an examination of the broader social, economic, and political factors that shape policy development, implementation, and outcomes. Lastly, the framework focuses on the dynamics and mechanisms through which policies are formulated, implemented, and evaluated.[153]

By utilizing the policy triangle framework, this study aims to move beyond a mere description of the policy recommendations and delve into a deeper analysis of the actors involved, the contextual factors shaping the policy landscape, and the processes through which these recommendations can be effectively implemented. The framework serves as a comprehensive lens through which the complexities of health policy in developing countries can be examined, ensuring a holistic understanding of the policy-making process and the potential barriers and facilitators that may arise.

Moreover, the policy triangle framework aligns well with the objectives of this study, which seek to identify and address the gaps in product development for neglected infectious diseases. By employing this framework, the analysis can capture the interplay between different actors, the contextual factors influencing policy decisions, and the processes driving policy change and implementation. This comprehensive approach enhances the study's ability to generate actionable insights and policy recommendations that are sensitive to the unique challenges and opportunities within the neglected infectious disease landscape.

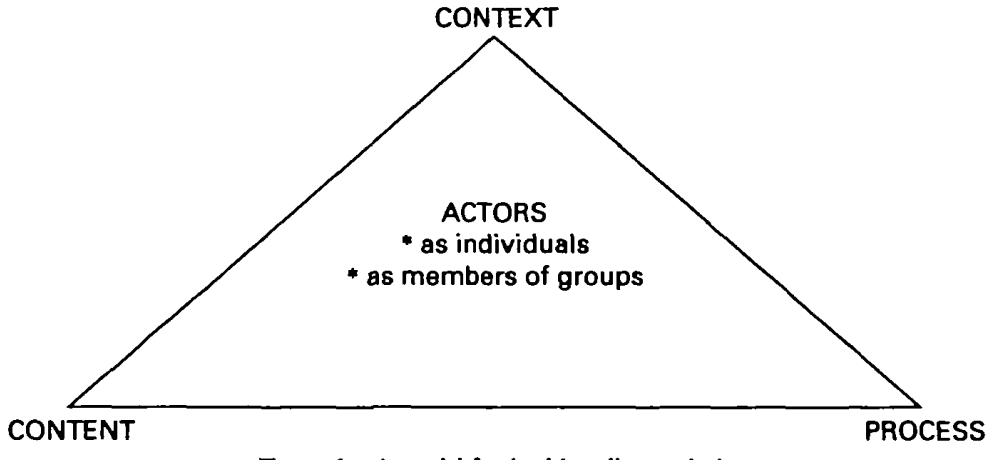


Figure 7. A model for health policy analysis[153]

7.3 Discussion of findings and suggested recommendations

The preceding analyses in Objective 1 and 2 presented a comprehensive examination of PDPs in global health R&D, focusing on their efficiency, success, and failure. The research employed a mixed-methods approach, combining qualitative and quantitative analyses in an iterative process to enhance the rigor and comprehensiveness of the investigation.

The key findings from the initial qualitative study via the semi-structured interviews with various stakeholders indicate that PDPs have been successful and valuable in addressing global health issues, though there remains room for improvement. The study reveals various pros and cons of the PDP model, along with key metrics for PDP success. Biopharmaceutical companies are identified as key players in the PDP system, with other actors such as universities, donors and funders, and public health stakeholders also mentioned to play an important, supplementary role. Additionally, the impact of COVID-19 on global health R&D funding was discussed.

The subsequent quantitative study (Objective 2) included an input-output analysis, a comparison

of efficiency versus pharmaceutical companies, and partnerships in Low- and Middle-Income Countries (LMICs). The results suggest that while PDPs have brought multiple new products to market, only a few of these products are considered innovative. In response to such criticisms that the majority of PDP products are not innovative, the study suggests that PDPs' focus on clinical development helped reduce the cost of development, and collaboration is crucial in drug development. The interviewees also underscore the value of innovation in making drugs more usable and cost-efficient for the public, defending PDPs against such arguments. The study further indicates that multinational pharma companies do not seem to engage in global health R&D without the partnership of PDPs, governments, research institutions, or donors.

Finally, an additional set of interviews investigated the innovativeness of products developed by PDPs, the reasons why pharmaceutical companies need to partner with PDPs in developing global health products, and the involvement of LMICs. The interviewees emphasize the importance of collaboration between pharmaceutical companies and PDPs, and the need to make the best use of intellectual property for society. There was also an overall agreement on the importance of local partnerships and the involvement of LMICs in research and development activities, noting, however, that this should be done strategically and with careful consideration of available resources.

Based on the abovementioned findings from the qualitative and quantitative analyses, as well as the existing literature, the following six policy recommendations were developed in regards to PDPs and their business model in order to further enhance product development for neglected infectious diseases.

1. Sustainable/Incremental Funding for PDPs
2. Foster Collaboration and Partnership

3. Develop Incentives for PDPs
4. Ensure Quality Control and Quality Assurance
5. Support Sustainable Business Models
6. Prioritize Capacity Building through Strong and Equal Partnerships

Key actors, context and process for each of the six policy recommendations were identified by using the policy triangle framework. (Table 9)[153]

Policy Recommendations	Actors	Context	Process
Sustainable/Incremental Funding for PDPs	Government agencies, international organizations, philanthropic organizations, private sector companies, PDPs	Public-Private partnerships in global health research and development are vital to addressing the unmet needs of low- and middle-income countries. PDPs are, by nature, reliant on sustainable and predictable funding to maintain their work, develop new drugs and vaccines, and advance research.	Governments, international organizations, philanthropic organizations, and private sector companies must collaborate to support PDPs through funding mechanisms such as grants, loans, and other financing instruments. Funding should be incremental and provide long-term commitments that offer predictability and stability for PDPs.
Foster Collaboration and Partnership	Governments, private sector companies, PDPs, civil society organizations, academia	Collaboration and partnership among different actors are essential to addressing global health challenges, and PDPs play a key role in facilitating these partnerships. PDPs bring together various stakeholders to collaborate on research and development of new drugs and vaccines to address diseases that disproportionately affect low- and middle-income countries.	Governments, private sector companies, PDPs, civil society organizations, and academia must establish shared goals and a common agenda through regular meetings, joint planning, and resource-sharing. PDPs can act as a convener to bring together different actors in the global health ecosystem, create partnerships, and facilitate the sharing of knowledge and resources.
Develop Incentives for PDPs	Governments, private sector companies, PDPs, civil society organizations	PDPs require incentives to attract private sector investment and support to advance research and development of new drugs and vaccines. Incentives can include financial rewards, tax breaks, and other benefits that encourage investment and engagement in global health research and development.	Governments, private sector companies, PDPs, and civil society organizations must collaborate to identify and design incentives that align with the goals of PDPs. Financial incentives such as grants and subsidies can be offered to incentivize private sector investment in global health R&D. Tax breaks and other financial rewards can also be developed to encourage companies to invest in PDPs. Non-financial incentives such as recognition, prestige, and other forms of public

			recognition can be developed to encourage engagement in global health R&D.
Ensure Quality Control and Quality Assurance	PDPs, regulatory authorities, experts in quality control and assurance	Limited knowledge and experience in product development, inadequate resources, difficulties in developing a quality management system	PDPs collaborating with experts in quality control and assurance to develop and implement a comprehensive quality management system that meets the standards set by regulatory authorities. Establishing partnerships with regulatory authorities to streamline the regulatory processes and promote transparency.
Support Sustainable Business Models and Strengthen Governance of PDPs	PDPs, private sector, LMICs	Lack of return on investment, difficulties in securing sustainable funding, lack of robust governance system	PDPs exploring alternative financing mechanisms through partnerships with the private sector, building strong relationships with LMICs to ensure the affordability and accessibility of products. Implementation of robust governance mechanisms, including self-cleaning action, ensures transparency, integrity, and accountability of PDPs.

Prioritize Capacity Building through Strong and Equal Partnerships	PDPs, academic institutions, industry partners, relevant organizations	Difficulties in attracting and retaining skilled professionals, limited training opportunities, a lack of mentorship and networking opportunities	PDPs prioritizing capacity building initiatives through the development of training programs, internships, and fellowships. Establishing mentorship and networking opportunities to enhance the skills and knowledge of staff and build sustainable networks with academic institutions, industry partners, and other relevant organizations.

Table 9. Policy recommendations with policy triangle framework

Each recommendation will be discussed in detail in the following sections, highlighting the evidence and reasoning behind them, as well as potential challenges and opportunities for implementation.

7.3.1 Sustainable/Incremental funding for PDPs

The first step to enhancing product development for neglected infectious diseases is to ensure sustainable/incremental funding for PDPs. Despite the critical role that PDPs play in global health R&D, the interviews revealed that securing sustainable funding for PDPs often gets difficult/convoluted. In terms of the portion of funding for PDPs in global health R&D, the recent analyses suggest that PDPs received $1.3 billion in 2018, which is less than 3% of the total funding for global health R&D[154]. It may be important to ensure sustainable, and incremental funding for PDPs to enable them to accelerate R&D efforts and develop innovative products for neglected infectious diseases.

The interviews also revealed that many PDPs would prefer to have their projects supported on a ‘portfolio-based’ approach instead of ‘project-based’ approach, as this could potentially increase the efficiency of product development. Therefore, given that some funders have only a ‘project-

based' approach in their investment mechanism, it is recommended that relevant funding agencies consider more options to fund R&D projects with flexibility, including a 'portfolio-based' approach. This approach could theoretically bring several advantages, including improved cost-effectiveness and accelerated development of new drugs. To be specific, by funding a portfolio of projects, resources can be allocated strategically, allowing for a diversified investment in different areas of research and development. This diversification spreads the financial risk and increases the likelihood of successful projects, reducing the overall cost per successful outcome.

The portfolio-based approach can also potentially expedite the development of new drugs. It allows for parallel development and testing of multiple candidates, increasing the chances of identifying effective interventions. Additionally, it facilitates the sharing of knowledge, expertise, and resources across different projects, leading to synergistic effects and accelerated progress in product development.

While specific studies directly comparing the cost-effectiveness and speed of drug development between portfolio-based and project-based approaches seem to be limited, case studies of funding organizations that have adopted a portfolio-based approach, such as the Bill & Melinda Gates Foundation, have demonstrated positive outcomes in terms of faster development of health interventions.

Considering the preference of PDPs for a portfolio-based approach, along with the potential cost-effectiveness and accelerated drug development it could offer, it is recommended that relevant funding agencies explore and adopt (where possible/appropriate) flexible funding mechanisms, including the incorporation of a portfolio-based approach. This approach aligns with the goal of optimizing resource allocation, maximizing research outputs, and ultimately

accelerating the availability of innovative products for neglected infectious diseases.

7.3.2 Foster Collaboration and Partnership

Collaboration and partnership between PDPs, academia, industry, and other stakeholders are essential for advancing R&D in the neglected infectious disease space. As the WHO publicly announces, "Governments, private foundations, and other stakeholders should encourage and facilitate collaboration and partnership to enable PDPs to leverage their collective strengths and resources to develop new products."[155] Thus, the importance of PDPs in global health R&D should be clearly stated in the relevant discussions. There is already an initiative launched by a coalition of PDPs ("Keep the Promise – Impact and Future of PDPs") to highlight their importance in advancing R&D for infectious diseases, which could serve as a hub to catalyze discussions with and among all stakeholders to further engage and encourage relevant parties for possible collaborations and partnerships. [156] It was also noted that PDPs, due to their different scope of work (e.g., disease, intervention, development stage), quite often work in "silos" and thus it is recommended to create environment/occasions where PDPs and other relevant organizations could openly share their current strategy/work in global health R&D, successes and failures so that they can learn from each other in order to improve their effectiveness and efficiency in the development of new products for neglected infectious diseases.

7.3.3 Develop Incentives for PDPs

PDPs face several challenges in developing and delivering innovative products for neglected infectious diseases. These include financial risks, uncertain market demand, and limited access to financing as was suggested by the qualitative and quantitative analyses. Unitaid, an international organization that focuses on product development and access of these products for

neglected diseases, clearly states that "Governments and other stakeholders should develop incentives for PDPs to encourage them to invest in the development of new products for neglected infectious diseases."[157] These incentives could include tax credits, grants, or subsidies for R&D, as well as market entry rewards for successful products.

Of great importance are the existing incentive mechanisms such as PRV, which was introduced in the U.S. and had an impact as a pull-incentive for global health product development. Under the PRV program, in exchange for securing FDA regulatory approval for a new chemical entity, an organization (a company or a non-profit) is granted a PRV that it can apply to one of their products or sell to another company.[36] As the name suggests, a priority review speeds up the review process and can help a company gain market advantage by getting a product onto the market ahead of a competitor. More than ten PRVs have been granted for NTD products and the prospect of winning a PRV has helped motivate a number of the companies to remain as the commercialization partner through development (GSK/malaria drug, Sanofi/HAT drug).[36] The PRV has also helped bring in some venture capital investment to global health R&D. Most notably, the Global Health Investment Fund, established with investments from Gates, JP Morgan, Pfizer, and others,[37] used returns from the sale of a PRV to return capital to its investors. The PRV in this case was earned by a small non-profit Australian biotechnology company called the Medicines Development for Global Health for a drug to treat river blindness (onchocerciasis).[38]

At the same time, it should be noted that PRV is not a "silver bullet" as it also encompasses possible issues and risks like the case of miltefosine – the oral drug for leishmaniasis. A PRV (equivalent of US$125M) was awarded at the time of registering miltefosine in 2014; however, there is no apparent impact on drug access to date.[39] This reflects the fact that PRV is not a perfect solution for addressing the burden of neglected diseases. Nevertheless, PRV has

certainly brought about much pull-incentives for global health R&D and possible opportunities to utilize this innovative system should be further considered by PDPs and their collaboration partners. In addition, similar types of incentivizing mechanism/framework should be further considered in different contexts, such as an introduction of PRV in additional stringent regulatory authorities (SRAs).

7.3.4 Ensure Quality Control and Quality Assurance

PDPs are typically multi-stakeholder initiatives that bring together various actors from both the public and private sectors to develop new health technologies that address the needs of low- and middle-income countries. With this respect, quality control/quality assurance (QC/QA) is a critical aspect of the PDP process, as it ensures that the resulting products are safe, effective, and of high quality.[158]

In terms of who is responsible for ensuring QC/QA of PDPs, there are several key actors involved. First and foremost, PDPs themselves are responsible for ensuring that the products they develop meet the necessary standards for safety, efficacy, and quality. This typically involves conducting rigorous testing and validation processes, as well as adhering to regulatory requirements in different countries and regions.

These testing and validation processes encompass a wide range of activities. PDPs engage in extensive laboratory research, preclinical testing, and optimization of prototypes to ensure safety and efficacy. Subsequently, rigorous clinical trials are conducted, adhering to internationally recognized guidelines and regulatory requirements. These trials assess the product's performance, safety profile, and potential side effects in diverse populations. Rigorous testing procedures also involve post-market surveillance to monitor product performance, identify adverse events, and ensure ongoing quality assurance.

It is worth noting that the application of rigorous testing and validation processes is not limited to therapeutics and vaccines alone; it extends to diagnostics as well. Diagnostics play a crucial role in detecting and diagnosing diseases accurately, enabling timely and targeted interventions. Therefore, a comprehensive QC/QA system for diagnostics is equally important. Diagnostic tests undergo rigorous evaluation to ensure their accuracy, reliability, and suitability for use in different settings. This includes rigorous analytical validation, field testing, and proficiency testing to assess their performance across diverse populations and conditions.[159]

In addition to PDPs, there are also several external actors who play a role in QC/QA for health technologies. These include regulatory bodies such as the World Health Organization (WHO) and national regulatory agencies, which are responsible for evaluating and approving new health products before they can be marketed or distributed. These agencies have established guidelines and standards for the development, testing, and approval of health technologies, which PDPs must adhere to in order to ensure that their products are safe and effective.[160]

Other key actors in the QC/QA process for PDPs include funders and donors, who may require PDPs to adhere to specific quality standards as a condition of funding. In addition, there are independent organizations such as the Medicines Patent Pool that provide support and oversight for PDPs, including quality control and assurance.[161] Funders and donors need to carefully monitor that all product development activities are carried out by PDPs and their collaboration partners with a sufficient level of quality standards and conduct inspections/audits on a regular basis and/or when there are concerns about quality standards, whether apparent or not.

Overall, QC/QA is a critical aspect of the PDP process, and there are multiple actors involved in ensuring that PDP products are safe, effective, and of high quality. By working together and

adhering to established guidelines and standards, PDPs can help to ensure that new health technologies are developed and delivered in a responsible and sustainable way.[162]

7.3.5 Support Sustainable Business Models and Strengthen Governance of PDPs

PDPs operate on a not-for-profit business model, which limits their ability to sustain their operations over the long term. Governments and other stakeholders should support PDPs in developing sustainable business models that enable them to cover their costs and invest in the development of new products.[163] This requires exploring alternative financing models that go beyond traditional grant funding. One such approach is impact investing, which involves attracting investments from private investors who seek both financial returns and social impact.[164] By leveraging impact investment mechanisms, PDPs can access additional financial resources while aligning their activities with the interests of socially conscious investors.

Another avenue for sustainable financing is social entrepreneurship, where PDPs can explore revenue-generating activities that align with their mission and contribute to their financial self-sufficiency. This may include licensing agreements, partnerships with the private sector, or the establishment of social enterprises that reinvest profits into R&D activities. By diversifying their revenue streams and adopting entrepreneurial approaches, PDPs can become more financially resilient and less reliant on traditional funding sources.

Moreover, enhancing the governance systems of PDPs is crucial to ensure transparency, accountability, and ethical conduct. Robust governance mechanisms can safeguard against conflicts of interest, ensure responsible decision-making, and foster trust among stakeholders. One aspect of governance that merits attention is the concept of "self-cleaning" action.

Self-cleaning action refers to the implementation of mechanisms within organizations that

promote integrity, ethical behavior, and accountability. While it may not be commonly present in PDPs, the adoption of self-cleaning practices can strengthen their governance systems and enhance their credibility. This may involve the establishment of internal control mechanisms, codes of conduct, and whistleblower protection policies. By creating a culture of integrity and accountability, PDPs can effectively address misconduct, corruption, or unethical behavior, thereby safeguarding their operations and maintaining public trust. To implement self-cleaning action, PDPs can draw insights from established governance frameworks and best practices. [152] These frameworks provide guidance on governance structures, ethics, and accountability, offering PDPs a roadmap for further strengthening their governance systems.

7.3.6 Prioritize Capacity Building through Strong and Equal Partnerships

Capacity building plays a pivotal role in advancing R&D in neglected infectious diseases. To ensure effective and sustainable outcomes, capacity building initiatives must be built upon strong and equal partnerships. This requires a collaborative approach that fosters shared ownership, mutual respect, and the integration of capacity building into the structure and objectives of the partnership. Governments and other stakeholders should prioritize capacity building for PDPs, academia, and other stakeholders to enable them to develop the skills and expertise required to develop innovative products[165].

A truly strong and equal partnership recognizes the unique contributions and needs of each stakeholder, valuing their expertise and perspectives. By establishing equitable partnerships, stakeholders can leverage their respective strengths, resources, and networks, leading to more impactful capacity building outcomes.

To achieve this, capacity building should be ingrained in the structure and governance of the partnership. This involves incorporating capacity building strategies, resources, and

accountability mechanisms into the partnership's operational frameworks. By making capacity building a shared objective, stakeholders commit to investing time, resources, and effort into building the capabilities of all involved parties. Moreover, the partnership should foster continuous learning and adaptation, remaining responsive to the evolving needs and priorities of the stakeholders. This requires open and transparent communication channels, regular knowledge sharing, and collaborative decision-making processes. By nurturing a culture of trust, inclusivity, and mutual learning, the partnership can create an enabling environment for capacity building to flourish.

In the context of neglected infectious diseases, community engagement and capacity building in LMICs assume particular significance. Recognizing the importance of conducting clinical trials and research within the local context, as suggested by many stakeholders during the interview process, capacity building efforts should be tailored to address the unique cultural, social, and ethical considerations of the communities involved. This involves engaging with local communities, respecting their values and customs, and ensuring that capacity building efforts are culturally sensitive and contextually relevant. [166]

By adopting a partnership-based approach to capacity building, stakeholders can foster an environment of shared learning, collaboration, and sustainability. It is through these strong and equal partnerships that capacity building becomes a transformative force, empowering individuals, organizations, and communities to develop the necessary expertise, infrastructure, and networks to address the challenges of neglected infectious diseases.

7.4 Study limitations

This study is underpinned by a comprehensive research approach encompassing both qualitative and quantitative analyses. The mixed methods design, while advantageous in capturing the

multifaceted aspects of PDPs and their success criteria, does present certain limitations.

In the context of the qualitative strand, the selection of interviewees underwent a meticulous process that involved the consultation of experienced supervisors and prominent figures in the global health R&D domain when necessary. Nevertheless, the limitation of this study lies in the potential underrepresentation of stakeholder voices. Although the study involved a judicious selection of participants, the inherent diversity and complexity of the global health R&D ecosystem might imply that some perspectives remain underexplored.

Moreover, the dual role of the researcher as both an investigator and a funder has the potential to introduce biases. The pre-existing relationships between the researcher and several interviewees could influence responses. Some interviewees may have inadvertently tailored their responses to align with the researcher's funder's strategies, thereby introducing a subtle form of response bias.

Language and communication-related challenges further underscore the limitations of this study. Technical issues during interviews, such as connectivity disruptions and time lags, presented hurdles in the data collection process. Additionally, language disparities between the researcher and the interviewees, who spoke diverse native languages, may have contributed to potential misinterpretations of interview content, despite diligent efforts taken to mitigate misinterpretation risks.

On the quantitative front, the study encountered limitations rooted in data availability. The information gleaned from public resources, including websites, brochures, and online materials, often presented constraints in addressing key research questions comprehensively. In some instances, a paucity of data restricted the completeness of qualitative analyses. It is noteworthy

that persistent efforts were exerted to augment the dataset with pertinent information when data insufficiency posed significant hindrances to the overall study's integrity.

These limitations underscore the intricacies of conducting research within the complex global health R&D arena. Despite these constraints, the study strives to present a robust analysis, seeking to advance the understanding of PDPs and their business model.

8 Chapter 8 Conclusion

Advancing the development of innovative products for neglected infectious diseases is crucial for addressing global health challenges given the fundamental issue of low marketability/profitability of such products. As discussed, PDPs play a critical role in advancing R&D in this space, but they face several challenges that must be addressed.

One of the main challenges faced by PDPs is funding. Sustainable and incremental funding mechanisms are required to ensure that PDPs have the resources they need to continue their work. This requires collaboration among various sectors to provide long-term commitments and stability for PDPs. In order to ensure sustainable funding/financial support for PDPs, careful consideration needs to be given among the various stakeholders as to what sort of systems/mechanisms could provide sufficient incentives for PDPs and related parties as a reason to get involved. Developing incentives for sustainable funding, such as tax breaks and subsidies, can encourage private sector investment and support PDPs in achieving their goals, for example. Implementing these incentives can be challenging and require careful consideration to ensure their effectiveness. Historically, some PDP projects have been supported by multiple funders. These types of co-funding models can help support projects in a more sustainable way and reduce risk among the parties involved. In this context, the regular sharing of each PDP's updated portfolio among PDPs, funders and other entities could potentially lead to more

projects with co-financing models.

Another critical factor in the success of PDPs is collaboration and partnership. Achieving shared goals and a common agenda requires cooperation between governments, private sector companies, PDPs, civil society organizations, and academia. PDPs can play a critical role in bringing together different actors in the global health ecosystem, creating partnerships, and facilitating the sharing of knowledge and resources. In this regard, political momentum has great potential to bring relevant parties together to take necessary action. For example, in May 2023, the G7 Summit was held in Japan, where the Kigali Declaration to address the burden of NTDs was endorsed and called for the acceleration of R&D, access, and delivery for NTDs ("Nagasaki Outcome Statement").[167] Within the context of global health R&D from and within Japan, it is also noteworthy that several NTD/PPP related initiatives have been taking place. For instance, the Nikkei-Financial Times (FT) Communicable Diseases Conference bring together relevant stakeholders, both domestic and global, to elucidate what it takes to transform the global health R&D to address the burden of NTDs and other infectious diseases[168]. Furthermore, The NTD Group within the Japan Pharmaceutical Manufacturers Association (JPMA) was established in 2018 to address issues and requests that pharmaceutical companies alone could not adequately tackle[169]. Initially formed after NTDs were added to the agenda of the 2016 Ise-Shima Summit, the group collaborates with the Pharmaceutical Association to compile recommendations. This NTD Group focuses on developing sustainable market mechanisms for new NTD therapeutics, submitting proposals to the G7 through the Nikkei FT Infectious Diseases Council. PDPs and other stakeholders in global health R&D could potentially use these types of opportunities to elevate the neglected disease R&D agenda and advocate for its necessity. Of course, the development and maintenance of these partnerships will always require ongoing efforts on the part of all relevant parties.

It will also be important to consider how each PDP could support one another and provide synergistic impact, even though their disease or intervention scope may differ. This aligns with the area for improvement regarding "silos" that were revealed from the semi-structured interview process. In practice, there are noteworthy examples of collaboration. For instance, multiple PDPs and funders have joined forces to develop and establish clear go/no-go criteria for the progression of hit and lead compounds for various neglected infectious diseases[170]. This collaborative effort has facilitated decision-making processes for stakeholders, including PDPs, industry, and academia, in the global health drug discovery space. Similar collaborative initiatives among PDPs are essential to sustain momentum in product development against neglected diseases.

Quality control and quality assurance are also essential for the success of PDPs. The development of new tools must meet rigorous scientific standards to ensure their safety, efficacy, and quality. Ensuring these standards require investments in regulatory capacity building, monitoring, and evaluation. Without adequate quality control and quality assurance, the development of new tools can be hindered, leading to delays in bringing products to the market and providing benefits to those in need. The responsibility for implementing quality control and quality assurance measures primarily lies with PDPs through their internal processes. In addition, PDPs also need to work with entities such as the World Health Organization (WHO), national regulatory agencies, and independent organizations such as the Medicines Patent Pool to strengthen QC/QA efforts in a collaborative manner, especially given the relevant expertise and resources (e.g., guidelines) that these external entities possess. Funders and donors also play a critical role in monitoring and ensuring adherence to quality standards throughout the development process. This collective effort to support the work of PDPs will ensure that new health technologies for neglected infectious diseases are developed and delivered responsibly, benefiting global health outcomes.

In addition, supporting sustainable business models and strengthening the governance of PDPs are essential for their long-term viability and impact. By exploring alternative financing models and embracing entrepreneurial approaches, PDPs can enhance their financial sustainability while remaining aligned with their mission. Additionally, the implementation of robust governance mechanisms, including self-cleaning action, ensures transparency, integrity, and accountability within PDPs. By incorporating these considerations, stakeholders can empower PDPs to navigate the complex landscape of neglected infectious disease research and development, ultimately contributing to improved global health outcomes.

Capacity building is also a critical component. PDPs require skilled personnel and adequate infrastructure to develop new tools. Capacity building initiatives can help build the necessary skills and infrastructure and support the development of the local ecosystem for R&D. It should be noted that these initiatives can be easily hindered by a lack of resources, political will, and institutional barriers. Most importantly, the importance of strong and equitable partnerships as a foundation for capacity building cannot be overemphasized. It should always be remembered that without equitable partnerships, stakeholders cannot leverage their strengths, resources or networks.

Enhancing product development for neglected infectious diseases is critical to addressing global health challenges. In this respect, PDPs will continue to play a critical role in advancing R&D in this space, and the policy recommendations discussed here aim to support and strengthen their efforts. The PDPs and the global community are expected to carefully consider the lessons learned from all the work that has been done in the past and the possible recommendations, such as those proposed here in this article, to accelerate the development of innovative products for neglected infectious diseases and improve global health outcomes. While there are challenges to

implementing these recommendations, addressing them is crucial for achieving a more equitable and healthier world.

Appendices

Appendix 1: Interview consent form

Consent form for participation in research interview

"Development of robust strategies for drug discovery and development for infectious diseases of the developing world"

I agree to participate in a research project conducted by Dr. Kei Katsuno, a student of the joint PhD Degree Programme between the London School of Hygiene and Tropical Medicine (LSHTM) and Nagasaki University.

1. ☐ I have been given sufficient information about this research project and I understand my role. The purpose of my participation as an interviewee in this project and the future management of my data has been explained to me and is clear.
2. ☐ My participation as an interviewee in this project is voluntary. There is no explicit or implicit coercion whatsoever to participate.
3. ☐ Participation involves being interviewed by Dr. Kei Katsuno. The interview will last approximately 60 minutes. I allow Dr. Katsuno to take notes during the interview. I also may allow the recording of the interview and subsequent dialogue by audio tape. It is clear to me that in case I do not want the interview and dialogue to be taped I am fully entitled to withdraw from participation.
4. ☐ I have the right not to answer questions and if I feel uncomfortable in any way during the interview session, I have the right to withdraw from the interview.
5. ☐ I have been given the explicit guarantee that the researcher will not identify me by name or function in any reports using information obtained from this interview, and that my confidentiality as a participant in this study will remain secure.
6. ☐ I have read and understood the points and statements of this form. I have had all my questions answered to my satisfaction, and I voluntarily agree to participate in this study.
7. ☐ I have been given a copy of this consent form co-signed by the interviewer.

_____ _____

Participant's Signature Date

_____ _____

Researcher's Signature Date

For further information, please contact:
Kei Katsuno, MD, MPH

1-9-10, Roppongi, Sengokuyama Mori Tower, Minato-ku, Tokyo, Japan

+81-80-5436-2359

Kei.katsuno@lshtm.ac.uk

Appendix 2: Interview information sheet

Interview Information Sheet

This interview will be conducted by Dr. Kei Katsuno, a student of the joint PhD Degree Programme between the London School of Hygiene and Tropical Medicine (LSHTM) and Nagasaki University (NU), in his aim to identify current obstacles for drug discovery and development for infectious diseases in the developing word. Below is the detailed information regarding the interview process.

Period: August 2020 – June 2021

Format: Videoconference, call (interview may be recorded upon interviewee's consent – please see the interview consent form.)

Interviewer: Kei Katsuno, MD, MPH (LSHTM-NU Joint PhD Degree Programme)

Key research question:

What are the success criteria of PDPs? How could we utilize such to develop strategies to drive forward innovations in the global health R&D space?

Interview questions:

Semi-structured interview will be conducted with the following questions (may be subject to change). The interview will take approximately one hour. Interview questions may include but are not limited to:

- The PDP model has existed for the past couple of decades in the global health R&D space. Has this particular model been successful/valid, and why?
- Aside from PDPs or a traditional pharmaceutical company model, what organizations and/or systems have played, or are expected to play, complementary roles in product development for global health? Any change in terms of context/architecture for global health R&D expected in the near future?
- In comparison to other models (e.g., pharmaceutical company), what are the advantages and disadvantages of PDPs?
- What are the key elements to determine success and failure of the PDP model from the perspective of each entity?
    - For instance, there are some reports that identified the following metrics for success and failure of PDPs – what are your views on them?
        - Clarity: Is there certainty about the market opportunity, and what is the nature of the underlying economics?
        - Effectiveness: Does the concept deliver on global health impact objectives?

        - Feasibility: What is the experience of the PDP in commercial environments, are the time and cost to implement likely to be reasonable, and do the PDP's core stakeholders support the approach?
        - Economy: Getting the best value.
        - Efficiency: Maximizing the outputs for a given level of inputs.
    - Aside from the above, what other parameters/determinants exist to measure success and failure of PDPs, and why are they important?
- PDP-specific question (to be asked when interviewing that PDP and its stakeholders): Looking back at the past track record of PDP "A," what are the major achievements and failures? What metrics could be used to measure such outcomes?
- If we are to develop guidelines for determining the success of PDPs, what are the benefits and pitfalls that we need to be aware of in utilizing them in the global health community?
- Who are the exact stakeholders that such criteria should be communicated with, and how? PDPs, funders (governments and philanthropical organizations), and others?

What approaches does each entity use to develop organizational strategies? Will success criteria of PDPs help, and how/why?

For further information, please contact: Kei Katsuno, MD, MPH
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Appendix 3: Notification Letter from Nagasaki University Ethical Committee (Approval)

倫理審査結果通知書

令和２年５月２５日

研究責任者
Kei Katsuno　殿

長崎大学大学院熱帯医学・グローバルヘルス研究科長
北　潔

受付番号：070
承認番号：NU_TMGH_2020_070_4
課 題 名：Identification of hurdles and possible solutions for global health R&D based on interviews with global health product development funders
版　　数：4th

令和２年４月３０日付けで申請のあった上記課題に係る実施計画(出版・公表原稿)について，倫理委員会で審査した結果を基に，下記のとおり判定しましたので通知します。

記

判定	(1) 承認 approved	(2) 条件付き承認 conditionally approved		
	(3) 変更の勧告 major revisions recommended	(4) 不承認 not approved	(5) 非該当 not applicable	
理由又は勧告／Recommendations (if any)				

Ethical Committee
Graduate School of Tropical Medicine and Global Health
Nagasaki University

APPROVAL FORM

May. 25, 2020

Project Title:	Identification of hurdles and possible solutions for global health R&D based on interviews with global health product development funders	
Principle Investigator:	Kei Katsuno	
Date Submitted:	April 30th, 2020	Ref.No.070
Approval Number:	NU_TMGH_2020_070_4	
Protocol version:	4th	

Dear Sir / Madam,

We are pleased to inform you that the above project has been approved.

Any serious adverse events or significant change which occurs in connection with this study and/or which may alter its ethical consideration, must be reported immediately to the Ethical Committee.

Sincerely,

Kiyoshi Kita
Dean, School of Tropical Medicine and Global Health
Nagasaki University, Japan

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