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Developing an aggregator mechanism for late-stage clinical trials of neglected disease product candidates

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ACRONYMS

AMR ..... Antimicrobial resistance

APC ..... Advanced purchase commitment

BCA ..... Benefit-cost analysis

BMGF ..... Bill & Melinda Gates Foundation

CARB-X ..... Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator

CEPI ..... Coalition for Epidemic Preparedness Innovations

CEWG ..... Consultative Expert Working Group on Research and Development

CRO ..... Contract research organization

CSO ..... Civil society organization

DALY ..... Disability-adjusted life year

DNDi ..... Drugs for Neglected Diseases initiative

EC ..... European Commission

EDCTP ..... European and Developing Countries Clinical Trials Partnership

EID ..... Emerging infectious disease

Gavi ..... Gavi, the Vaccine Alliance

GARDP ..... Global Antibiotic Research and Development Partnership

G-FINDER ... Global Funding of Innovation for Neglected Diseases study

GHIF ..... Global Health Investment Fund

GHIT ..... Global Health Technology Fund

GBD ..... Global burden of disease

GDP ..... Gross domestic product

GSK ..... GlaxoSmithKline

HECT ..... Highly efficient clinical trials

HIC ..... High-income country

IAVI ..... International AIDS Vaccine Initiative

IHME ..... Institute for Health Metrics and Evaluation

IFFIm ..... International Finance Facility for Immunisation

IRB ..... Institutional review board

IVI ..... International Vaccine Institute

LMICs ..... Low- and middle-income countries

KII ..... Key informant interview

MDR-TB ..... Multidrug-resistant tuberculosis

MMV ..... Medicines for Malaria Venture

MNC ..... Multinational pharmaceutical company

MRI ..... Medical Research Institute

MIC ..... Middle-income country

NCD ..... Non-communicable disease

NCE ..... New chemical entity

PATH ..... Program for Appropriate Technology in Health

PRNDs ..... Poverty-related and neglected diseases

PDP ..... Product development partnership

R&D ..... Research and development

SDGs ..... Sustainable Development Goals

TB ..... Tuberculosis

TDR ..... Special Programme for Research and Training in Tropical Diseases

UNICEF ..... United Nations Children's Fund

USA ..... United States of America

UK ..... United Kingdom

US NIH ..... US National Institutes of Health

WHO ..... World Health Organization

XDR-TB ..... Extensively drug-resistant tuberculosis

EXECUTIVE SUMMARY

There have been significant improvements in recent years in the early stage development of products for poverty-related and neglected diseases (PRNDs). However, there are still major challenges in the funding of late-stage clinical trials of candidate products for these diseases. For vaccine development specifically, Rappuoli and colleagues recently concluded that "these improvements in the early development process have revealed a new, and possibly more perilous, Valley of Death in the late vaccine development phase."[1]

There are three major challenges in conducting phase III trials for PRND product development. First, such trials are expensive and companies often shy away from investing in them because there is no commercial market for most PRNDs. Second, there is poor coordination on late-stage trials across R&D initiatives. At present, there is no overarching global mechanism that is "steering the ship"—there is no universally agreed upon process for prioritizing R&D investments for PRNDs, for selecting the most promising candidates, or for coordinating the multiple, overlapping research programs worldwide. The result is duplication, waste, and ultimately delays in the development of products. Third, current R&D efforts for PRNDs are "top-down"—they are controlled by high-income countries (HICs) and have generally done poorly at including decision-makers from high-burden countries. It is policymakers in low- and middle-income countries (LMICs) who are in the trenches when it comes to controlling PRNDs—yet they are often not at the table when it comes to deciding on what gets funded, where research is conducted, who gets access to intellectual property, and where and how the technologies end up being manufactured. All these steps need to be "globalized" if we are to develop and deploy new control tools.

This study examines whether and how these challenges could potentially be addressed through a new kind of global funding platform for late-stage clinical trials (an "R&D aggregator"). Two key aims of this study were:

- To assess the **demand for and design of** an R&D aggregator
- To assess the **health and economic benefits** of a global aggregator (i.e., to assess the investment case).

This working paper presents results on the demand for/design of an aggregator and on the investment case for a global aggregator. It examines how the launch of a new funding platform could potentially (i) mobilize additional funding, (ii) establish consensus on R&D priorities, (iii) bring LMIC partners to the table (including in conducting trials and manufacturing products), (iv) facilitate information sharing across investors and research institutions, and (v) curate a portfolio of prioritized R&D investment opportunities.

Methods

We conducted a mixed methods study based on three approaches.

First, we performed a literature review, including an assessment of existing aggregator-type mechanisms (e.g., product development partnerships [PDPs], the Coalition for Epidemic Preparedness Innovations [CEPI], and the European and Developing Country Trials Partnership [EDCTP]).

Second, we conducted two rounds of key informant (KI) interviews. In the first round, between September 2019 and May 2020, we conducted KI interviews with 165 individuals from all major sectors across four high-income countries (Germany, the Netherlands, the United Kingdom, and the United States), four middle-income countries (China, India, Kenya, and South Africa), and other geographies (e.g., we interviewed

multinational pharmaceutical companies, PDPs, and university researchers across other countries). These KI interviews were used to assess the demand for an aggregator mechanism for late-stage clinical trials and to develop initial design options. In the second round, between June and August 2020, we interviewed an additional 27 KIs—including a range of potential funders from LMICs and HICs. This feedback loop helped us to "road test" our initial design options and to assess whether our recommended aggregator mechanism reflected the perspectives of the global and national "communities" to the extent possible.

Third, we conducted quantitative modelling to estimate the health and economic returns to investing in late-stage clinical trials through an aggregator—that is, to develop an investment case for the launch of an aggregator.

Global support for an aggregator

We found widespread buy-in for the notion of a new aggregator mechanism in our first round of KI interviews. Most KIs were supportive of launching such a mechanism for late-stage clinical trials: 48% of all stakeholders strongly supported the creation of an aggregator mechanism and 38% gave moderate support. The availability of funding for late-stage trials is seen as the number one benefit of an aggregator. Other benefits would include improved global coordination of R&D for PRNDs and helping to expand qualified human resources (e.g., trialists, scientists, and data experts) in high-burden settings. Stakeholders that opposed the notion of an aggregator (14%) worried that it would divert funding from existing initiatives, such as PDPs.

KIs would be more likely to participate in an aggregator if it provided five key incentives:

- Support for clinical trial capacity in LMICs.
- Domestic commercial benefits to LMICs through local manufacturing, ownership of intellectual property, and free licensing. Boosting local manufacturing is an incentive not just for LMICs but also for donors from HICs—greater use of LMIC manufacturing capacity could lower manufacturing costs (a "win-win" situation).
- The wide availability of low-cost products in LMICs.
- Facilitating global knowledge sharing.
- Promoting an equal partnership between Northern and Southern countries across all dimensions, e.g., participation in global governance structures, data ownership, and trial leadership (making sure, for example, that trials have principal investigators from the Global South).

KIs also argued that a new aggregator would need a robust, independent scientific process for prioritization of research funding.

Options for the design of an aggregator mechanism for late-clinical trials

Our analysis of the results of the rapid literature review, the benchmarking of aggregator-type mechanisms, and the KI interviews suggests that there are three major options for an aggregator mechanism for late-stage clinical trials, as shown in Figure ES1 (the options staircase). The three options differ in scope (i.e., the range of diseases and product types that an aggregator would include) and in the levels of funding required.

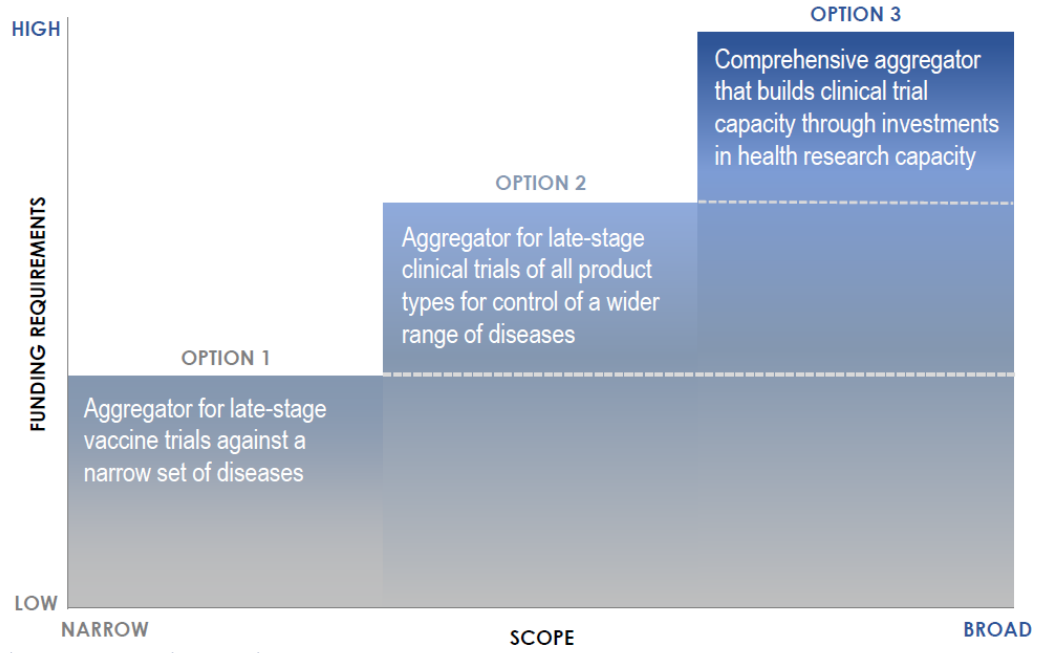

Figure ES1. Options staircase

Option 1 reflects the large gap in the global health R&D architecture for late phases of vaccine development, which was acknowledged in our consultation process. The key benefit of this option would be the availability of funding for late-stage vaccine trials and the de-risking of investments. In addition, the aggregator would make targeted strategic investments into local manufacturing capacity.

Option 2 would fund all product types (medicines, vaccines, diagnostics, etc.) for the control of a wider set of diseases. In addition to clinical trial costs, the aggregator would set aside funding for building clinical trial systems and manufacturing capacity in LMICs.

Option 3 would fund all product types for the control of all PRNDs. In addition to covering the trial costs, this third type of aggregator would invest substantially in the health research systems of LMICs and in their manufacturing capacity. The overall goal is to build sustainable trial networks and to better embed the clinical trial system into the overall health system.

Assessment of the three options

We analyzed the business case for each of these options along three dimensions: scope; costs and benefits; and feasibility (Table ES1). For each option, we estimated the health benefits in terms of deaths and disability-adjusted life years (DALYs) averted. In addition, we conducted an economic analysis, including a cost-benefit analysis (CBA) and a cost-effectiveness analysis (CEA), for the three options. Finally, we modeled the efficiency gains that would result from requiring that the aggregator funds more efficient ("adaptive") trial designs—especially faster cycle times and lower trial costs. In addition to a baseline scenario, which assumes that no efficiency gains would arise from the aggregator, we modeled two additional scenarios – a "feasible" scenario in which 50% of the trials supported by the aggregator adopted adaptive designs and an "ambitious" scenario in which all trials (100%) supported by the aggregator use such designs. The results presented below refer to the feasible scenario.

Table ES1. Criteria for analyzing design options for an aggregator

Dimension	Criteria
Scope	• Product types supported • Diseases supported • Functions performed by the aggregator (e.g., mobilizing funding, building trial capacity, sharing best practices) • Development phases supported
Costs and benefits	• Pipeline/development costs • Set up and running costs • Capacity building costs • Efficiency gains • Benefits (e.g., DALYs/deaths averted)
Feasibility	• Likelihood of mobilizing political support from key decision-makers to implement the option • Potential for rapid implementation, considering the complexity of the option (e.g., expertise needed, complexity of governance and number of actors involved, resource needs) • Risks

Option 1 offers substantial impact at moderate costs (Table ES2). If this option is implemented, we estimate that it would cost US$2.6 billion over 11 years and it would avert 19.8 million deaths and 566 million DALYs. The benefit-cost ratio (BCR) would be 5.65 (i.e., each US$1 invested would return US$5.65). Since a number of key stakeholders were interested in launching a funding mechanism for late-stage trials of vaccine candidates to tackle high burden diseases (e.g., HIV, TB, malaria, pneumonia), rapid implementation of this option seems feasible.

If this option proves to be successful by showing that a dedicated funding mechanism for late-stage vaccine development can effectively accelerate the R&D process, the mechanism could be broadened to include additional product types (e.g., medicines, diagnostics) and a broader range of diseases (i.e., Option 2).

Table ES2. Assessment of Option 1 based on key criteria

Scope	**Product type**	Vaccines
	Disease focus	Small subset of prioritized diseases. Modelling for the investment case assumes the diseases are HIV, TB, malaria, and pneumonia (based on high global burden of disease)
	Functions performed	• Mobilization and allocation of funding for late-stage vaccine trials • Targeted investments in building manufacturing capacity in LMICs (US$50 million per year over 5 years) • Vaccine-related coordination and knowledge sharing • Accountability for trials funded by the aggregator
Costs and benefits	**Total costs (from 2021-2031)**	US$2.6 billion
	Deaths and DALYs averted (from 2021-2035)	Deaths averted: 19.8 million DALYs averted: 566 million
	Benefit-cost ratio	5.65
	Cost-effectiveness	Cost per death averted: US$2,282 Cost per DALY averted: US$80
Feasibility	**Political support**	Rapid launch possible as key funders expressed great interest in a vaccine-focused aggregator
	Ease of implementation	• Low start-up costs • Fewer resource needs compared to other options due to narrow vaccine focus • Likely requires launch of a new organization (but some potential to add a funding window to CEPI, an existing organization)

Option 2 covers all product types and a moderately expanded subset of prioritized diseases compared with Option 1 (Table ES3). This expanded set includes diseases that the WHO has designated as "neglected tropical diseases" (e.g., visceral leishmaniasis and Chagas disease), which have attracted the least funding for product development to date. The wider scope would make a rapid launch less feasible (particularly given the current global focus on product development for COVID-19). Option 2 would have a larger public health impact than Option 1, as measured by deaths and DALYs averted. However, the estimated costs for option 2 are US$9.2 billion over 11 years, which are more than 3.5 times higher than the costs for Option 1. The BCR for Option 2 would be 4.06 (i.e., every US$1 invested would return US$4.06), which is lower than the BCR for Option 1 (which is 5.68). Nevertheless, Option 2 is more cost-effective than Option 1—it has a lower cost per death and per DALY averted.

Table ES3. Assessment of Option 2 based on key criteria

Scope	**Product type**	All product types
	Disease focus	Moderately expanded subset of prioritized diseases (compared with Option 1). Modelling for the investment case assumes the diseases are HIV, TB, malaria, pneumonia, Chagas disease, schistosomiasis, leishmaniasis, dengue, and leprosy
	Functions performed	• Mobilization and allocation of funding for late-stage trials across all product types and several diseases • Moderate investments in strengthening clinical trial systems and manufacturing capacity in LMICs (US$100 million per year over 5 years) • Substantial knowledge generation and sharing, and a key role in coordination of product development • Accountability for trials funded by the aggregator
Costs and benefits	**Total costs (from 2021-2031)**	US$9.2 billion
	Deaths and DALYs averted (from 2021-2035)	Deaths averted: 24.7 million DALYs averted: 738 million
	Benefit-cost ratio	4.06
	Cost-effectiveness	Cost per death averted: US$2,145 Cost per DALY averted: US$72
Feasibility	**Political support**	A large number of key informants suggested that global coordination and prioritization is needed, so there is likely some support
	Ease of implementation	• Requires the launch of an entirely new mechanism • Larger resource requirements than those for Option 1

Option 3 (Table ES4) appeals to health generalists, particularly those who see building health research capacity as a critical plank in strengthening primary health care (PHC) and reaching universal health coverage (UHC). This audience noted the importance of trials as a tool not only for assessing candidate health technologies for PRNDs and potentially other conditions (e.g., non-communicable diseases [NCDs]) but also to test different PHC service delivery, financing, and governance approaches. Under this option, the aggregator would contribute to the creation of a sustainable trial network in LMICs that could go beyond trials of PRND products. As such, it could broaden the funding base for the aggregator through mobilization from a broader array of development agencies and ministries of health in LMICs (currently, PRND product development is mostly funded by public science and technology agencies and private developers rather than by health and aid agencies). But the total costs are very high (US$17.3 billion) and the feasibility of this option is currently low. It appears very unlikely that it could be implemented in the near future. However, the option is an important longer-term vision for the aggregator. The BCR for Option 3 would be 2.73 (i.e., every US$1 invested would return US$2.73). Implementing this option would avert 30 million deaths and 1.2 billion DALYs.

Table ES4. Assessment of Option 3 based on key criteria

Scope	**Product type**	All product types
	Disease focus	All PRNDs (plus potentially NCDs)
	Functions performed	• Mobilization and allocation of funding for late-stage trials for all product types and diseases • Substantial capacity building investments to integrate the clinical trial system into the larger health system and to bolster manufacturing capacity • Strong coordination and knowledge sharing function
Costs and benefits	**Total costs (from 2021-2031)**	US$17.3 billion
	Deaths and DALYs averted (from 2021-2035)	Deaths averted: 30.0 million DALYs averted: 1,156 million
	Benefit-cost ratio	2.73
	Cost-effectiveness	Cost per death averted: US$4,209 Cost per DALY averted: US$105
Feasibility	**Political support**	Some donors will like the focus on R&D as a tool for strengthening PHC and achieving UHC. However, resource needs are high and it is unclear if these supportive donors would provide the funding
	Ease of implementation	• Substantial start-up costs • Large resource requirements

Trade-offs between the three options

Each option has specific advantages and disadvantages and prioritizing between them inevitably involves trade-offs. Option 1 could potentially be rapidly implemented and have a substantial impact at a moderate annual cost. It would also generate efficiencies, streamlining, and accountability in the vaccine development space, while testing a new approach of funding late-stage clinical trials in a targeted manner. Overall, this option promises a pragmatic yet ambitious approach to strategically address the weaknesses in the global R&D ecosystem through coordinated funding for late-stage clinical trials.

If we benchmark Option 1 against Option 2, Option 1 appears to be more attractive for three reasons. First, its costs (US$2.6 billion) are much lower compared to the costs of Option 2 (US$9.2 billion). Second, it also has a higher BCR than Option 2 (5.65 vs. 4.06; see Figure ES2). Third, rapid implementation seems to be feasible given the focused nature of the design and that key stakeholders were interested in an aggregator that focuses initially on vaccines. Option 2 would have a larger public health impact, as measured by deaths and DALYs averted (Figure ES2, right-hand panel), and is also more cost-effective (the costs per death and per DALY averted are lower in Option 2 than in Option 1). Option 3 would avert the largest number of deaths and DALYs, but it is arguably a much larger and much more costly enterprise, and thus seems to be the least feasible at present.

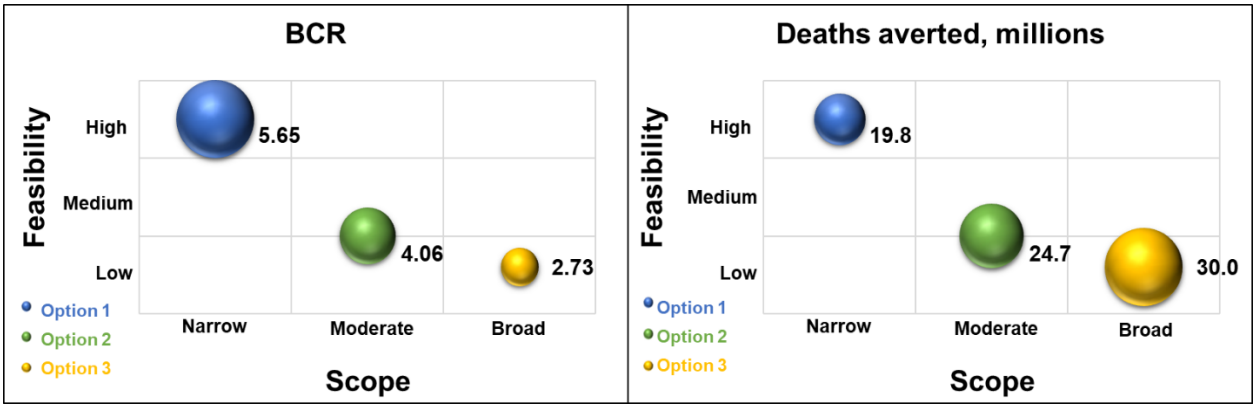

Figure ES2. Trade-offs in feasibility, scope, benefit-cost ratio, and deaths averted between options.
The bubble size reflects the size of the BCR (left panel) or the number of deaths averted (right panel).

Perspectives adopted

We adopted two perspectives for this investment case: (i) a societal perspective with all costs and benefits measured at the societal level, and (ii) a modified investors' perspective to measure how much benefit accrues to society for each dollar invested in the pooled fund by the investor. Details of our approach are described in Annex 8. When viewed from the investors' perspective, there are three striking findings: (i) the BCR for all options is much higher; (ii) Option 1 in particular becomes much more attractive for investors; (iii) the efficiency gains arising from the aggregator are substantial.

Table ES5. Comparison of estimates from societal and investors perspectives

	Business as usual (No efficiency gains)		Feasible efficiency improvement scenario (50% adaptive trials)		Ambitious efficiency improvement scenario (100% adaptive trials)	
	Societal perspective	Investors' perspective	Societal perspective	Investors' perspective	Societal perspective	Investors' perspective
Option 1	5.53	70.78	5.65	81.18	5.65	96.02
Option 2	3.88	15.90	4.06	18.67	4.18	22.56
Option 3	2.52	10.62	2.73	13.18	2.89	17.19

Feedback from road-testing our options

We shared an initial version of this working paper with 27 selected stakeholders from different sectors, including with a range of potential funders from LMICs and HICs, to "road test" our initial design options and to assess whether our recommended aggregator mechanism reflects the perspectives of these key stakeholders. The second round of KI interviews was also important for another reason: most of the first-round interviews were conducted before the COVID-19 pandemic began. COVID-19 has led to substantial changes in the global R&D landscape (e.g., the launch of the ACT Accelerator, the COVAX Facility, and the COVAX AMC). The second-round interviews thus gave us an opportunity to collect additional feedback, especially from KIs who we interviewed prior to the pandemic, on (i) whether the pandemic has changed their views on an aggregator for late-stage clinical trials for PRNDs, and (ii) whether there are any transferable lessons from COVID-19 product development to late-stage trials for PRNDs.

In the initial version of our working paper, based on the first round of interviews, we recommended pursuing Option 1 for the reasons outlined above (large number of deaths/DALYs averted; highest BCR; lowest costs; highest feasibility). We also suggested that Option 1 could serve as a proof of concept and become a stepping-stone for Option 2, and potentially also for Option 3 in the long run.

Overall, most KIs in the second-round interviews agreed with our recommendation to pursue Option 1 and to potentially expand the vaccine aggregator to include additional product types and diseases if it proves to be successful. KIs argued that an aggregator *should* have a narrow focus, at least initially – making the mechanism too broad will make it more difficult to mobilize funding and to get it off the ground.

A few KIs preferred Option 2 and recommended immediate implementation of this option. Chinese officials in particular were in favor of Option 2, while Kenyan representatives were split evenly between Option 1 and Option 2. Those in favor of Option 2 emphasized the need for new treatments against diseases such as TB, and the need to develop new technologies for the most neglected diseases, such as leishmaniasis.

Two KIs from one HIC government agreed that Option 1 would make the most sense, but argued that the aggregator should either be broadened so that it includes a larger number of emerging infectious diseases (EIDs) or that it should even be focused entirely on EIDs. However, CEPI focuses on the Blueprint Diseases and is already expanding towards later development stages in response to the COVID-19 crisis and so there is no need for a second mechanism to fund late-stage trials for Blueprint Diseases. We thus recommend that the aggregator's focus should be on PRNDs (not EIDs), because this is where there is a huge need and gap. This view was also widely shared by KIs from our second round of interviews.

A critical transferable lesson from the COVID-19 pandemic is the linkage between late-stage development and manufacturing. Unless the aggregator covers tech transfer, local manufacturing, and post-licensure studies (Phase IV), it will leave major gaps and fall short of facilitating access to affordable products in LMICs. Only a few LMICs currently have their own production capacity, especially for vaccines, and due to the COVID-19 crisis, there is a new impetus for building such capacity. A main added value of the aggregator would thus be that it not only addresses tech transfer to countries with existing manufacturing capacity, such as India, but also contributes to building regional production capacity in Africa. Building this capacity is expensive and HIC donors alone are unlikely to provide sufficient resources to build this capacity. In addition to smaller strategic investments into local manufacturing capacity, the aggregator will have to be a platform for forging partnerships with governments and companies to strengthen this capacity. At the same time, it is important that LMICs step up and invest in their own national production capacity.

We believe that the aggregator should include the matching of resources—contributions by HIC donors should be matched with contributions by LMICs governments in local manufacturing capacity (including through tax benefits for companies). Such investments by LMICs into manufacturing capacity, which will be used to manufacture products funded by the aggregator, should be counted as contributions to the aggregator. The aggregator would enable LMICs to become a true part of the innovation spectrum. Rather than purchasing new technologies from Northern companies, LMICs could do the local manufacturing themselves. In this sense, the aggregator would also promote access and affordability.

Clearly, if the aggregator ignores the importance of manufacturing right from the start, this will reduce the chances of developing and scaling up a product and making it widely available. COVID-19 has shown the

crucial role of manufacturing "at risk." Just as it would not be acceptable to first develop a COVID-19 vaccine and then have a delay of many years to scale up manufacturing capacity, it would also not be acceptable to develop new products for PRNDs and then have a 5-year delay before they can be manufactured at scale (arguably a failed outcome). Thus, the aggregator would also support the at-risk manufacture of the most promising products.

How the aggregator would be governed

There are existing governance models that could be replicated by the aggregator—there is no need to "reinvent the wheel." Similar to CEPI's governance arrangements, the aggregator's governance mechanism would have three key structures: (i) a board, comprising a smaller investors group, (ii) a scientific committee that advises on the selection of candidates to fund, and (iii) a secretariat for the day-to-day management of the aggregator. Strong representation of participating LMICs in these governance bodies would be essential.

Overall, we envision a two-stage prioritization process. The first step would be a WHO process to prioritize a list of needed products. The second step would be for the aggregator's scientific committee to take this list and further select candidate products that should enter late-stage trials. This is similar to CEPI's process: CEPI's Scientific Advisory Committee used the WHO's list of Blueprint diseases as a starting point and then prioritized the list further. The details of the aggregator's prioritization process would have to be developed as part of a business plan for the aggregator, which would have to be established based on an inclusive process.

The final decisions on funding specific candidates for late-stage trials would rest with the investors group, though these decisions should be (a) based on guidance from the aggregator's scientific committee (which itself has incorporated WHO guidance), and (b) linked with or even embedded into WHO processes. Such scientific legitimacy and buy-in from the WHO will be crucial. There has been renewed interest at the WHO in the need for more joined-up thinking on R&D. Under the envisioned restructure, WHO wants to take more of a streamlined end-to-end approach to supporting product development, which would connect a number of activities at WHO in a strategic, sequenced manner. These activities include the development of target product profiles, R&D prioritization processes, pre-qualification, the essential medicines list, and WHO's work on access to medicines. The R&D accelerator in the Global Action Plan for SDG3 also aims to improve the coordination of late-stage trials. WHO's Product Development for Vaccines Advisory Committee (PDVAC) would also have a key role to play in the selection of vaccines.

Conclusion and recommendations

Our working paper has presented a compelling case for launching a new aggregator that would pool funds for late-stage clinical trials of products to control PRNDs. Such an aggregator would have a substantial public health impact. We estimate that one dollar invested in late-stage clinical trials of products for PRNDs through such an aggregator could generate returns of about US$2.73 to US$5.65 depending on the design of the mechanism. There also appears to be substantial support for a new mechanism, with almost 9 out of 10 respondents (86%) expressing strong or moderate support for an aggregator.

Based on a combination of likely impact, feasibility, and an in-depth global consultative process that encompassed two rounds of interviews, we recommend that the international community pursues Option 1—an aggregator that funds late-stage trials of vaccines for a narrow range of high-burden PRNDs. This type of aggregator has currently the greatest potential to be implemented and would have substantial impact at a

moderate annual cost. It would also drive efficiencies, streamlining, and accountability in the vaccine development space, while testing a new approach of funding late-stage clinical trials in a targeted manner. When viewed from the investors' perspective, the attractiveness of Option 1 becomes even more apparent (see Table ES5 above).

If this vaccine-focused aggregator proves to be successful in the development of new vaccines for PRNDs and contributes to local manufacturing and access, it could be a stepping-stone for Option 2. CEPI is currently being discussed as a vehicle for funding trials of COVID-19 therapeutics (which could potentially reduce viral transmission) and so it appears to be evolving along a similar path (i.e., starting very narrow and then broadening to include later trial phases and new product types). Option 3 is much less feasible but it will be important to keep this option in sight given the value of strengthening health research capacity.

We believe that the COVID-19 pandemic, and the current urgency to fund COVID-19 control tools, is not a threat to launching an aggregator for PRNDs but rather the opposite: it opens a window of opportunity. It is true that the funding needed for the development, manufacturing, deployment, and delivery of COVID-19 technologies could end up being diverted from current funds for PRND product development. Nevertheless, the conversations that are now happening at the highest political levels—for example, on mobilizing funds for R&D, scaling up and globalizing manufacturing capacity, funding manufacturing at risk, creating trial networks in the Global South, and establishing fair pricing and allocation—are setting the terms for new forms of governance in global health R&D. There is also more attention being paid towards the development and production of vaccines, especially in LMICs—many of these countries have been vocal in saying that they urgently need to set up their own manufacturing capacity. There are already examples of companies in HICs entering into licensing agreements with companies in LMICs to manufacture COVID-19 control tools. For example, Gilead has signed non-exclusive voluntary licensing agreements with companies in Egypt, India, and Pakistan to manufacture remdesivir for distribution in 127 countries (almost all LMICs, plus some HICs that face obstacles to access). These developments are creating a window of opportunity to establish a new system for funding a *broader range* of technologies for neglected diseases, not just for EIDs.

Although we have argued that the launch of an aggregator focusing on vaccines for an initially narrow set of diseases is feasible, we recognize that getting any new initiative off the ground is challenging—both financially and in its governance. We estimate that Option 1 would cost around US$2.6 billion over 11 years, a price tag that in theory at least should not cause "sticker shock" among funders. However, the fact that the ACT Accelerator faces a massive funding gap (it has raised only about 10% of what it needs) suggests that resource mobilization for a PRNDs aggregator will not necessarily be straightforward. Despite this caveat, our study suggests that the timing is right for launching an aggregator that funds late-stage trials of candidate products to control PRNDs.

1 INTRODUCTION

Achieving many of the health targets in the Sustainable Development Goals (SDGs) will not be possible without increased financing for global health research and development (R&D).[2] Similarly, achieving "grand convergence"—a universal reduction in deaths from infections and maternal and child health conditions—will not be possible using today's tools alone. Increased funding is needed to develop tomorrow's tools.[3] To give just one example, if the global trends in mortality reduction for tuberculosis (TB) from 2010-2016 were to continue, the convergence target (4 deaths per 100,000 population) would not be reached until 2074.[3] New TB control tools—diagnostics, new chemical entities (NCEs), and highly effective vaccines—are desperately needed to accelerate the mortality decline.

The funding trends for product development for poverty-related and neglected diseases (PRNDs) paint a picture of a "glass half full." As measured in the annual G-FINDER survey published by Policy Cures Research, annual funding for such product development increased from US$3.7 billion in 2017 to US$4.1 billion 2018.[4] In addition, the total number of candidates in the PRNDs product development pipeline grew by just over a quarter between 2017 and 2019, from 538 candidates for 35 PRNDs in 2017 to 690 candidates against the same 35 PRNDs in 2019.[5] However, there is still a significant gap between current levels of investment and the level that will be required to (a) move these existing candidates all the way through the pipeline to launch, and (b) fill the many gaps in the current pipeline.

The funding gap is particularly large for late-stage (phase III) clinical trials. As shown by the 2019 G-FINDER report, basic and early-stage research continues to account for the largest share of global funding for neglected disease product development (43% in 2018). In 2018, funding for all clinical development and post-registration studies only received about a third of the share (34% or US$1.4 billion); the remaining 26% of funding was unspecified by R&D stage.[4]

Phase III trials are expensive and companies often shy away from investing in them because there is no market for most PRNDs. For example, GlaxoSmithKline (GSK) estimated the costs for the phase III trial of its TB vaccine candidate (M72/AS01E) to be around US$300-500 million (and the additional post licensure costs to be US$100-$300 million).[6] As the company was reluctant to put money into the phase III trials, the vaccine was licensed to the Bill & Melinda Gates Medical Research Institute (MRI), which will lead the development of the vaccine candidate and fund the trials.

In addition to insufficient funding, there are two other major barriers to the development of new technologies for PRNDs. The first is the lack of coordination across R&D initiatives. At present, there is no overarching global mechanism that is "steering the ship"—there is no universally agreed upon process for prioritizing R&D investments for PRNDs, for selecting the most promising candidates, or for coordinating the multiple, overlapping research programs worldwide. The result is duplication, waste, and ultimately delays in the development of products.[7]

The second major barrier is the often "top down" nature of current R&D efforts for PRNDs, which have generally done poorly at including decision-makers from high-burden countries. It is policymakers in low- and middle-income countries (LMICs) who are in the trenches when it comes to controlling PRNDs—yet they are often not at the table when it comes to deciding on what gets funded, where research is conducted, who gets

access to intellectual property, and where and how the technologies end up being manufactured. All these steps need to be "globalized" if we are to develop and deploy new control tools.

In August 2019, we began a study to examine whether and how these challenges could potentially be addressed through a new kind of global funding platform for late-stage clinical trials (the "R&D aggregator"). Two key aims of this study were:

- To assess the **demand for and design of** an R&D aggregator
- To assess the **health and economic returns** of a global aggregator (i.e., to assess the investment case).

This working paper presents results on the demand for/design of an aggregator and on the investment case for a global aggregator. It examines how the launch of a new funding platform could potentially (i) mobilize additional funding, (ii) establish consensus on R&D priorities, (iii) bring LMIC partners to the table (including in conducting trials and manufacturing products), (iv) facilitate information sharing across investors and research institutions, and (v) curate a portfolio of prioritized R&D investment opportunities.

Based on interviews with 192 stakeholders across all key sectors, a literature review, and quantitative modeling, this report presents **three different options for a global aggregator**. We assessed these options along a common set of dimensions, including the scope, feasibility of launch, and the estimated costs and benefits of the different options. Based on these options, we developed a global investment case that estimates the costs of creating a global aggregator funding mechanism for late-stage clinical trials and the likely economic and health benefits of such an aggregator.

Our study began prior to the start of the COVID-19 pandemic, and our focus was on PRNDs, rather than on product development for emerging infections with epidemic or pandemic potential. Nevertheless, the flurry of R&D activity for COVID-19, such as the launch of the Access to COVID-19 Tools (ACT) Accelerator, has opened a window of opportunity to put global health R&D higher on the policy agenda, which we reflect on in this paper. For example, in a recent working paper that we developed for the World Bank/Coalition for Epidemic Preparedness Innovations (CEPI) consultation on financing COVID-19 vaccine development, we stated:

> *"While the urgent need is to develop COVID-19 vaccines, this crisis could potentially also be an opportunity to begin developing a sustained mechanism to mobilize new financing for development and product manufacturing for a broad range of emerging infectious diseases (EIDs) and neglected diseases."*[8]

Structure of this paper

This paper is organized as follows. **Section 2** provides an overview of the methodology of this study. **Section 3** assesses the current funding for neglected disease R&D, including for late-stage clinical trials, and the financial resources needed for such late-stage trials. Based on this assessment, the section includes our estimate of the annual funding gap for late-stage clinical trials. The section also summarizes the main findings from our literature review and the rapid analysis of the global ecosystem for PRND product development. **Section 4** presents the results from our key informant interviews. **Section 5** outlines options for an aggregator mechanism and assesses the investment case for each of these options. **Section 6** lays out our conclusions and recommendations.

2 METHODS

The analysis conducted for this report used a mixed methods approach, with three key components:

1. An assessment of the literature and relevant databases on product development for PRNDs, including a rapid analysis of the current global ecosystem for R&D on PRNDs.
2. Key informant interviews conducted with 192 key stakeholders. A large number of these interviews were conducted in person. Members of the research team traveled to China, India, Kenya, and South Africa. In addition, several interviews in Europe and the US were also conducted in person.
3. Quantitative modeling to estimate the costs and benefits of an aggregator mechanism.

Literature review

We conducted a review of the relevant literature on product development for PRNDs, including on global funding for neglected disease R&D, the costs of developing new products, approaches to mobilizing new financial resources, and barriers to late-stage clinical trials for PRNDs. The review included both the peer-reviewed literature as well as documents and reports published by global health foundations, think tanks, research institutes, and others.

In addition, we conducted a rapid assessment of the governance systems and R&D portfolios of PDPs and other existing aggregator mechanisms to understand their financing focus and business models. To quantify some of our findings, we used (1) annual revenues as a proxy for calculating the amount of funds mobilized, and (2) publicly available pipeline data to evaluate distribution of products across clinical trial phases. The assessment of the R&D ecosystem informed our development of options for an aggregator mechanism.

Key informant interviews

We conducted a first round of KI interviews between September 2019 and May 2020. During this first round, we conducted 132 high-level key informant interviews (KIIs) with a broad array of stakeholders in person or by telephone. In total, we spoke to 165 individuals (i.e., some of the interviews were conducted as small focus groups) during this first round. These stakeholders included representatives of governments (particularly the ministries of science and technology, health, and development), major multilateral health and development agencies, multinational pharmaceutical companies (MNCs), contract research organizations (CROs), philanthropies, medical research councils, PDPs, and university researchers. The aim of this "pulse-taking" consultative process was to (a) understand whether or not there was widespread appetite for launching a new financing aggregator for late-stage clinical trials, and (b) define the need for and ideal characteristics of such an aggregator (e.g., whether it should focus on a narrow or broad set of PRNDs, and whether it should focus on phase III trials alone or a broader range of activities).

Between June and August 2020, we interviewed an additional 27 KIs – including a range of potential funders from LMICs and HICs – to road-test our initial design options. This feedback loop helped us to assess whether our recommended aggregator mechanism reflected the perspectives of the global and local "communities" to the extent possible.

Our study focused on **four priority high-income countries (HICs)**: Germany, the Netherlands, the United Kingdom, and the USA. It focused on **four middle-income countries (MICs)**: China (upper-middle income),

India (lower-middle income), Kenya (lower-middle income), and South Africa (upper-middle income). There were several factors that shaped our choice of countries:

- **Selection of HICs**. The key factor in selection of HICs was their significant role in providing **public funding for R&D for PRNDs**, as reported by the G-FINDER 2019 report. The four selected high-income countries collectively made up 78% of total funding in 2018: 68% of funding was from the USA, 8.8% from the United Kingdom, 2.8% from Germany, and 0.8% from the Netherlands.[4] In selecting HICs, we also wanted to reflect a **diversity in funding priorities and approaches** in their support for R&D for PRNDs. The four HICs included in this study differ to some extent in their global health R&D priorities and in how they fund such R&D (e.g., in their support for pooled approaches, PDPs, etc.).
- **Selection of MICs**. LMICs contribute a substantially smaller share of total funding than HICs (3.7% versus 93% in 2018[4]), yet they are becoming increasingly important funders. Out of all funding from LMICs, the largest share comes from India (70%) followed by South Africa (14%).[4] China has only been included in the most recent year's G-FINDER report, and available data in G-FINDER likely underestimated China's contribution since the data only come from one agency (the National Natural Science Foundation of China). However, even limited to this agency, in 2018 China provided the same level of funding for R&D for PRNDs as South Africa provided (US$13 million) (Table 1). In selecting MICs, we aimed to include countries that have **a range of capacities in conducting clinical trials for PRNDs** and that are of **different income levels** within the MIC category (two lower-MICs and two upper-MICs).

Table 1. Public funding for product development for PRNDs from the eight countries included in the study

Country	2018 public funding for R&D (US$ millions)	% of total public funding for R&D
High-income countries		
USA	1,779	68%
UK	230	8.8%
Germany	73	2.8%
Netherlands	21	0.8%
Middle-income countries		
India	66	2.6%
South Africa	13	0.5%
China*	*13**	*0.5%**
Kenya*	*n/a*	*n/a*

Adapted from G-FINDER 2019 report[4] (Table 38: Top public R&D funders 2018)
*Only includes data from the National Natural Science Foundation of China. G-FINDER notes that these data are not representative of total Chinese investment since they are data from a single agency. This figure excludes any contributions from the central government or local governments.
**Data for Kenya were not available in the report.

For the KIIs, we used a semi-structured interview questionnaire (Annex 1), which was tailored to different groupings of interviewees (e.g., there were differences in the guide for HIC versus MIC interviews, and there were specific questions for ministry versus industry interviewees). The questions aimed to broadly assess:

- Key informants' perspectives on the main barriers impeding product development for PRNDs
- The possible role of an aggregator in overcoming these barriers, including benefits and risks
- The value of a global mechanism versus regional mechanisms
- The overall political appetite for launching an aggregator and potential funders and supporters
- The value to LMICs of investing in an aggregator
- The ideal design of an aggregator, including governance, priority setting, and allocation of resources
- Whether an aggregator should pursue capacity building goals, and, if it should, the specific goals it should pursue
- How an aggregator would deal with ownership of intellectual property, pricing, licensing, trial data, tech transfer, and local manufacturing.

This study was approved by Duke University's institutional review board (IRB) and by the relevant national research agency or IRB in each of the MICs. All KIs received an information sheet and gave informed consent. To protect the confidentiality of the interviewees, we have given no identifying information about them in this paper. Similarly, when we describe results broken down by country, we only give *aggregate* data (e.g., we give the overall proportion of respondents in each HIC that supported the idea of an aggregator). We do not give any disaggregated data that could identify key informants—for example, we do not present the views of any specific bilateral or multilateral development agency.

Modeling the health and economic returns from an aggregator: how we estimated the health benefits, cost-effectiveness, and benefit-cost ratios

Types of aggregator options modeled. As described later in this paper, we developed three key aggregator options based on findings from the surveys and review of important literature. For this working paper, we developed an investment case for all three options. For each option, we modeled three efficiency scenarios: (i) a business-as-usual scenario with no efficiency gains, (ii) a "feasible" scenario with efficiency gains from funding a portfolio with 50% adaptive trials, and (iii) an "ambitious" scenario with efficiency gains from funding a portfolio of 100% adaptive trials.

The three aggregator options modeled are:

- Option 1: An aggregator for late-stage trials of vaccines to control a narrow set of diseases: HIV, TB, malaria, and pneumonia.
- Option 2: An aggregator for late-stage trials of a broader set of products (vaccines and therapeutics) for a wider range of diseases: HIV, TB, malaria, pneumonia and five diseases that the WHO has designated as "neglected tropical diseases" (Chagas disease, schistosomiasis, visceral leishmaniasis, dengue, and leprosy). Such neglected tropical diseases have been the "most neglected" of the PRNDs in terms of funding for product development.

- Option 3: An aggregator for all PRNDs and products, which would also make substantial investments into the health research capacity of LMICs to build a sustainable clinical trial network in these countries.

Estimating the costs of an aggregator for phase III trials. As a starting point for estimating the benefit-cost ratio of these three aggregator options, we built a discrete-events simulation model in SimEvents (Matlab R2020a). We designed the SimEvents model to mirror the architecture of an Excel-based financial modeling tool called the Portfolio-to-Impact (P2I) tool, which we have described in detail in three published studies that we co-authored.[5,9,10] The advantage of our new model over P2I for this analysis is that it allowed us to: (i) treat each candidate product as a separate entity rather than as a homogenous group, and (ii) introduce stochasticity which is a better representation of the product pipeline development process. In brief, our model estimates the costs to move a portfolio of candidate health products through the pipeline from advanced preclinical to launch (launch is defined as a candidate making it through phase III), as well as the product launches that would result. The tool is based on assumptions for costs, attrition rates, and cycle times per phase for different product types (e.g., repurposed drugs, NCEs, simple vaccines, complex vaccines). In a new study funded by TDR, we conducted a pipeline portfolio review as of August 31, 2019 to identify existing candidates for 45 PRNDs (as defined by Policy Cures Research).[5] For the aggregator study, we modeled the investments needed and the potential successful candidate products over an 11-year period between 2021 and 2031. We identified those candidates that were in advanced preclinical development, phase I, or phase II. We then assumed that the early-stage pipeline of candidate health products will be replenished every year, at a rate similar to the current rates at which candidates enter the advanced preclinical phase. We then used our model to estimate (i) the number of these candidates that would make it into phase III trials and would thus be funded by an aggregator, (ii) the eventual number of successful candidates that make it to the launch stage for each disease and product type, and (iii) the expected year for each successful product launch.

Estimating the benefits of the aggregator. For each successful product launch, we estimated the health and financial benefits that will accrue between the launch year and 2035. We assumed that a product will enter the market one year after launch because of the various market entry requirements that might be imposed by different governments. We make the simplifying assumption that the primary benefits of vaccines arise through reduction in incidence while therapeutics provide benefits through expansion in coverage and/or increase in therapeutic effectiveness. For this working paper, we model the effect of therapeutics as primarily occurring through coverage expansion alone, while the effect of diagnostics will occur through improved diagnostic accuracy which would lead to increases in treatment coverage. Consequently, upon market entry, we assume that vaccines will provide a 10 percentage-point reduction in annual incidence of the disease in the first year, and an additional 10 percentage points for each subsequent year afterwards for a maximum of a 90-percentage point decrease. For therapeutics, we assumed that baseline coverage will increase by 10% in the first year and by an additional 10% for each year up to 2035 or to a 95% treatment coverage rate, whichever comes first. We reviewed the literature to identify baseline disease burden by age group in terms of incidence, prevalence, annual number of deaths, disability weights for different disease states, and treatment costs. We used these inputs along with other key assumptions to estimate the following for each of four scenarios—a baseline scenario, Option 1, Option 2, and Option 3:

- The annual number of cases, deaths, and disability adjusted life years (DALYs)

- The treatment costs of the product
- The annual number of needed product doses
- The procurement costs for vaccines and drugs.

We compared Option 1, Option 2, and Option 3 against the baseline scenario to estimate number of cases averted, deaths averted, DALYs averted, treatment costs averted, and incremental costs for vaccines and therapeutics. Using these estimates, we calculated the cost-effectiveness of the different design options i.e., the cost per DALY averted and the cost per death averted. We also estimated the benefit-cost ratios for each of the three aggregator options. Both a societal perspective and the perspective of the funders who invest in the aggregator were considered in this analysis (Table 2).

Table 2. Impacts included in the investment cases for the two types of aggregator options

Type of impact	Included in this analysis from which perspective?	
	Societal[1]	Fund investors[1]
Costs		
Program costs (start-up + operational)	✓	✓
Phase III investments	✓	✓
Costs to procure new products[2]	✓	
Benefits		
Deaths averted	✓	✓
DALYs averted	✓	✓
Treatment costs averted	✓	✓[3]
Profit accrued from new products[4]		

Notes:

1. The societal perspective answers the question: "how much does society benefit for each dollar society invests in the aggregator." The investors' perspective answers the question: "how much does society benefit for every dollar added to the fund by the investor?"
2. We assumed that all costs incurred beyond launch are implicitly reflected in the product's unit price. This includes cost of the product and cost of distribution.
3. For the investors' perspective, societal benefits were estimated as the net sum of treatment costs averted and costs of new treatments procured.
4. We assumed a profit of 0% i.e., we assumed aggregator funders do not receive any profits from any successful launches. Note: A detailed description of the methods that we used to conduct the BCA are in Annex 2.

Estimating the efficiency gains: For each aggregator option, we estimated gains that might accrue to society from improvements in efficiency of the product development process as a result of the new aggregator mechanism. We assume that an aggregator mechanism could improve efficiency in several ways, such as: (i) improved allocative efficiencies from better decision making about investments; (ii) improved operational efficiencies and reduced operational costs from centralizing application/disbursements and use of shared administrative resources; and (iii) improved technical efficiencies of clinical trials through increased funding of cutting-edge approaches such as adaptive clinical trials. We describe each of these in more detail below.

i. Potential improvements in allocative efficiencies include decision-making to allocate aggregator funds in ways that prioritize development of candidate products with higher potential for success, and/or higher market potential. Based on responses from the interviews we conducted, there is a

clear preference for this mechanism to be a non-profit fund rather than a fund driven by return-seeking behavior. Therefore, disease burden will be the main prioritization factor—not market size or profit potential. The aggregator could also choose to prioritize candidates with higher potential for success (i.e., optimizing the number of launches per dollar spent), or allow multiple parallel trials of similar candidates where possible (i.e., optimizing speed by shortening time to market). For this analysis, we assume the latter, such that any product candidate ready to enter phase III will be funded regardless of whether there are other similar candidates in phase III. Our results should be interpreted through that lens.

ii. Improvements in operational efficiencies from an aggregator mechanism (compared to not having an aggregator) could arise from centralizing applications, reviews, and disbursement of funds. Such centralization in turn will translate to lower transaction costs. Indeed, interview respondents believe that this would be an improvement over the current mechanism and would save multiple hours currently spent on fund raising. However, current data on transaction costs from donors and recipients are not available, making a quantitative assessment of efficiencies impracticable. Therefore, for this analysis, we included only qualitative assessments of potential efficiency gains from reduction in transaction costs. Moreover, compared to pipeline development costs, setup and administrative costs comprise a small fraction of total aggregator costs. For example, setup costs for an aggregator ranged from US$ 36 million for Option 1 to US$ 87 million for Option 3, while operational costs ranged from US$ 25 million per annum for Option 1 to US$ 60 million per annum for Option 3. By contrast, drug development costs were US$ 2.1 billion for Option 1, US$ 8.3 billion for Option 2, and US$ 15.6 billion for Option 3.

iii. Potential gains from improved technical efficiencies include gains that would accrue from funding adaptive clinical trials. Following expert consultations, we surmise that adaptive trial designs can shorten phase-times by up to six months per phase, lower study sample size by up to 40%, and lower overall trial costs by up to 15%. We therefore modeled three efficiency scenarios. The first was a business-as-usual scenario with no efficiency gains. The second was a "feasible" efficiency improvement scenario in which 50% of the trials supported by the aggregator adopted adaptive designs (which translates into an aggregate reduction of 3 months in phase length for all phases and a 7.5% reduction in late-stage trial costs). The third was an "ambitious" efficiency improvement scenario in which all trials supported by the aggregator use adaptive designs (translating into a reduction of 6 months in phase length for all phases and a 15% reduction in late-stage trial costs).

Due to data limitations, we limited the analysis for this working paper to the potential gains from improved technical efficiencies that would accrue from funding adaptive clinical trials.

Limitations of our study

This study used a novel mixed-methods approach to examine the feasibility and potential impact of a new funding aggregator for late-stage trials. Over a short timeframe, we conducted a very large number of KIIs (165 KIs in the first interview round and 27 KIs in the second wave) with all key organizations in the R&D landscape for PRNDs, and we complemented this consultative approach with quantitative modeling to build an investment case.

Despite these strengths, our approach also had a number of limitations. We highlight several of these below.

Literature review. Given time constraints, we conducted only a rapid synthesis of the literature, including a rapid assessment of existing aggregator-type mechanisms. But these were not formal systematic reviews or meta-analyses—they were aimed at quickly gathering key background data.

Key informant interviews. Our KIIs were semi-structured interviews aimed at gaining an in-depth understanding of stakeholders' views about a new funding mechanism (they were not a formal quantitative survey). KIs sometimes did not wish to answer all questions. When we present numerical results (e.g., the proportion of KIs who were supportive of an aggregator), these are therefore not based on all first-round interviews with 165. Throughout the paper, when we present these types of numerical data, we have given the sample size (N). The 27 KIs interviewed during the second round of interviews received a different set of questions related to our initial options, and were not included in the counts.

Data on costs, success rates, and cycle times. Our models used the same data inputs from the P2I model. These data on costs, success rates, and cycle times were based review of 25,000 development candidates. They were validated with peer-reviewed estimates, and industry records. They therefore represent averages over the entire pool (not the highest or lowest) and therefore more reflective of a real-world experience.[9]

Modeling for the benefit-cost ratio. As described in detail in Annex 2, as with all models, our modeling was based on a number of assumptions, such as the potential impact of new health technologies. For all assumptions, we based these on the best available data, but there will always be uncertainties around these assumptions. For example, we only have data about candidates that are currently in the pipeline so we made assumptions about the future flow of new candidates into the pipeline (see Annex 2 for details on these assumptions). In addition, our model only includes four phases of development: advanced pre-clinical, phase I, phase II (it does not distinguish between phase IIa and phase IIb), and phase IIII, and thus it under-estimates the full costs of developing a new product for PRNDs. However, since we are primarily interested in the phase III costs, this did not affect our estimates.

3 THE VALLEY OF DEATH IN FUNDING LATE-STAGE DEVELOPMENT FOR PRNDS

In this section, we assess the annual funding gap for late-stage clinical trials. We also summarize the main findings from our literature review and from our rapid analysis of the global ecosystem for PRND product development.

3.1 Quantifying the valley of death

There is a large funding gap for late-stage clinical trials of products for PRNDs. While our own research shows that annually about US$1.7 billion is needed for such late-stage clinical trials, current spending on these trials amounts to an estimated US$700 million. As such, there is an annual funding gap of around US$1.0 billion. While this gap is substantial, it would be feasible to mobilize this amount from the global community.

Our new study of the pipeline of candidates under development for PRNDs (medicines, vaccines, diagnostics, reproductive health technologies, and vector control products) has illustrated a valley of death at the late-stage of development.[5] There is a large drop-off in the pipeline of candidates from phase II to III, which partly reflects the very high costs of phase III trials (see Annex 3 for the number of candidates in phase II). As of August 31, 2019, just 49 out of the 522 candidates (9.4%) in the pipeline for PRNDs were in phase III (this number excludes diagnostics due to their different R&D process) (Table 3).[5]

Table 3. Candidates under development for PRNDs in phase III (total, and as a % of all candidates), as of August 31, 2019*

Pipeline	Number of candidates in phase III	Total number of candidates across four phases (advanced pre-clinical, phases I-III)	Percentage of all candidates that are in phase III
PRNDs	49	522	9.4%

*Table excludes diagnostics.

Key reasons for this valley of death in late-stage trials are that there is too little funding for such trials, there are too few funders, and the financing is highly fragmented, creating inefficiencies. The result is that for many fatal or disabling conditions, the prospects for developing urgently needed control tools are very poor. Funding for basic and early-stage research has historically received the largest share of all funding for neglected disease R&D, and it still received the largest share (43%) in 2018. Funding for *all clinical development and post-registration studies* only accounted for about a third of all R&D funding for PRNDs (34% or US$1.4 billion) in the same year (the remaining 26% of funding was unspecified by R&D stage). [4]

How much additional funding is needed for late-stage trials of products for PRNDs? A reasonable estimate of the need comes from our new study on the current R&D pipeline for neglected diseases.[5] We used the P2I tool to estimate (a) how much it would cost to move current candidates through the pipeline, (b) the likely associated launches, and (c) the costs to develop critically needed "missing" products that are unlikely to be launched based on the current pipeline. We had previously done this analysis based on the 2017 pipeline for 35 PRNDs (comprising the list of diseases that Policy Cures Research used for its annual G-FINDER survey),[9]

and we repeated this analysis for the current pipeline (as of August 31, 2019).[5] For the current pipeline review, Policy Cures Research expanded its list to include a total of 45 diseases (see Annex 4). For these 45 diseases, we identified 754 candidates. Our modeling using the P2I tool found that it would costUS$21.0 billion to move these 754 candidates through the pipeline, leading to 207 launches by 2031 (Annex 5).

For the purposes of this paper, we then amended the list of diseases included in our costing so that we could compare the estimated costs of moving candidates through the pipeline with the annual disbursements from the 2019 G-FINDER report.[4] We tried to make this an "apples to apples" comparison. This amendment was necessary because our initial costing of 45 diseases does not fully match the list of diseases included in the G-FINDER report. For example, the G-FINDER report does not include funding for product development for sexual and reproductive health, Ebola, and a few other diseases that were all part of our costing. On the other hand, snakebite envenoming was not included in our costing but has since been included in the G-FINDER report. Thus, our comparison of costs versus the disbursements documented in the G-FINDER report has some limitations.

Based on the amended list of PRNDs, the costs of moving product candidates through the pipeline total US$15.9 billion. Almost two thirds (US$9.9 billion, 62%) of the US$15.9 billion needed would be for late-stage clinical trials (Annex 6). Over three quarters of the costs would be incurred in the first 5 years – a total of US$7.41 billion or US$1.48 billion per year over the next 5 years.

In addition, there would still be 16 highly needed "missing products" based on the current pipeline (e.g., a hepatitis C vaccine, a vaccine for multiple diarrhea diseases). It would cost a median of about US$9.85 billion (ranging from US$5.5-14.2 billion, depending on product complexity) to develop these products, of which US$1.74 billion (US$1.37 billion to US$2.1 billion) would be required for phase III trials through 2031. Seventy percent of these additional costs would be incurred in the next five years (US$1.21 billion) – the annual cost would thus amount to US$0.24 billion.

The total annual resource needs for late-stage trials of products for PRNDs are therefore estimated to be US$1.72 billion (US$1.48 billion + US$0.24 billion). As highlighted above, currently all annual funding for all clinical development and post-registration studies is around US$1.4 billion.[4] If we assume that half of this US$1.4 billion is spent on phase III trials, a conservative estimate is that there is an annual funding gap of at least US$1.0 billion for late-stage clinical trials (Table 4).

This is a substantial gap – however, when put into perspective, the gap seems to be manageable. In 2018, official and private donors provided a total of US$26.2 billion in official development assistance for health. The financing gap for late-stage clinical trials is only 3.9% of this amount.[10] If compared with estimates from the Institute for Health Metrics and Evaluation (IHME), which uses a different definition of global health financing and gives the estimated global funding at US$38.9 billion in 2018, the amount needed for late-stage clinical trials is an even smaller proportion (2.6%).[11]

Table 4. Annual funding gap for phase III trials over next 5 years

Cost category	Annual costs, US$ billion	Available annual funding, US$ billion	Annual funding gap, US$ billion
Costs to move current candidates through the pipeline	1.48	0.7*	1.02
Additional costs to launch "missing" products	0.24		
Total	1.72		

*Assumes that 50% of all funding for clinical and post marketing R&D (i.e., 50% of US$1.4 billion) is currently being spent on phase III.

3.2 A mismatch between funding and needs

In addition to highlighting the financing gap for late-stage trials, our new study of the pipeline of candidates for PRNDs also shows that (a) there continues to be insufficient R&D for a number of the "most neglected" diseases, and (b) there has been little growth in recent years in the number of candidates that are NCEs.

Specifically, we found that the size of the R&D pipeline (i.e., the number of candidates under development) for diarrheal diseases, salmonella infections, helminth infections, and kinetoplastid infections (Chagas disease, visceral leishmaniasis, and sleeping sickness) either fell or was at best unchanged from 2017 to 2019. Of the 35 diseases included in our review of the 2017 pipeline, 15 still had fewer than four candidates each in the pipeline in 2019. Many of these are neglected tropical diseases, whose funding has remained more or less stagnant over the course of the last decade, while funding for HIV/AIDS, TB, malaria, and Ebola has grown significantly.[4] It is also very concerning that there was no increase in the number of NCE candidates in the R&D pipeline (in fact there were two fewer in 2019 than in 2017), despite the overall pipeline growing by more than a quarter.

3.3 The valley of death for vaccine trials

The current global ecosystem for R&D suffers from a particularly large gap for late-stage clinical trials for vaccines.

For vaccine development specifically, Rappuoli and colleagues have recently shown the challenges of conducting late-stage trials (Figure 1).[1] While there have been improvements in early stage development, thanks to investments by the Bill & Melinda Gates Foundation, PATH, and others, "these improvements in the early development process have revealed a new, and possibly more perilous, Valley of Death in the late vaccine development phase." According to Rappuoli *et al*, late development is responsible for 70% of total vaccine development costs. However, there is a major gap in the financing architecture for such late development (Figure 1 shows this gap, which is denoted by "?"). The large costs and time commitments are explained by the need to (a) produce vaccine candidates according to good manufacturing practice standards in purpose-built production facilities, (b) conduct large-scale phase III trials, (c) submit data to regulators, and

(d) conduct post-marketing surveillance. Although not shown in the figure, phase IV costs can also be substantial.[1]

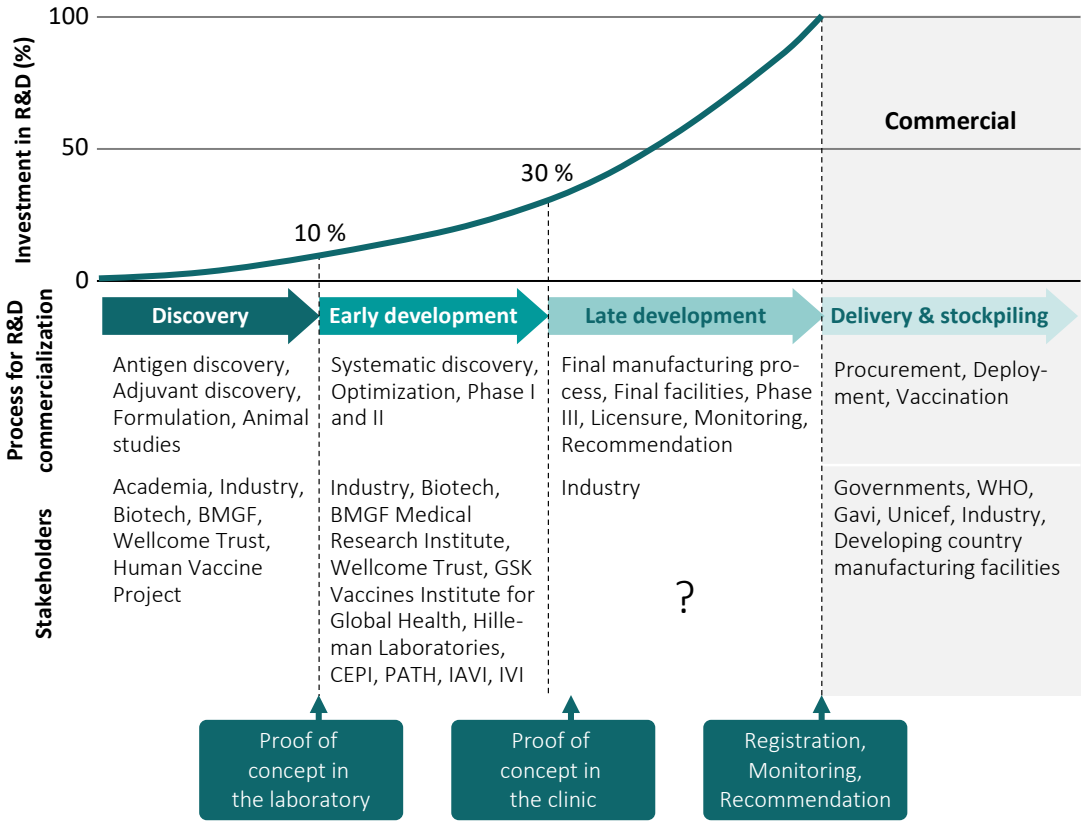

Figure 1. Stages of vaccine development and delivery

The figure shows three stages of vaccine development: discovery (10% of the R&D budget), early development (20% of the budget), and late development (70% of the budget). Under the graph are the funders and stakeholders involved at each step. A major gap can be seen in the financing architecture for late development (denoted by "?"). Figure adapted from a figure in reference 1.

3.4 The current R&D landscape for PRNDs

How has the valley of death arisen, why is there a mismatch between funding and R&D needs, and how has the international community attempted to address these challenges? Below, we briefly address these questions. We show how the current R&D architecture, despite yielding successes, still has a major gap when it comes to funding late-stage trials. In launching a new aggregator, it would be important to (a) build on and complement the existing architecture, and (b) fill a "niche" that has clearly not been filled to date.

As argued above, funding of late-stage clinical trials for PRNDs is extremely limited in the current landscape with only about 10% of all candidates in clinical development currently in phase III. Late-stage trials of PRND candidates conducted in LMICs are costly. In the P2I model, for example, which is based on historical data from around 25,000 product development candidates, the assumption is that the phase III costs for development of a complex vaccine are US$223 million, compared with US$2.5 million for phase I and US$13.9 million in phase II. There are at least three main factors that prevent the mobilization of large amounts of financing for late-stage trials.

Barriers to financing late-stage trials

The first barrier is the "free-rider" problem in global health R&D. If one country can potentially benefit from the investments made by another country, there is a temptation for countries to stay on the sidelines when it comes to funding R&D (they can reap the benefits without taking any risks). The phenomenon may contribute to aggregate global underinvestment in R&D, including late-stage trials.[13]

The second factor is market failure, especially for the "most neglected" PRNDs. Governments and patients in countries where PRNDs dominate have limited purchasing power. These diseases predominantly affect countries in LMIC markets where per capita income is almost thirty times less than high-income markets.[14] As a result, pharmaceutical companies have no incentive to produce diagnostics, drugs, and vaccines for these diseases since high-income country markets will likely have no reason to purchase these products.[4]

Third, there is limited existing late-stage clinical trial capacity and expertise in some LMICs. Grover and colleagues highlighted these barriers in the context of gynecological malignancies.[15] In some LMICs, concerns include poor quality of informed consent, sub-optimal regulatory processes for new drugs and clinical trials, inadequate protection of patients' rights and compensation, too few facilities, lack of trained human resources, and limited expertise and motivation to conduct research. These findings are in line with a recent report specifically focused on late-stage clinical trials capacity and innovation in South Africa.[16] In-country barriers thus limit global appetite to fund clinical trials in countries where there is a large population affected by PRNDs.

Initiatives aimed at financing product development for PRNDs

Over the past two decades, a number of "push" and "pull" incentives have been developed and tried in an attempt to address these barriers. Push mechanisms, such as R&D tax credits and research subsidies, reduce R&D costs. Pull mechanisms provide financial incentives aimed at increasing revenues—examples include priority review vouchers, milestone prizes and competitions, and advanced market commitments. Other policy initiatives that have aimed to improve the overall R&D ecosystem for PRNDs include open science approaches, patent pools, and providing technical assistance with technology transfer to build research and production capacity.

An important governance innovation that has shaped the PRNDs R&D landscape is PDPs. In addition to offering centralized coordination, PDPs also have lower research costs than research-based pharmaceutical companies due to (i) lower capital costs (because they can leverage in-kind inputs) and (ii) selectively investing in projects from a pool of existing public/private projects.[17] Examples of PDPs that have brought drugs for PRNDs to market include the Medicines for Malaria Venture (MMV), which has helped develop eleven new medicines or formulations for malaria, and the Drugs for Neglected Diseases initiative (DNDi), which has successfully developed two new medicines for sleeping sickness. Of note, very few PDPs have brought new vaccines to market for PRNDs – PATH's RTS,S/AS01 malaria vaccine is the most notable one currently in registration.[18]

PDPs have not been the only mechanism for improving R&D coordination. The World Health Organization (WHO) and the European Commission have also strived to streamline coordination of funding for clinical trials, particularly in the pre-clinical and early clinical trial stages, to varying degrees of success.

The WHO's Consultative Expert Working Group on Research and Development (CEWG) proposed the creation of a voluntary pooled fund to finance global health R&D needs in LMICs, accompanied by a global observatory to monitor such R&D and a series of demonstration projects to show how the fund would work.[19] While a few countries initially pledged funds to this pooled mechanism (e.g., Switzerland pledged US$6 million, Norway pledged US$1.3 million, and Brazil pledged US$1 million), the mechanism failed to gain traction.

The European Parliament and Council created the European and Developing Countries Clinical Trials Partnership (EDCTP) in 2003 with a similar mandate to promote collaborative research supported by multiple funding agencies. The EDCTP is funded by the European Commission (EC), matched by contributions from participating states. Under the EU's Horizon 2020 program, the EU is providing up to €683 million for the period 2014-2024. The first two programs (EDCTP1 and EDCTP2) have funded more than 184 clinical trials to date.[20]

There have been similar efforts for AMR. The Global AMR R&D Partnership (GARDP) was launched in May 2016 by the WHO and DNDi to improve coordination and collaboration in global AMR R&D and increase investments into R&D for AMR. Since its launch, over US$60 million has been pledged and four products have achieved registration status with investments from GARDP.[21] GARDP also works closely with a global knowledge center called the Global AMR R&D Hub that attempts to centralize global priorities for AMR R&D across the one health continuum.[22]

Assessment of aggregator-type mechanisms

To better understand the landscape of existing coordination mechanisms (which we call "aggregator-type mechanisms"), we conducted a rapid assessment of 12 mechanisms that vary in terms of their size, scope, focus, and approach. The 12 mechanisms comprised (a) five PDPs (the International AIDS Vaccine Initiative [IAVI], MMV, PATH, DNDi, and the TB Alliance) that collectively receive about 65% of total annual funding to PDPs, and (b) seven intermediary funding mechanisms (EDCTP, the Global Health Technology Fund [GHIT], the Global Health Investment Fund [GHIF], CEPI, GARDP, the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator [CARB-X], and UNITAID) that account for US$1 billion in annual funding.[2] These initiatives target the development of drugs, diagnostics, and/or vaccines for PRNDs, AMR (CARB-X), and EIDs with epidemic potential (CEPI). Annex 7 summarizes the key features of these 12 aggregator-type mechanisms, including their partners, the amount of funding they have mobilized, their governance, and the status of their products/trials to date.

Four key findings emerged from our assessment of these mechanisms:

First, most mechanisms are narrow in scope, focusing on just one or two diseases. For example, in an analysis of eight projects in its portfolio, DNDi spent almost 75% of its funding to develop two trypanosomiasis (sleeping sickness) drugs.[23] Similarly, HIV, TB, and malaria accounted for about two-thirds of all grants disbursed by EDCTP in 2018.[3] The GHIF is an example of mechanism that has invested funds across a broader range of diseases—it has made investments in eleven products to treat/prevent conditions such as polio, measles, rubella, zika, malaria, and dengue – with grants averaging US$5-10 million.[24] Some global health researchers argue that a disease-specific focus (as in the case of DNDi and EDCTP) in the setting of limited coordination across funding platforms can contribute to competition for scarce resources.[7]

Second, an analysis of the portfolios of these 12 mechanisms shows that there are very few late-stage products in the pipeline for PRNDs, AMR, and EIDs. As mentioned above, although most coordination

platforms fund product development across phases I-IV, most candidates are still highly concentrated in preclinical research and early-stage trials rather than in phase III (Tables 5 and 6). For example, of IAVI's 20 candidates currently in the pipeline, only two candidates are in phase III.[4] Although these mechanisms have few candidates in phase III and IV, these late-stage clinical trials are still responsible for the bulk of their expenses. For example, in a 2018 report of DNDi's portfolio, phases II, III and registration accounted for 65-70% of all expenses.[23] This finding is in line with our own estimate that about 62% of the total cost of moving candidates through the pipeline can be attributed to phase III (Annex 6).[5] Thus, even with the many aggregator-type mechanisms in place today, we still see a gap when it comes to late-stage trials, explained in part by the high trial costs.

Table 5. Number of candidates in the pipeline for top 4 PDPs by funding (based on publicly available information as of September 15, 2020)

PDP	Discovery and pre-clinical	Phase I	Phase II	Phase III	Registration and beyond	Source
PATH (Malaria Vaccine Initiative)	6	5		0	1	https://www.malariavaccine.org/projects/mvi-portfolio
IAVI	8	10		2	0	https://www.iavi.org/our-science/pipeline
TB Alliance	n/a	2	2	3	2	https://www.tballiance.org/portfolio
DNDi	19	6	11		13	https://dndi.org/wp-content/uploads/2020/06/DNDi-June2020-RDPortfolio.pdf

NOTES: Because PATH only provides a breakdown of candidates by stage for malaria vaccine projects, reported numbers may not be indicative of PATH's entire portfolio. MMV is one of the top five PDPs by funding, but is not captured in the table given its use of a different taxonomy for reflecting a product's status. MMV focuses on malaria drugs. According to MMV's website, as of September 2020, there are nine products in the translational phase, nine products in the development phase, and 13 products approved/available for access. For IAVI, phase I and II candidates are combined given the way its candidates are reported in its pipeline. The breakdown as reported by IAVI is as follows: phase I (3), phase I/II (5), phase II (1), phase IIb (1).

Table 6. Number of candidates in the pipeline for selected funding mechanisms (based on publicly available information as of September 15, 2020)

Funding mechanism	Discovery and pre-clinical	Phase I	Phase II	Phase III	Registration and beyond	Source
EDCTP	n/a	6	16	18	8	https://edctp.maglr.com/international-partnerships-against-infectious-diseases/cover
GHIT	38	1	3	1	1	https://www.ghitfund.org/investment/portfolio
CARB-X	38	1	0	0	0	https://carb-x.org/portfolio/portfolio-pipeline/

CEPI	16	11	3	0	https://cepi.net/research_dev/our-portfolio/

NOTE: For EDCTP, we relied on data from its 2018 annual report. Candidates may have changed and are not reflected in the above table. EDCTP does not report diagnostic trials by phase. According to its 2018 annual report, there were a total of four candidates in observational studies and eight candidates in non-phase diagnostic trials.

A number of these mechanisms are considering expanding their focus to include more late-stage clinical trials. For example, CARB-X is considering expansion from preclinical research and phase I to include support for Phases II and III for candidates that have successfully graduated from CARB-X. A coalition of PDPs is advocating that EDCTP double its funding to 1.36 billion Euros to successfully support "EDCTP3's goal of funding more Phase III and IV trials."[25]

Third, disaggregating by product type shows that mechanisms that have a broad product type focus are more likely to fund drugs and diagnostics in phase III than vaccines. For example, in 2018, out of 14 vaccine studies funded by EDCTP, only three (21%) were categorized as candidates in phases III or IV; in contrast, out of 33 drug studies, 22 (67%) were categorized as candidates in phases III or IV. Similarly, out of 30 drug candidates funded by GHIT, one (3%) was in phase III; in contrast, out of 14 vaccine candidates, none (0%) was in phase III. In addition, two out of the top five PDPs by funding focus only on drugs (DNDi and MMV). Since its inception, DNDi has funded clinical trials for drug therapies targeting sleeping sickness, leishmaniasis, and Chagas while MMV has funded pediatric formulations and new combination drug therapies for malaria. The focus on drugs over vaccines may reflect the likelihood of market failure for high-risk, low-margin products, like vaccines, and underscores the need to develop innovate funding mechanisms for such products.

Fourth, aggregator-type mechanisms have historically relied on funding from governments and foundations to fund clinical trials, but there have been some recent initiatives to diversify funding streams by leveraging private funding. Annual private sector funding of product development for PRNDs has increased from US$331 million in 2009 (9% of all funding for such product development) to US$598 million 2018 (17% of all funding).[4] This shift can be partially attributed to an increasing push to develop incentives for private sector pharmaceutical companies using impact investing principles. For example, in 2013, GHIF pioneered a funding model where investors receive a small return on investment for funding R&D for PRNDs. The Bill & Melinda Gates Foundation offers a loss-sharing agreement to private investors that limits downside risk of any investments that fail in the long-term. A number of companies such as JP Morgan, GSK, Pfizer, and Merck have invested into GHIF since 2013 with almost US$108 million total committed.[26] Governments have offered innovative value propositions to partner with pharmaceutical companies, as seen with GHIT in Japan.

In summary, the current landscape of product development for PRNDs, AMR, and EIDs is fragmented across aggregator-type mechanisms with no concerted coordination or priority setting between them. The mechanisms we reviewed predominantly focus on funding early-stage product development; the gap in funding late-stage trials for vaccines is particularly acute. Few aggregators take a multi-disease approach. The gap in the existing architecture points to the need for a new kind of aggregator funding mechanism that could play a critical role in coordination of late-stage trials. In their review of existing aggregator-type mechanisms, Beyeler and colleagues also conclude that a global health R&D coordination platform is needed, and that it should (1) develop broad-based and public ownership and management, (2) separate coordination and financing functions, (3) create multi-disease platforms, (4) pair global and national efforts, (5) develop an

international roadmap for conducting R&D, and (6) develop a strategy for the sustainability of the platform's secretariat.[7]

What COVID-19 means for the R&D landscape

The flurry of R&D activity devoted to development of COVID-19 control tools shows that if a single infectious disease threatens all nations (not just LMICs), large amounts of financing for product development can be quickly mobilized and new aggregator-type structures can be rapidly launched:

R&D financing for COVID-19. R&D financing has been raised through a combination of existing mechanisms (e.g., CEPI has mobilized financing for COVID-19 vaccine development) and new approaches (e.g., the May 4 2020 COVID-19 pledging conference, hosted by the European Union).

Aggregator-type mechanisms for COVID-19 R&D. On April 24 2020 a new aggregator-type governance mechanism was launched, the Access to COVID-19 Tools (ACT) Accelerator. The ACT Accelerator is defined as a "landmark, global and time-limited collaboration to accelerate the development, production and equitable global access to new COVID-19 essential health technologies."[27]

The accelerator has four pillars:

- The diagnostics pillar, co-led by FIND and the Global Fund
- The therapeutics pillar, co-led by UNITAID and the Wellcome Trust
- The vaccine pillar, co-led by Gavi, CEPI, and the WHO
- The health systems pillar, led by the World Bank and Global Fund, and supported by the WHO, which aims to support the delivery of diagnostics, therapeutics, and vaccines.

In addition, on June 4 2020, Gavi launched an advanced market commitment for COVID-19 vaccines, the first building block of a broader mechanism, the COVAX Facility. Countries that participate in the facility will be guaranteed access to enough vaccine to cover 20% of their population (i.e., high-risk groups such as health workers and the medically vulnerable). HICs and upper middle-income countries will participate as self-funding countries, while lower middle-income countries and low-income countries will be funded by Gavi to participate. The deadline for the first binding financial commitments to the Facility is August 31, 2020.

Overall, the COVID-19 pandemic has led to an increased awareness of global health (i.e., of the inter-connectedness of nations) and of the need for global health R&D. As the closure of businesses and stay-at-home orders ravage economies, governments are realizing the importance of investing in the development of new technologies to save trillions of dollars down the road. But it remains unclear whether there are transferable lessons from COVID-19 to PRNDs. Clearly high-income nations have been hit hard by COVID-19 in terms of numbers of cases and deaths (for example, as of August 12, 2020, the US accounts for about a quarter of the world's cases), so these countries have an incentive to invest in R&D. Similarly, the pharmaceutical industry has an incentive to invest in COVID-19 diagnostics, treatments, and vaccines because there is a huge global market for COVID-19 technologies.

While the incentive structure is different for COVID-19, the crisis could potentially have a positive impact on product development for PRNDs. The international efforts that have emerged to fund COVID-19 R&D and to channel such funding to multiple, simultaneous development efforts show that large-scale global investment

for targeted health R&D can be mobilized. COVID-19 has also raised awareness of the large gaps in global health funding more broadly, including funding for product development. Crucially, this awareness has gone far beyond the "usual suspects" and it could help to convince decision-makers that a new funding system for PRNDs is needed. COVID-19 has shown, very clearly, that the current global health R&D system has major weaknesses, not just a lack of financing but lack of prioritization, coordination, and information. The pandemic has shown now, more than ever, why we need an overarching aggregator that not only aggregates financing, but also know-how, technical expertise, prioritization, and other critical functions.

4 DEVELOPING AN AGGREGATOR FOR LATE-STAGE CLINICAL TRIALS

In the previous section, we showed that there is a funding gap for late-stage clinical trials alongside an institutional gap in the global ecosystem for PRND product development. In this section and the following sections, we present the results from our first round of KIIs, which we conducted to better define the need for and ideal characteristics of an aggregator.

4.1 Overall levels of support, main advantages, and risks

There is substantial support for the creation of an aggregator mechanism for late-stage clinical trials: 86% of consulted stakeholders expressed strong or moderate support for such an aggregator. The availability of funding for late-stage trials is seen as the number one benefit of an aggregator. Stakeholders would also want such an aggregator to invest in infrastructure and human resources to build sustainable clinical trial systems in LMICs. Stakeholders that opposed the notion of an aggregator (14%) believe that it could divert funding from existing initiatives.

We found widespread buy-in for the notion of a new aggregator mechanism. Most key informants were supportive of launching such a mechanism for late-stage clinical trials: 48% of all stakeholders strongly supported the creation of an aggregator mechanism and 38% offered moderate support. Fourteen percent of stakeholders opposed the idea of an aggregator (Figure 2).

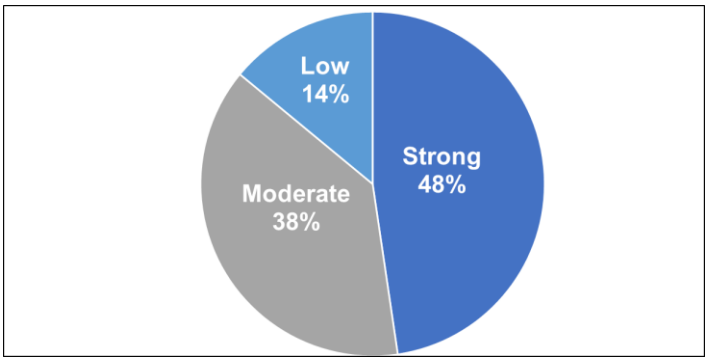

Figure 2. Do consulted stakeholders support the creation of a new aggregator mechanism? (N= 107)

What would be the main benefits of an aggregator? The number one benefit offered by key informants, proposed by 77% of those interviewees who expressed an opinion on this topic, was mobilization of funding (Figure 3). Stakeholders saw a range of other potential benefits of an aggregator. Forty-four percent argued that the aggregator should help to boost qualified human resources (e.g., trialists, scientists, and data experts) and 37% argued that an aggregator could mobilize increased investment in the clinical trial infrastructure in LMICs. Building such capacity would have benefits beyond PRNDs. Strong clinical trials systems could also support trials for other areas, such as NCDs, EIDs, and AMR. Some KIs expressed an even broader vision in which strengthened trial capacity could be valuable for LMICs in reaching universal health coverage and in strengthening primary health care and health systems—for example, if this capacity was used to test different service delivery approaches or provider payment mechanisms.

Other benefits identified by key informants were global coordination, the improved availability of technologies for PRNDs, and a faster product development process. Half of consulted stakeholders were concerned about inefficient regulatory processes at both global and country levels, and suggested that the aggregator should help to address this challenge.

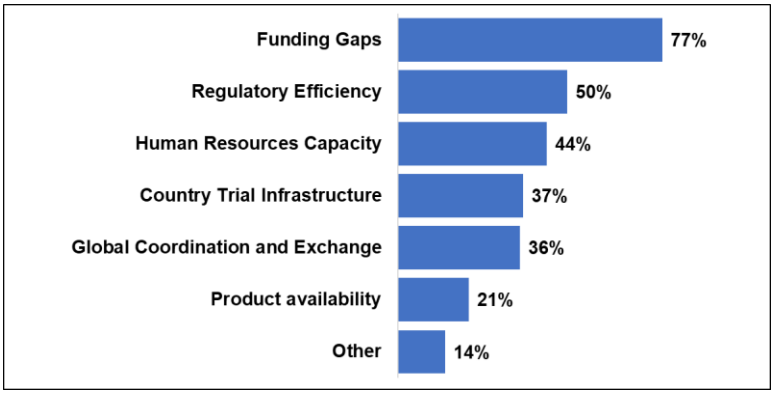

Figure 3. What late-stage bottlenecks could an aggregator mechanism help address? (N = 101)

Only 27 key informants pointed to potential disadvantages of an aggregator mechanism (Figure 4). Stakeholders who did not support the creation of a new aggregator were more likely to describe disadvantages. The main concern was that any new institution would likely divert funding from existing mechanisms, that it would duplicate the work of these existing processes, and that it would further fuel competition for funding. These key informants argued that existing institutions, such as PDPs, EDCTP, and UNITAID, should be used to fund late-stage clinical trials. In addition, stakeholders feared that the priority setting would be controlled by a small group of actors, particularly the funders of the aggregator.

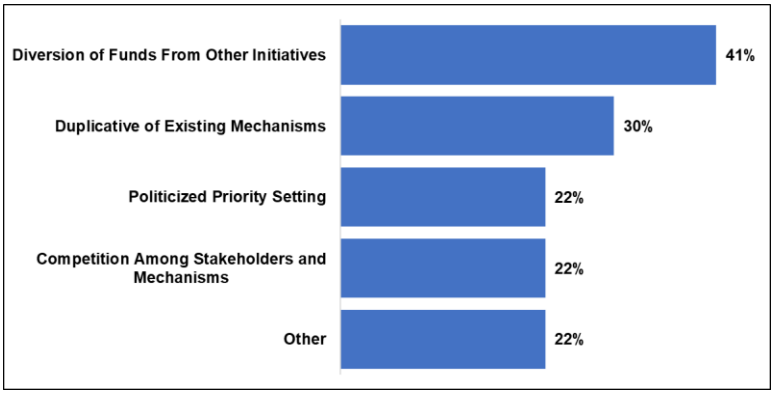

Figure 4. What are the key risks and disadvantages of an aggregator? (N = 27)

Supporters of an aggregator (those who showed strong or moderate support) provided more specific thoughts on what they would need to fully buy into an aggregator. A total of 41 supporters offered a number of **key incentives** that would make them more likely to be supportive (Figure 5).

- **Building clinical trial capacity in developing countries** was the most commonly expressed condition for support; almost half (44%; N = 18) of those who linked their support to certain design features mentioned this incentive.

- To make an aggregator mechanism attractive to MICs, informants argued that it would need to have **domestic commercial benefits** through local manufacturing, ownership of intellectual property, and free licensing. It was not just MIC interviewees who expressed this view. Donors from high-income countries also expressed interest in greater use of MIC manufacturing capacity because of lower costs (a win-win situation).
- Supporters would be incentivized by the aggregator having a **narrow focus** on a specific set of priority diseases and by it providing **sustainable support** (including for infrastructure).
- There needs to be an **equal partnership** between Northern and Southern countries across all dimensions, such as participation in global governance structures, data ownership, and trial leadership (making sure, for example, that trials have principal investigators from the Global South).
- **Affordability and low product costs** were cited as being as important (especially to MICs) – any new products funded by the mechanism need to be affordable to countries.
- The aggregator should **leverage and support existing PDPs**.

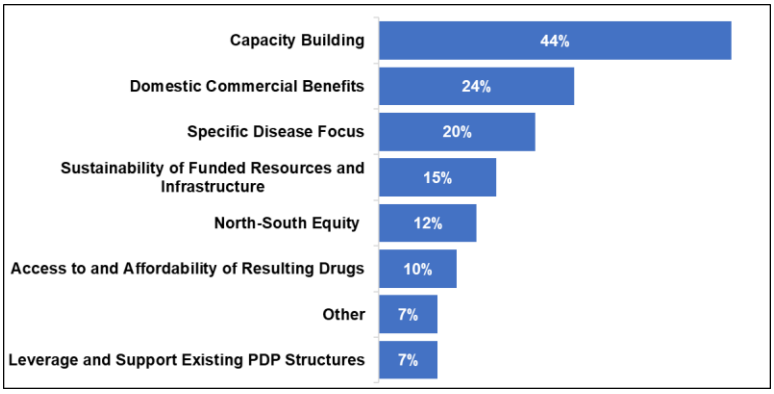

Figure 5. What supportive stakeholders need to fully buy into an aggregator (N = 41)

4.2 Support for an aggregator across geographies and stakeholder types

Stakeholders from MICs voiced strong support for an aggregator for late-stage clinical trials. The level of support differs significantly across high-income countries and across different groupings of global experts and stakeholders.

Support was particularly strong among key informants based in the four MICs: 64% of stakeholders in MICs strongly supported the creation of an aggregator mechanism and 36% gave moderate support (Figure 6). No stakeholders in MICs opposed the creation of an aggregator. In Europe, 41% strongly supported the creation of a mechanism and 34% gave moderate support. The lowest levels of support came from the US, with only 24% strongly supporting the creation of a new mechanism while 24% expressed low support for a new mechanism.

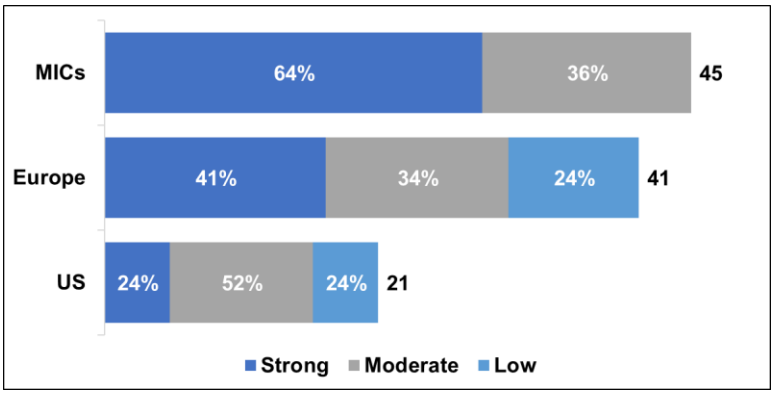

Figure 6. Levels of support by broad geography (N = 107)

A high proportion of key informants across all stakeholder types expressed strong support for an aggregator, ranging from 43% among regulators to 67% among private sector KIs (Figure 7). Half (50%) of consulted philanthropic organizations and 49% of government stakeholders strongly supported the launch of a new mechanism for late-stage clinical trials. Within each stakeholder group, more than two-thirds of interviewees expressed strong or moderate support for a mechanism. A grouping that we categorized as "other stakeholders" (e.g., civil society organizations) was most skeptical about a new mechanism – only 33% of stakeholders from this group voiced strong support for the creation of an aggregator mechanism. Notably, no private sector informants opposed the mechanism and only 9% of government stakeholders expressed low levels of support.

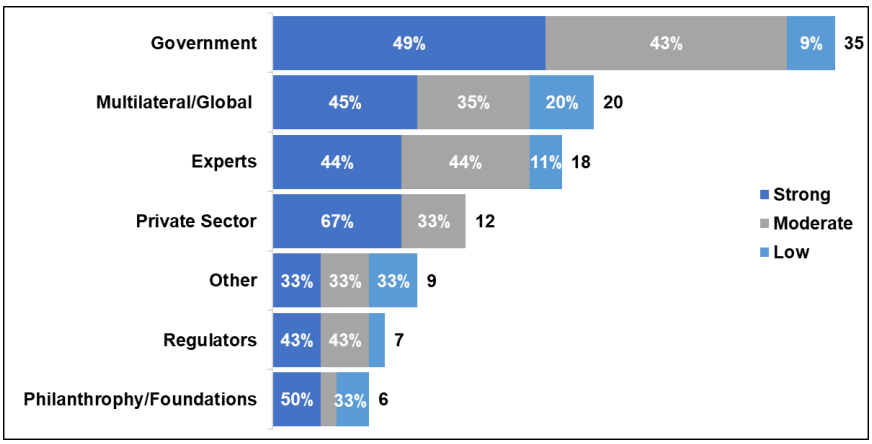

Figure 7. Levels of support by stakeholder type

Support from MICs

Most interviewees from MICs, both as a whole as well as by individual countries, strongly support the establishment of a new mechanism. Very solid support for an aggregator came from Kenya and India, where 79% and 64% of consulted stakeholders, respectively, expressed strong support for a new mechanism (Figure 8). Stakeholders in each country expressed that they would be willing to contribute trial infrastructure to a mechanism, and to some extent financing.

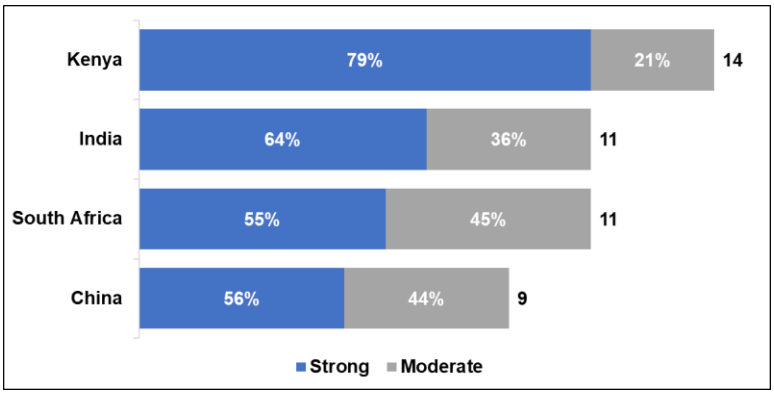

Figure 8. Levels of support for an aggregator across four MICs

Conditions for support. All four MICs noted that both capacity building and domestic commercial benefits (e.g., job creation) are key conditions to giving their support, although KIs in South Africa and India expressed the importance of these conditions more than KIs in Kenya and China. All four MICs recognize that there are shortcomings in their clinical trial systems, and specifically mentioned that they face limitations in their regulatory capacity, human resources, and infrastructure. Pooling expertise and facilitating cross-country knowledge sharing is of high importance across these countries. Capacity building is considered essential for the success of an aggregator mechanism in these settings.

Consensus areas. There was broad consensus across these countries on three key issues: pricing of products, priority setting, and governance. Stakeholders in all MICs argued that any resulting product from this mechanism must be affordable. All MIC stakeholders said that disease burden should be the driving factor for prioritizing diseases and guiding allocation decisions. However, all MICs emphasized the need for ensuring domestic stakeholders are engaged in the priority setting process to ensure local buy-in. Stakeholders were united in their vision for North-South equity in the governance of an aggregator, and some argued that there should be representation from civil society organizations (CSOs), faith-based groups, and affected populations. There was no concern expressed in the KIIs conducted in MICs in engaging the private sector in the mechanism, as long as technical experts guide decision-making and a balance is struck between profitability and affordability of resulting products.

Key incentives. MIC informants described three incentives that an aggregator could offer. The first is affordable access to domestically manufactured products. The second is ensuring sustainability—i.e., making sure that the government can continue such manufacturing after an aggregator mechanism ends. Attracting local manufacturing was also seen as a major incentive for engagement, although this was emphasized more in India and South Africa than China and Kenya.

Differences between countries. There were a number of key differences in how different countries saw the value of an aggregator. KIs in China and India said knowledge sharing is potentially more valuable to them than receiving funding, whereas the other countries expressed a need for financial support for late-stage trials. South African informants expressed interest in identifying ways to embed the clinical trial system into the broader health system. Indian stakeholders noted that while the country has significant experience with generics, it needs support to develop innovative products– an external mechanism could help support entry into this space, including through the distribution of knowledge and best practices. Kenya's R&D system, said

KIs in Kenya, remains heavily reliant on external funders. Kenya has interest in expanding its R&D footprint, but requires more infrastructure and investment to do so.

Support from HICs

We found variation in support levels for a new aggregator across the four HICs included in our study. The proportion of KIs in each country who offered "strong support" ranged from 24% in the US to 60% in Germany (Table 7).

Table 7. Levels of support in HICs and from global/regional/other stakeholders

High-Income Countries						
Support Level	**US**	**UK**	**Germany**	**Netherlands**	**Global/ Regional**	**Other**
Strong	24%	50%	60%	33%	20%	46%
Moderate	52%	40%	40%	33%	50%	15%
Low	24%	10%	0%	33%	30%	38%

Common themes across all HICs. We identified a number of common themes. First, across the four HICs included in our study, there was a very strong sense that an aggregator must pool not just money but expertise and capabilities (as one KI said, it should be a "center of excellence that maps global capabilities and makes connections"). Second, a view expressed across all HICs was that an aggregator must clearly do something different to what PDPs are already doing, and should be careful not to weaken or divert funds from existing PDPs. It should build on the success of PDPs and not be duplicative. Third, an aggregator should link and coordinate with existing initiatives – for example, EDCTP and the US National Institutes for Health (US NIH) trial networks.

Differences in funding approaches and priorities. We also identified some important differences in the ways that HICs fund product development for PRNDs and in their research priorities. The US is an outlier in that it has not traditionally put funding for such R&D into pooled mechanisms over which it has no control. The US has, however, provided technical assistance and other assets (e.g., trial sites) to pooled R&D funding mechanisms. A good example is US support for CEPI—the US has not funded CEPI but has supported it in other ways. KIs in the US also had more positive views on the role of return-seeking behavior in an aggregator and in general on the role of the for-profit pharmaceutical industry. With respect to priorities, different HICs have publicly stated their own priorities when it comes to global health R&D. Some countries, for example, strongly prioritize sexual and reproductive health (SRH) in their global health efforts and indicated that an aggregator should also include SRH-related R&D.[28] There was also no agreement about the scope of the aggregator. A range of KIs from HICs thought that the aggregator should have a broad scope (in terms of product types and diseases) so that it can help to coordinate and rationalize the R&D ecosystem. Other HICs think that an aggregator with a narrower mandate (e.g., vaccine-focused) would be more valuable.

4.3 Contributions to the aggregator

Contributions to the aggregator's global pool of funding would have to come from HIC donors but LMICs will also have to contribute – either through direct investments into the global pool or through financial support to trials that are conducted in their own countries. In this sense, LMICs would "match" the contributions of HICs.

Stakeholders agreed that there should be a global funding pool to finance late-stage clinical trials of candidate products for PRNDs. Contributions to the global pool of funding would certainly come from traditional donors—that is, governments of HICs and philanthropic organizations, though some key informants in HICs argued that it should not just be the "usual donors" that come forward.

Some stakeholders from China, India, and South Africa indicated that these countries should also contribute to the global pool, although government representatives from these countries indicated that their contributions would rather be made through in-country investments. These MIC government stakeholders proposed that they could support the trials through the provision of funding to public and private research institutes and developers within their own country (India is taking such an approach in its funding to CEPI). In addition, LMICs would cover the costs for human resources and infrastructure. They could also put in place policies to move trials forward and increase regulatory capacity. In this sense, LMICs would "match" the contributions of HICs. Investments from LMICs will be critical and MICs signaled in our conversations a willingness to invest. In exchange for providing these matched contributions, LMICs could be given manufacturing rights—which could be a powerful incentive to bring LMICs to the table.

Representatives from industry indicated that they could provide expertise and potentially funding for trials on a case by case basis (i.e., cost sharing). However, the KIs who we interviewed from industry said that they would not be able to make contributions to the pool. However, they were very supportive of an aggregator as it would provide predictable funding for late-stage clinical trials, facilitate exchange of information, and provide a list of prioritized products. As such, industry was very interested in an aggregator.

As we highlighted above, stakeholders in all MICs argued that any resulting product from this mechanism must be affordable. Country stakeholders made it very clear that their participation is linked to affordable products. Even many MICs struggle to purchase health technologies due to high prices, which is one of the reasons why there is so much concern worldwide about the final price of COVID-19 vaccines once they are developed.[29] The price of the products is a "deal breaker" for the aggregator, argued many KIs. For this reason, it is very unlikely that an aggregator could be funded from return-seeking investors (or even a blend of public and return-seeking investment), since the expected financial returns would drive up product prices unaffordable to many poor countries. While recent research has suggested that up to US$1 billion annually could be mobilized from return-seeking investments by 2030, these types of investments are unlikely to be a good fit for a late-stage trials aggregator.

4.4 Scope of an aggregator mechanism for late-stage clinical trials

In terms of which development phases an aggregator should support, consulted stakeholders agreed that phase III funding is key, though many argued that mobilizing funds for phase IIb vaccine trials and for phase IV are also crucial. However, consulted stakeholders had different views about the scope of an aggregator (i.e., the product types and diseases). One group was in favor of a broad aggregator mechanism that would support the entire spectrum of product types and all PRNDs from the G-FINDER list. A second, albeit smaller, group was in favor of a narrower, more targeted aggregator mechanism that at least initially focusses on late-stage clinical trials for vaccines and a smaller number of diseases. The group that favored a narrow approach argued that such a mechanism would be more feasible and less costly to launch and it could help to show proof of principle by bringing some targeted quick wins.

Consulted stakeholders fully recognized that there is a need for an aggregator for phase III trials (Figure 9). No single interviewee disagreed that an aggregator mechanism should provide funding for phase III. A total of 21 consulted stakeholders made the case to include Phase IV funding. They argued that post-marketing costs can be substantial and that these studies are critically important.

Other stakeholders rather opted to "go down a bit" in phase, i.e., to also include earlier phases, especially phase IIb trials for vaccines (a total of 15 stakeholders suggested including phase IIb). This group of stakeholders argued that very few candidates make it to and survive phase III. They argued that if the phase III trial is successful, there will be funders who come in and fund phase IV activities.

A few KIs also made the case for a much broader mechanism, including for early clinical stages and basic research. Five consulted stakeholders suggested that the mechanism should include phases IIa through IV. Only two stakeholders suggested that the new fund work with existing delivery mechanisms or surveillance systems in addition to funding phases IIb to IV.

R&D Phases (# of Respondents)						
	I	**IIA**	**IIB**	**III**	**IV**	**Delivery**
	3					
		2				
			3			
				4		
				14		
		5				
			2			
Total	**3**	**10**	**15**	**33**	**21**	**2**

Figure 9. Which product development phases should an aggregator fund?

How to read this table. The first row shows that 3 interviewees suggested an aggregator should include phase I to phase III. The second row shows that 2 interviewees suggested that the aggregator should include phase IIA to phase III. The total in the second column (labeled phase IIA) shows that 10 interviewees said that phase IIA should be funded by an aggregator.

Almost two-thirds of stakeholders (64%) suggested that an aggregator mechanism should fund late-stage trials for all product types (drugs, vaccines, diagnostics, and vector control products). The remaining 36% indicated that the mechanism should at least initially have a focus on specific product types: (a) 24% advocated for an aggregator mechanism that would target vaccines, and (b) 12% argued in favor of a mechanism that would fund late-stage clinical trials for TB therapeutics because of the increasing number of cases of multi-drug resistance TB (MDR-TB) and extensively drug-resistant TB (Figure 10).

In addition, 80% of stakeholders argued that an aggregator should cover all PRNDs, while 20% found a more targeted disease focus more viable (Figure 11). The need to develop new technologies for TB control was mentioned most often (N = 6).

A few stakeholders offered a different vision and advocated for an aggregator that would only fund "truly" neglected tropical diseases (e.g., kinetoplastid infections), which receive very little attention and for which a substantial treatment gap persists. These stakeholders believed that HIV, TB, and malaria should be excluded from the list of supported diseases because they receive the lion's share of the funding (the three diseases collectively received 69% or US$2.8 billion of all global funding for neglected disease R&D in 2018[4]). Yet others acknowledged this fact and made the case to earmark a share of the aggregator's funding for clinical trials for the most neglected diseases.

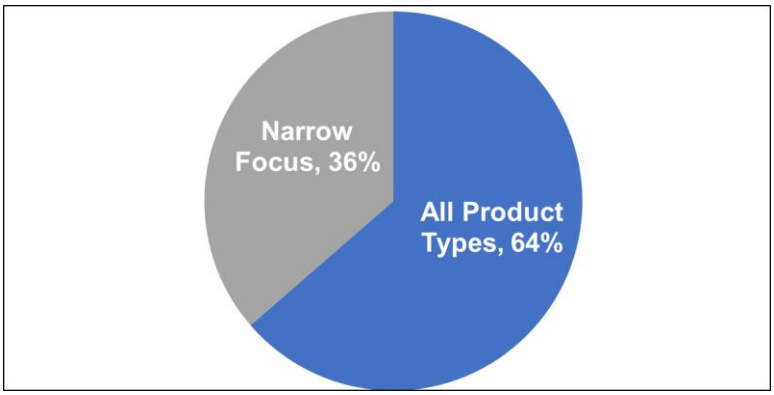

Figure 10. Scope of aggregator in terms of product types supported (N=33)

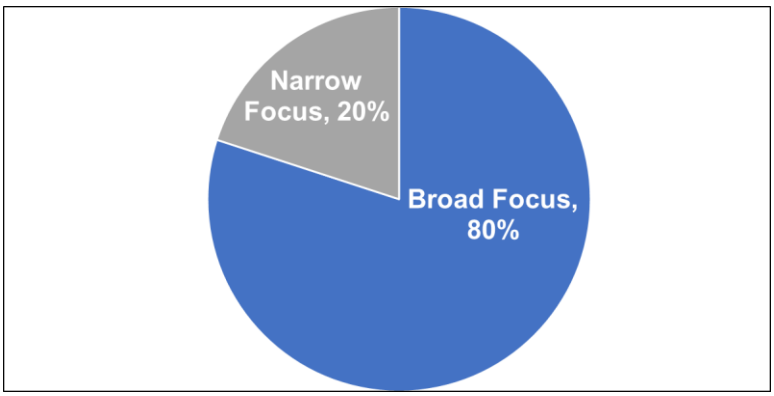

Figure 11. Scope of aggregator in terms of diseases supported (N=55)

As such, stakeholders fell in two groups with respect to the scope:

- A first group was in favor of a **broad aggregator mechanism**, which would support the entire spectrum of product types and all PRNDs from the G-FINDER list. This group emphasized the need to coordinate the fragmented and inefficient global community that works on product development for PRNDs. For this group, the main benefit of the aggregator is to rationalize the product pipeline based on a strong prioritization process (see the section on governance below) and to provide coordinated funding to late-stage clinical trials.
- A second, albeit smaller, group made the case for a **narrower, more targeted aggregator mechanism** that at least initially focusses on clinical trials for vaccines and a smaller number of diseases. Once this narrow mechanism has proven to be effective, its scope could potentially be broadened. This group believes that a targeted approach would have several advantages:
    - A targeted scope is more appealing to donors because the initial investments would be smaller than for a broad aggregator.
    - The return on investment would be easier to measure.
    - The set up and annual running costs would be lower. The management unit (secretariat) would require less expertise (e.g., it would need expertise just in vaccines and not in all product types) compared to a broader mechanism, and the governance could also be organized in a more efficient way.
    - A narrowly defined aggregator could be launched much faster.
    - The aggregator mechanism could be more easily attached to an existing organization (e.g., CEPI or Gavi for vaccines); in contrast, a broader, more encompassing aggregator would very likely require the launch of a new institution.

Overall, stakeholders from the second group referred to CEPI as a successful example of a funding mechanism with a narrow focus on infections with epidemic potential, and suggested that a similar design and process to the one used by CEPI could be a useful approach. The rapid launch of new mechanisms to fund product development for COVID-19 control has also shown the feasibility of launching a very narrow aggregator with a tightly defined scope for a disease that threatens all nations.

4.5 Governance and prioritization of product candidates

The governance of an aggregator mechanism should include multiple stakeholders, including from LMICs. In addition, strong governance must also include a robust, independent scientific process for prioritization of research funding.

Stakeholders argued that there are successful existing governance models (e.g., those used by CEPI, the TB Alliance, or Gavi) that could provide a valuable blueprint for the governance of the aggregator—there is no need to "reinvent the wheel." In addition, KIs referred to broad governance principles:

Membership model: Key informants proposed that the aggregator would be based on a "membership" model, i.e., those who are members of the aggregator mechanism must make contributions (funding, policy or other contributions), and thus get representation on the board. Stakeholders stressed that representation from LMICs will be critically important because PRNDs mostly affect these countries, and thus the decisions

made by the aggregator board affects them the most. As one key informant noted, the aggregator needs "to balance out considerations: technically strong countries may not have a heavy burden of disease. Beneficiary countries should have a voice too."

Strong participation of LMICs in the aggregator's scientific committee: KIs argued that there needs to be a scientific committee that provides scientific guidance and recommends which product candidates should be prioritized. Depending on the scope of the mechanism, there may need to be multiple committees – for example, one for diagnostics, one for vaccines, and one for therapeutics. Key informants considered that the inclusion of LMICs in the scientific panel would be crucial to ensure both bottom-up and top-down views (LMICs cannot just be included as "window dressing"). There is a need for a "domestic group" on the panel, when deciding on projects, as LMIC scientists "understand the capacity, the national situation better."

Well-resourced secretariat: The secretariat needs expertise in a range of areas (e.g., the science of R&D, coordination, partnership management, fundraising, communications, and M&E) and there needs to be an adequate budget for supporting these functions (some KIs argued that the aggregator's secretariat should be based in an LMIC, to counterbalance the fact that all major funding mechanism for PRND R&D are in the Global North).

A global versus a regional aggregator mechanism. Overall, stakeholders agree that a global mechanism would be most appropriate, though there could be strong regional roles within a global mechanism (i.e., a global system with strong regional factions). For example, regional bodies could make a global fund more efficient by limiting the mechanism's interactions with individual countries. One stakeholder recommended that funding allocations by a global fund could be made regionally (e.g., 25% to Latin America), and regional bodies could further decide on how best to implement. Another stakeholder suggested making some accommodations to LMICs to gain buy-in for a global fund, for example by ensuring their contributed funds could remain local/regional. Finally, a few stakeholders suggested that piloting this mechanism in one region before expanding globally could help mitigate some of the perceived risks of a global mechanism. Table 8 summarizes the trade-offs in launching a global versus a regional aggregator.

Table 8. Advantages and disadvantages of a global or regional mechanism

	Advantages	Limitations (in comparison to other option)
Global mechanism	• Coordination/reduced fragmentation • Greater diversity of trial sites and trial data • Shared use of experts and knowledge exchange • Balances out potential nationalistic tendencies	• Lack of LMIC ownership • Greater complexity
Regional mechanism	• Closer to decision-making authority • Improved priority setting • More likely to have LMIC buy-in	• Potential to become too country-specific • Increased administrative burden • Not necessarily more effective than global bodies • Increased competition for resources/benefits would remain domestically

Health impact and scientific/technical feasibility are considered to be the two most important criteria for prioritizing products. However, stakeholders felt that the development of technologies for the most neglected diseases should also be in the mix. Stakeholders agreed that there need to be approved metrics to prioritize across potential candidates to be funded, but there was less consensus about the decision-making process (i.e., who gets to decide and how). Investors cannot dominate the allocation process. The role of funders and of the WHO in the prioritization process were both areas of contention among stakeholders.

Assuming an aggregator for late-stage trials is launched, and mobilizes new financing, we asked stakeholders about the criteria that they would use for choosing which candidates are funded. Eighty-five percent of respondents referred to health impact (burden of disease) and 51% to scientific and technical feasibility (Figure 12). In addition to these two criteria, a substantial share of respondents (46%) felt that the most neglected diseases should also be in the mix. These stakeholders believe that the aggregator should set aside funding for diseases for which there is a large treatment gap.

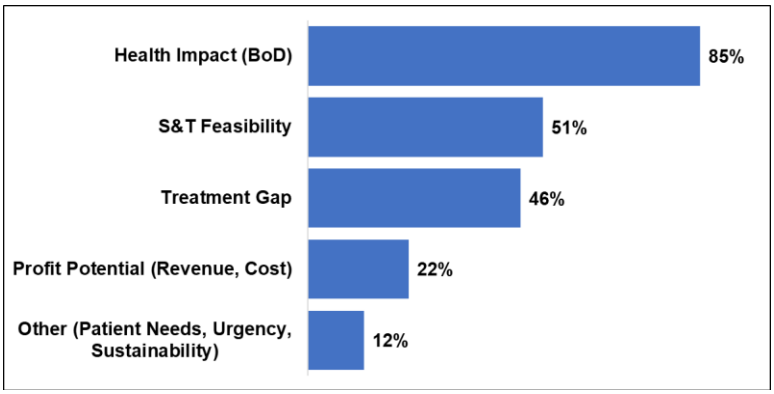

Figure 12. Which prioritization criteria should an aggregator use? (N=41)
Abbreviations: BoD: burden of disease; S&T: scientific and technical

Overall, there was agreement among consulted stakeholders that there needs to be a strong scientific process to prioritize among potential candidates and allocate available funding. This process would draw on a range

of data from multiple sources, such as WHO (e.g., from the Global Observatory on Health R&D), universities, academics (e.g., Duke University's work on the pipeline of products for PRNDs[5]), the G-FINDER report,[4] the World Bank, and high-burden countries themselves. As one key informant said, "funding allocation should be based on need, given to projects that have passed all the robust stage gates, and agnostic as to disease or technology."

The role of WHO. One area of contention was the role of WHO in the prioritization process:

- One group of stakeholders saw a ***very strong role for WHO in the prioritization process***. While the aggregator's pooled fund itself should be housed somewhere independent, this group argued that the prioritization process should be led by WHO. These stakeholders believed that WHO clearly has crucial role for priority-setting, but it has been under-funded. For example, there has been pushback against the WHO's role in R&D priority setting from countries such as the US, who not want to be constrained in terms of what they can invest in. The group that sees a strong role for WHO also argues that WHO represents all countries and that it is already doing a lot of prioritization, pointing to examples such as the WHO's role in developing the roadmap for neglected diseases 2021-2030,[30] the WHO's access to medicines initiatives,[31] the R&D Blueprint,[32] and the End TB Strategy's R&D priorities.[33] KIs in this group argued that WHO "had done a good job" on prioritizing R&D for AMR and EIDs and on the ESSENCE on health research initiative.[34] There has also been renewed interest at WHO in the need for more joined-up thinking on R&D—for example, the R&D accelerator in the Global Action Plan for SDG3 is supposed to look at the complete product development pipeline and how this is linked to product prequalification, access, and the R&D Observatory. Under the restructure, WHO wants to take more of a streamlined end-to-end approach to supporting product development, and one KI said that "inherent in this is the idea of priority setting." The idea behind the streamlined approach is that it would connect together a number of disparate activities at WHO in a more strategic, better sequenced manner (e.g., development of target product profiles, R&D prioritization processes, pre-qualification, the essential medicines list, and WHO's work on access to medicines).
- A second group took more of a middle-ground perspective and argued that ***WHO could play a technical advisory role***, supporting the decision-making on candidates. Rather than "outsourcing" the prioritization, WHO would be a key actor – an advisor – at the table but it would not manage the process. One KI in this group argued: "I'm not sure the WHO is best, given that the CEWG [the Consultative Expert Working Group on R&D Financing and Coordination] was a resounding disaster." However, this second group argued that alongside WHO, the prioritization process would involve many other actors with technical expertise in science and innovation as well as public health expertise. For example, PDPs would have a role, given that they have joint drug development and public health expertise. "When it comes to deciding what to fund," said one KI, "it can't just be scientists who decide. You must have people with pharma experience, with in-country experience, people who know how the interventions would actually be used, etc."
- A third group believed that the prioritization should be performed by ***independent experts from academia***. Everybody (including WHO) with financial or political interests would be excluded from the decision-making. WHO could be an observer.

The role of funders. Another contentious area was the role of funders. Stakeholders agreed that a scientific process is essential, but some also acknowledged that "there is always a political process in the end," which

would reflect the interests of the investors. However, stakeholders made clear that funders cannot and must not dominate this new aggregator fund – there must be a strong scientific process. Others went a step further and argued that funders who provide money into the financing mechanism should not be involved in the decision on which priority trials will be funded. Funders should 'trust' the decision-making body to make the right decision. This is a critical aspect that needs to be carefully managed – some of the stakeholders opposed the idea of an aggregator because they fear that it could be controlled by a small group of investors.

With respect to the role of industry in governance, stakeholders argued that industry's capacity and expertise would be critical to have but that it needs some careful thinking. Industry could be an observer in the scientific committee but would have no voting rights in the prioritization.

5 DEVELOPING OPTIONS FOR THE DESIGN OF AN AGGREGATOR MECHANISM FOR LATE-STAGE CLINCAL TRIALS

In section 3 of this paper, we showed that the current ecosystem for neglected disease R&D is biased towards earlier stages of development, with insufficient attention given to late-stage clinical trials. In addition, our stakeholder consultation indicated that there is substantial support for an aggregator mechanism to accelerate development of products for neglected diseases (section 4). The consultation process, in which we consulted with 165 key stakeholders in our first round of KIIs and with 27 selected stakeholders in a second interview wave, also helped us to delineate the potential scope and other key design features of an aggregator for late-stage clinical trials.

Based on the literature review and the KIIs, we developed three options for an aggregator mechanism. We analyzed these options along three dimensions: scope, costs and benefits, and feasibility.

Scope: As described previously, in our first interview wave, KIs had different views on the scope of the mechanism. One group was in favor of a broad aggregator mechanism that would support all product types and all PRNDs. A second group was in favor of a targeted aggregator that at least initially focusses on late-stage clinical trials for vaccines against a small number of diseases. A range of KIs also emphasized the need to build clinical trial capacity in LMICs. We reflected these aspects in the development of our options.

Costs and benefits: For each option, we estimated the costs and benefits (based on a number of different assumptions, as described below). There are two broad cost categories – the costs of the clinical trials themselves, which we calculated based on our model, and the operational costs of the mechanism itself (including the costs of supporting the secretariat). As described in Section 2, we also modeled the health benefits in terms of deaths and DALYs averted for the three options and estimated their cost-effectiveness and benefit-cost ratio. We modeled the benefit-cost ratio and the cost effectiveness from both a societal perspective and the perspective of the aggregator's investors. In this section, we first present the results from a societal perspective, and then the results from the investors' perspective. The benefit-cost ratios from the investors' perspective are much higher than the benefit-cost ratios from the societal perspective. Annex 8 gives further details of the modeling of costs and benefits and includes an overview of potential product launches by years and type.

Efficiency gains: As described earlier, our quantitative models focused on estimating potential gains from improving the technical efficiency of clinical trials funded by the aggregator. We modeled the efficiency gains that would arise from the aggregator's ability to use adaptive designs in clinical trials, which could potentially shorten phase times, reduce the required study sample size, and lower trial costs. In addition to a business-as-usual scenario with no efficiency gains, we modeled two efficiency improving scenarios. The first – a "feasible" efficiency improvement scenario – was one in which 50% of the trials supported by the aggregator adopted adaptive designs (which translates into an aggregate reduction of 3 months in phase length for all phases and a 7.5% reduction in late-stage trial costs). The second – an "ambitious" efficiency improvement scenario – was one in which all trials (100%) supported by the aggregator use adaptive designs (translating into a reduction of 6 months in phase length for all phases and a 15% reduction in late-stage trial costs). We

report the results for the feasible (50%) efficiency improvement scenario in this report and compare the results of all three scenarios in Annex 8.

Feasibility: Finally, we also assessed the potential to rapidly launch a new mechanism in the near future. This included an assessment of likely political support from key actors.

Table 9 further operationalizes our three assessment categories.

Table 9. Criteria for analyzing design options for an aggregator

Dimension	Criteria
Scope	• Product types supported • Diseases supported • Functions performed by the aggregator (e.g., mobilizing funding, building trial capacity, sharing best practices) • Phases supported
Costs and benefits	• Pipeline/development costs • Set up and running costs • Capacity building costs • Efficiency gains • Benefits (e.g., DALYs/deaths averted)
Efficiency gains	• Operational efficiencies e.g., improvements in global coordination (qualitatively assessed) • Technical efficiencies e.g., through adaptive clinical trials (quantitatively modelled) • Allocative efficiencies (qualitatively assessed)
Feasibility	• Likelihood of mobilizing political support from key decision-makers to implement the option • Potential for rapid implementation, considering the complexity of the option (e.g., expertise needed, complexity of governance and number of actors involved, resource needs • Risks

The three options are not necessarily mutually exclusive. If the first option (the narrowly defined aggregator for vaccine trials) were to be launched and was effective, the aggregator's scope could expand to include additional product types and diseases (Figure 13).

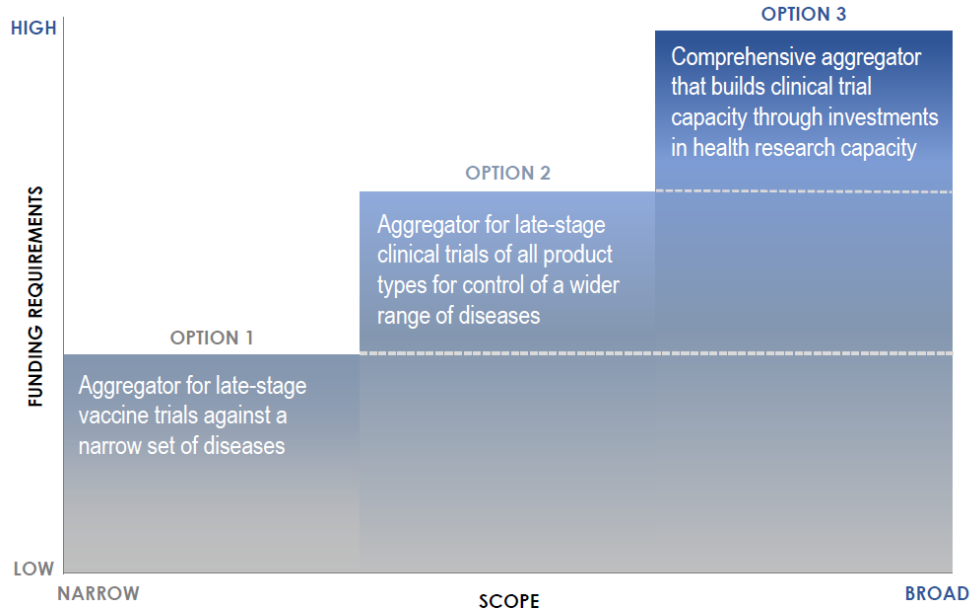

Figure 13. Options staircase

Option 1: Aggregator for late-stage vaccine trials against a narrow set of diseases

Option 1 reflects the large gap in the global health R&D architecture for the late vaccine development phase, which was also acknowledged in our consultation process. The key benefit of this option would be the availability of funding for late-stage vaccine trials and the de-risking of investments. In addition, through the prioritization process, the aggregator would also contribute to the rationalization of the pipeline for vaccines. Table 10 gives an overview of Option 1.

Scope: Option 1 is the narrowest in terms of the aggregator's scope. It focuses on late-stage clinical trials for vaccines against a targeted subset of PRNDs, which would have to be agreed upon at (or shortly after) the launch of the aggregator. Our analysis assumes that the aggregator funds vaccine trials for the four PRNDs with the highest global burden of disease as measured using DALYs (HIV, TB, malaria, and pneumonia).

The aggregator would cover the costs of late-stage trials. It would also make targeted strategic investments into the manufacturing capacity of LMICs (US$50 million over five years) but participating LMICs would have to use their own resources to build their clinical trial systems as part of the matching approach (i.e., funds from the global pool would not be used to build clinical trial capacity).

Costs and benefits: The start up and running costs would be relatively low compared with those of Options 2 and 3, as the secretariat and the scientific committee could be small—both would just need expertise on vaccines (rather than all product types). We estimate that the cost for this option would total US$2.6 billion over 11 years, including US$2.1 billion in pipeline costs and US$250-300 million in start-up and running costs. In addition, the aggregator would provide US$50 million per year over five years for building manufacturing capacity in LMICs. If this option is implemented, we estimate that it would avert 19.8 million deaths and 566 million DALYs in the period 2021-2035. The benefit-cost ratio is 5.65 (i.e., for every US$1 invested, there is a return of US$5.65).

Feasibility: An aggregator of this type could be quickly launched, given that it is narrow in scope and that key stakeholders signaled interest. Option 1 will probably require the launch of a new organization as no current institution could easily expand its mandate. However, CEPI – which currently funds vaccine development for EIDs with epidemic potential across R&D stages – seems to potentially open to the possibility. CEPI has already expanded its initial mandate to also include late-stage trials, and it is currently considering expanding to fund COVID-19 therapeutics (which, like vaccines, could reduce viral transmission).

If this option proves to be successful and shows that a dedicated funding mechanism for late-stage vaccine development can effectively accelerate the R&D process, the mechanism could be broadened to include additional product types and diseases (i.e., Option 2).

Table 10. Key features of Option 1: an aggregator for late-stage vaccine trials against a narrow set of diseases

Scope	**Product type**	Vaccines
	Disease focus	Small subset of prioritized diseases. Modelling for the investment case assumes the diseases are HIV, TB, malaria, and pneumonia (based on high global burden of disease)
	Functions performed	▪ Mobilization and allocation of funding for late-stage vaccines trials ▪ Targeted investments in building local manufacturing capacity (US$50 million per year over 5 years) ▪ Vaccine-related coordination and knowledge sharing ▪ Accountability for trials funded by the aggregator

	R&D phases:	Phase III
Costs and benefits	**Pipeline costs (2021-2031)**	US$2.1 billion
	Set-up/running costs (2021-2031)	Initial set up costs of US$36 million and annual running costs of US$25.0 million
	Capacity building costs	US$50 million per year over the first 5 years (for building LMIC manufacturing capacity)
	Deaths and DALYs averted (2021-2035)	Deaths averted: 19.8 million DALYs averted: 566 million
	Benefit-cost ratio	5.65
	Cost-effectiveness	Cost per death averted: US$2,282 Cost per DALY averted: US$80
	Efficiency gains	▪ Global coordination/prioritization will reduce duplication ▪ Using adaptive trial designs would drive efficiencies over a business-as-usual case with no adaptive trials. 50% is a feasible percentage of adaptive trials in the portfolio
Feasibility	**Political support**	Rapid launch possible as funders expressed interest in a vaccine-focused aggregator
	Ease of implementation	▪ Low start-up costs ▪ Fewer resource needs compared to other options due to vaccine focus ▪ Likely requires launch of a new organization but some potential to add a funding window to CEPI as an existing organization
	Risks	Option is less attractive to bilateral development agencies and LMIC health ministries as the focus is strictly on product development rather than strengthening health research capacity more broadly

Option 2: Aggregator for late-stage clinical trials of all product types for control of a wider range of diseases

Compared with Option 1, Option 2 tackles a broader range of diseases with a wider range of product types. Table 11 gives an overview of Option 2.

Scope: Option 2 would fund all product types for the control of a larger set of diseases. In addition to clinical trial costs, the aggregator would set aside funding for building clinical trial systems and manufacturing capacity in LMICs (we assume about US$100 million per year over the first 5 years).

Costs and benefits: Costs for this option will be substantial. Set up and running costs are higher than those for Option 1 because the secretariat and the scientific committee would need expanded capacity, including expertise across all product types and a larger number of diseases. Different scientific committees are likely to be needed for different product types (e.g., a vaccines committee, a therapeutics committee, and a diagnostics committee). We estimate the start-up costs at US$58 million and the annual running costs at US$40 million. The cost for the trials amount to US$8.3 billion. Adding a capacity building cost of US$100 million per year over the first 5 years, the total costs for this option are US$9.2 billion (the individual costs do not total US$9.2 billion because we used the net present value of future costs using a discount rate of 3%). The total costs of US$9.2 billion are more than 3.5 times higher than those of Option 1. The BCR of Option 2 is also lower (4.06 compared with a BCR of 5.65 for Option 1). However, Option 2 is more cost-effective than Option 1 - it has a lower cost per death and per DALY averted. The overall impact (deaths and DALYs averted) is also higher due to its wider scope. If this option were implemented, it would avert 24.7 million deaths and 738 million DALYs between 2021 and 2035.

Feasibility: Launching Option 2 would be more challenging than launching Option 1. For Option 2, the resource needs would be greater, and we found less support from funders for this option who considered this mechanism as too broad.

Table 11. Key features of Option 2: an aggregator for all product types to control a wider range of diseases

Scope	**Product type**	All product types (current modelling for the investment case includes vaccines and drugs)
	Disease focus	Moderately expanded subset of prioritized diseases (compared with Option 1). Modelling for the investment case assumes the diseases are HIV, TB, malaria, pneumonia, Chagas, schistosomiasis, visceral leishmaniasis, dengue, and leprosy
	Functions performed	• Mobilization and allocation of funding for late-stage trials across all product types and several diseases • Moderate investments in building clinical trial systems and manufacturing capacity in LMICs • Substantial knowledge generation and sharing, and a key role in coordination of product development • Accountability for trials funded by the aggregator
	R&D phases:	Phase III
Costs and benefits	**Pipeline costs (2021-2031)**	US$8.3 billion
	Set-up/running costs (2021-2031)	Start-up costs of US$58.0 million and annual running costs US$40.0 million
	Capacity building costs (2021-2025)	US$100 million per year over the first 5 years
	Deaths and DALYs averted (2021-2035)	Deaths averted: 24.7 million DALYs averted: 738 million
	Benefit-cost ratio	4.06
	Cost-effectiveness	Cost per death averted: US$2,145 Cost per DALY averted: US$72
	Efficiency gains	• Modest gains from global coordination/prioritization, which reduces duplication • Using adaptive trial designs would drive efficiencies over a business-as-usual case with no adaptive trials. 50% is a feasible percentage of adaptive trials in the portfolio.
Feasibility	**Political support**	A number of KIs suggested that global coordination and prioritization is needed, so there is likely some support
	Ease of implementation	• Larger resource requirements than those for Option 1 • Requires the launch of a new mechanism
	Risks	The mechanism might be considered as being too broad and thus lacking in focus. Start-up/running costs are more significant compared with Option 1

Option 3: Comprehensive aggregator that builds clinical trial capacity through investments in health systems

This option would be the broadest type of aggregator, not just in scope but in the functions that it supports. Table 12 gives an overview of Option 3.

Scope: Option 3 would fund all product types and all PRNDs. In addition to covering the trial costs, this third type of aggregator would invest substantially in the health systems of LMICs. The overall goal is to build sustainable trial networks to gain efficiencies and to fully embed the clinical trial system into the overall health system.

Costs and benefits: Costs for this option will be high because of higher investments into the health system and pipeline costs. We estimate the start-up costs at US$87 million and the annual running costs at US$60 million. The cost for the trials amount to US$15.6 billion. Adding a capacity building cost of US$250 million per year over the first 5 years (for building heath research and manufacturing capacity), the total costs for this option are US$17.3 billion (the individual costs do not total to US$17.3 billion because we used the net present value of future costs using a discount rate of 3%).

The BCR for Option 3 would be US$2.73 (i.e., every US$1 invested would return US$2.73). Implementing this option would avert 30.0 million deaths and 1.2 billion DALYs. Option 3 is the least cost effective with a cost per DALY averted of US$105, and cost per death averted of US$4,209.

Feasibility: This option appeals to health generalists, particularly those who see building health research capacity as a critical plank in strengthening PHC and reaching UHC. This audience noted the importance of trials as a tool not only for assessing candidate health technologies for PRNDs and potentially other conditions (e.g., NCDs) but also to test different PHC service delivery, financing, and governance approaches. Under this option, the aggregator would contribute to the creation of a sustainable trial network in LMICs that could go beyond trials of PRND products. As such, it could broaden the funding base for the aggregator through mobilization from a broader array of development agencies and ministries of health in LMICs (currently, PRND product development is mostly funded by public science and technology agencies and private developers rather than by health and aid agencies). But the overall feasibility of this option is currently low. It appears unlikely that it could be implemented in the near future. However, the option is an important longer-term vision for the aggregator.

Table 12. Key features of Option 3: an aggregator for all product types for all PRNDs

Scope	**Product type**	All product types
	Disease focus	All PRNDs (plus potentially non-communicable diseases and EIDs)
	Functions performed	• Mobilization and allocation of funding for late-stage trials for all product types and diseases, and for local manufacturing, including from LMICs • Substantial capacity building investments to integrate the clinical trial into the larger health system • Strong coordination and knowledge sharing function
	R&D phases:	Phase III
Costs and benefits	**Pipeline costs**	US$15.6 billion
	Set-up/running costs	Start-up costs of US$87.0 million and annual running costs US$60.0 million
	Capacity building costs	US$250 million per year over the first 5 years
	Deaths and DALYs averted (2021-2035)	Deaths averted: 30.0 million DALYs averted: 864 million
	Benefit-cost ratio	2.73
	Cost-effectiveness	Cost per death averted: US$4,209 Cost per DALY averted: US$105
	Efficiency gains (not yet quantified)	• Large gains due to coordination at global level, i.e., cost savings due to less duplication/waste/fragmentation • Initial upfront investment in health care systems will pay off later • Using adaptive trial designs would drive efficiencies over a business-as-usual case with no adaptive trials. 50% is a feasible percentage of adaptive trials in the portfolio
Feasibility	**Political support**	Some donors will like the focus on R&D as a tool for strengthening PHC and achieving UHC. However, resource needs are high and it is unclear if these supportive donors would provide the funding
	Ease of implementation	• Substantial start-up costs • Large resource requirements
	Risks	• Success depends on multiple global and domestic funders • High costs • Diverts focus from product development to the strengthening of clinical trial systems, which could scare off traditional R&D funders and those interested in clearly measurable and attributable return on investment (the broad mandate of Option 3 makes it difficult to measure success)

Trade-offs between options and recommendation

Each option has specific advantages and disadvantages and prioritizing between them inevitably involves trade-offs (Figure 14). If we benchmark Option 1 against Option 2, Option 1 appears to be attractive for three reasons. First, its costs (US$2.6 billion) are about 3.5 times lower than the costs of Option 2 (US$9.2 billion). Second, it also has a higher BCR than Option 2 (5.65 vs. 4.06). Third, rapid implementation seems to be more feasible given its more narrow focus and that key stakeholders were interested in an aggregator that focuses initially on vaccines. And while Option 3 is arguably a much larger enterprise—and ranks low in feasibility—it would be important to keep it in sight for pursuing goals that go beyond developing new health technologies to also using R&D as a tool for achieving UHC through PHC.

Based on a combination of likely impact and feasibility, we recommend that the international community pursues Option 1—an aggregator that funds late-stage trials of vaccines for a narrow range of high-burden PRNDs. This type of aggregator could be rapidly implemented and would have substantial impact at a moderate annual cost. It would also drive efficiencies, streamlining, and accountability in the vaccine development space, while testing a new approach of funding late-stage clinical trials in a targeted manner.

Overall, most KIs in the second-round interviews agreed with our recommendation to pursue Option 1 and to potentially expand the vaccine aggregator to include additional product types and diseases if it proves to be successful. Only a few of them, in particular Chinese officials and some representatives from Kenya, were in favor of Option 2 (those in favor of Option 2 emphasized the need for new treatments against diseases such as TB, and the need to develop new technologies for the most neglected diseases, such as leishmaniasis).

We thus recommend launching Option 1. Option 1 could serve as a proof of concept and become a stepping-stone for Option 2. Option 2 has a larger public health impact, as measured by deaths and DALYs averted, and is also more cost-effective (the costs per death and per DALY averted are lower in Option 2 than in Option 1).

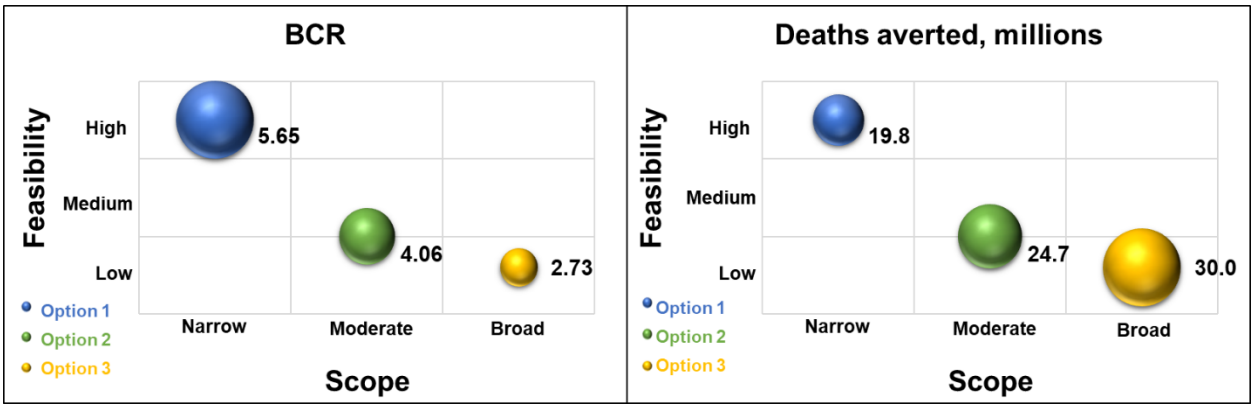

Figure 14. Trade-offs in feasibility, scope, benefit-cost ratio, and deaths averted between options

Societal perspective vs. investors' perspective

In addition to our investment case modeling from a societal perspective, we also modeled the investment case from the perspective of the funders of the aggregator mechanism. The societal perspective seeks to answer the question: "how much would society benefit for each dollar invested in the aggregator mechanism?" In contrast, the investors' perspective seeks to answer the question: "how much would society benefit for each dollar the investor puts into the aggregator mechanism?" We adopted this modified

investors' perspective for two reasons. First, a plurality of respondents would like the aggregator mechanism to be non-profit therefore we did not model potential profits to the aggregator from commercialization of launched products. Second, social investors are more likely to make investment decisions based on the potential benefit to society for each dollar investment they make, therefore this metric would be useful for decision-making at the level of individual investors.

The benefit-cost ratios are understandably larger for the investors' perspective compared to the societal perspective (Table 13). In addition, when viewed from the perspective of the innovator, Option 1 becomes much more attractive compared to the other options. Moreover, for each option, the gains from efficiency improvements are substantially higher from the investors' perspective than from the societal perspective (Table 13). Therefore, from an investor's perspective, participating in the aggregator would make a big difference compared to supporting individually-funded trials because of the aggregator's ability to systematically support the use of adaptive trial designs. This added value of an aggregator mechanism is less visible from the societal perspective because this perspective includes other costs to be covered by society (see Annex 8),

Table 13. Comparison of benefit-cost ratios from societal and investors' perspectives

	Business as usual (No efficiency gains)		Feasible efficiency improvement scenario (50% adaptive trials)				Ambitious efficiency improvement scenario (100% adaptive trials)			
	Societal Perspective	Investors Perspective	Societal Perspective		Investors Perspective		Societal Perspective		Investors Perspective	
	BCR	BCR	BCR	% gain	BCR	% gain	BCR	% gain	BCR	% gain
Option 1	5.5	70.8	5.7	4	81.2	15	5.7	4	96.0	36
Option 2	3.9	15.9	4.1	5	18.7	18	4.2	8	22.6	42
Option3	2.5	10.6	2.7	8	13.2	25	2.9	16	17.2	62

6 KEY FEATURES OF AN AGGREGATOR MECHANISM FOR LATE-STAGE CLINICAL TRIALS

We recommend the development of an aggregator for late-stage clinical vaccine trials. In this section, we describe a number of the underlying features of such as late-stage trial aggregator for PRND vaccine development.

Governance

There are existing governance models that provide a valuable blueprint for the governance of the aggregator—there is no need to "reinvent the wheel". The aggregator's governance mechanism would have three key structures: (i) a board comprising the investors group (ii) a scientific committee that advices on the selection of candidates to fund, and (iii) a secretariat for the day-to-day management of the aggregator.

Governing board: The aggregator would be based on a "membership" model, i.e., those who are make final decisions must make contributions (funding, policy or other contributions). However, there is also the need for strong LMIC participation and not all LMICs will make financial contributions to the aggregator (e.g., they may fund domestic manufacturing capacity to support manufacturing of aggregator products). Strong LMIC representation will be important because PRNDs mostly affect these countries, and thus the decisions made by the aggregator board affects them the most. In addition, there is the need for technical expertise in a range of areas, such as science, global health, industry, and finance. The board structure needs to balance out these demands to satisfy the requirements of the membership while simultaneously ensuring broad participation and strong technical expertise.

To balance out these different demands, we envision a similar governance structure to the one that CEPI uses. CEPI's primary governing body is the board, but there is also an investors' council, which nominates investor representatives to the board. This council has some specific rights, including approval of any single investment overUS$100 million. The aggregator could function in the same vein - there would be a smaller investors' group within the board that would have specific rights on the final investment decisions based on guidance from the scientific committee and other forums (see below). Overall, we expect strong interest and investment from LMICs (see subsection on resource mobilization and contributions below).

Scientific committee: There needs to be a scientific committee that provides scientific guidance and recommends which product candidates should be prioritized. The inclusion of LMICs in the scientific panel would be crucial to ensure both bottom-up and top-down views (LMICs cannot just be included as "window dressing"). There is a need for a "domestic group" on the panel, when deciding on projects, as LMIC scientists "understand the capacity, the national situation better." One way to engage LMICs is by inviting leading institutions (rather than individuals or projects); leading institutions usually have comprehensive capacity and even a mature R&D industry chain that covers basic science, pharmacology, and clinical trial sites.

Secretariat: The secretariat needs expertise in a range of areas (e.g., the science of R&D, coordination, partnership management, fundraising, communications, and M&E) and there needs to be an adequate budget for supporting these functions. The secretariat would also be responsible for the global pool of funding and for ensuring that LMICs make substantial national contributions as part of the matching approach. The global pool of funding could be administered through a World Bank financial intermediary fund (FIF).

Overall, we envision a two-stage prioritization process – a list of priority products established through a WHO process, based on which the aggregator would further select products to be funded. While the very final decisions on which product candidates should be funded will be taken by the investors group, strong inputs by WHO need to be made earlier in the process based on guidance provided by WHO. This is critical in order to facilitate the best selection of candidates and increase the legitimacy of the aggregator. This process is similar to CEPI's process. CEPI's Scientific Advisory Committee used the WHO's list of Blueprint diseases as a starting point and then made further decisions about which priority diseases and candidates to fund. The details of this process would have to be developed as part of a business plan for the aggregator, which would have to be established based on an inclusive process.

There has been renewed interest at WHO for more joined-up thinking on R&D. Under the planned restructure, WHO wants to take more of a streamlined end-to-end approach to supporting product development, which would connect a number of activities at WHO in a strategic, sequenced manner. These activities include the development of target product profiles, R&D prioritization processes, pre-qualification, the essential medicines list, and WHO's work on access to medicines. The R&D accelerator in the Global Action Plan for SDG3 also aims to improve the coordination of late-stage trials. WHO's Product Development for Vaccines Advisory Committee (PDVAC) would also have a key role to play in the selection of vaccines.

Resource mobilization and contributions

Contributions to the global pool of funding would need to come from traditional donors—that is, governments of HICs and philanthropic organizations. While traditional donors will remain critical, there is a need for other funders to step up, given the large costs of vaccine development. Regional investment banks, for example, could become a new source of funding: in July 2020, a new AMR Action Fund was launched, which aims to develop two to four new antibiotics by 2030. This fund is also supported by the European Investment Bank, which has shown more interest in the health sector – especially the AMR field – in recent years.

Contributions by LMICs will be most crucial – either to the global pool or through significant domestic contributions. In the past, R&D decisions were dominated by the North and this dominance needs to come to end. But this shift will require LMICs to contribute to the aggregator in a substantial way. While LMICs are unlikely to contribute to a global pool of funding, they need to make substantial financial contributions within their own borders. From our perspective, these financial contributions could be done in many different ways – countries could take over the costs of the late-stage clinical trials, they could help with post-licensure studies, address regulatory issues, build local manufacturing capacity including through tax benefits for local manufacturers, and make advanced purchasing commitments to buy the new technologies. Overall, there needs to be flexibility regarding these contributions due to different country contexts and the differing ability of countries to pay. A threshold would probably have to be set for different groups of countries to become part of the investors group. The detailed criteria would have to be established as part of the business planning for the aggregator.

As we highlighted in Section 4, private sector key informants were very supportive of the aggregator because it would contribute to the availability of predictable funding for late-stage clinical trials, a prioritized list of products, and an exchange of information between key stakeholders. The Access to Medicines Foundation

identified these three factors as crucial for driving pharmaceutical engagement (Box 1).[35] In this context, the Foundation's 2018 Access to Medicine Index shows that five pharmaceutical companies account for the majority of "priority R&D" (defined as R&D for products needed as a priority for people living in LMICs) – an even smaller number than in previous years because large MNCs decided to leave this space.[36,37] As the aggregator would provide substantial incentives for companies to rethink their investment strategies, it could help to bring MNCs back to PRND product development. The COVID-19 pandemic has pushed access to medicine up the agenda,[38] and the aggregator could help prolong and reinforce this recent trend.

1. Clear priorities endorsed by the international community of experts in global health. For companies, a clear and agreed-upon agenda lowers the barrier to engagement.
2. Publicly funded de-risking or market-shaping mechanisms, which enable resource sharing and reduce uncertainty.
3. Long-term and coordinated financial support from multiple donors and sustained investment in health from national governments, including to support healthy markets.

Box 1. Three critical factors for driving pharmaceutical engagement in global health product development[35]

Finally, country stakeholders made it very clear that their participation is linked to affordable products. For this reason, it is very unlikely that an aggregator could be funded from return-seeking investors (or even a blend of public and return-seeking investment), since the expected financial returns would drive up product prices to levels unaffordable to many poor countries. In addition, social impact investors might also be reluctant to pool funding.

End-to-end thinking and local manufacturing

In addition to the three entities described above (the board, the scientific advisory committee, and the secretariat), a crucial aspect of governance is to ensure that the aggregator is embedded within the larger global health architecture. The funding aggregator for late-stage trials needs alignment both upstream and downstream with other key global health entities so that there is a "seamless transition" between the different development phases and major delivery mechanisms. Partnership agreements with initiatives focusing on earlier stages of development will be key. Based on such partnership agreements, the aggregator could make commitments to companies, universities, and other early stage clinical developers to invest in their candidates if the early stage clinical development is successful. This would incentivize additional investment into earlier development stages. Likewise, vaccine development by the aggregator should also be linked to procurement agencies—for example, it should be linked to Gavi's vaccine investment strategy to ensure that vaccines are purchased and distributed to the poorest countries.

As the aggregator will likely mostly be funded through public funding, there is a very strong argument that it must also ensure that products launched through the aggregator are accessible and affordable in LMICs. Thus, an aggregator would have a key role in ensuring that LMICs have access to the technical know-how and intellectual property that they need to manufacture products themselves.

Support for the development of manufacturing capacity would be part of the aggregator's remit. Unless the aggregator covers tech transfer, local manufacturing, and post-licensure studies (Phase IV), it will leave major

gaps and fall short of facilitating access to affordable products in LMICs. Only a few LMICs have vaccine production capacity. The COVID-19 crisis has brought a new impetus for building local production capacity, including as a way to overcome disruption in the supply of other key vaccines. Some MICs, such as India and China, already have capacity to manufacture vaccines. Other MICs, particularly in Sub-Saharan Africa, are eager to develop their capacity and build their own domestic manufacturing industries. Kenya, for example, plans to become a vaccine manufacturing hub for East Africa over the next years. The aggregator could link with many activities that are up and running, such as a partnership between the East African Community, Merck, the Kenyan government and the local manufacturer Dawa Limited to build a vaccine production facility.

A main added value of the aggregator would thus be that it not only addresses tech transfer to countries with existing manufacturing capacity, such as India, but also contributes to building regional production capacity in Africa. In addition to smaller strategic investments into local manufacturing capacity, the aggregator will have to be a platform for forging partnerships with governments and companies to strengthen this capacity. This will also require incentivizing more pharmaceutical companies to become involved in PRND vaccine development again (multinationals; small and medium-sized enterprises, and biotechs).

Although newer approaches to building country capacity in manufacturing, such as using modular ("prefabricated") manufacturing techniques, could help bring the costs down, these costs remain substantial. HIC donors are unlikely to provide sufficient resources to build this capacity. It is thus important that LMICs invest in their own national production capacity. The aggregator would enable LMICs to become a true part of the innovation spectrum. Rather than purchasing new technologies from Northern companies, LMICs could do the local manufacturing themselves. In this sense, the aggregator would also strongly promote access and affordability, as well as vaccine security. Donors also highlighted the need to scale up local manufacturing capacity as this would imply the ability to manufacture more products at better prices.

Clearly, if the aggregator ignores the importance of manufacturing right from the start, this will reduce the chances of developing and scaling up a product and making it widely available. COVID-19 has also shown the crucial role of manufacturing "at risk." Just as it would not be acceptable to first develop a COVID-19 vaccine and then have a delay of many years to scale up manufacturing capacity, it would also not be acceptable to develop new products for PRNDs and then have a 5-year delay before they can be manufactured at scale (arguably a failed outcome). Thus, the aggregator would also support the at-risk manufacture of the most promising products.

7 CONCLUSIONS

Our working paper has presented a powerful case for launching a new aggregator that would pool funds for late-stage clinical trials of products to control PRNDs. Our modeling suggests that one dollar invested in such an aggregator could generate returns of about US$2.73 to 5.65, depending on the design of the mechanism (the BCR is indicated by the size of the "bubble" in the left-hand panel of Figure 14). There also appears to be substantial support for a new mechanism, with 86% of KIs expressing strong or moderate support for an aggregator.

We recommend that the international community pursues Option 1—an aggregator that funds late-stage trials of vaccines for a narrow range of high-burden PRNDs. This type of aggregator could be rapidly implemented and would have substantial impact at a moderate annual cost. It would also drive efficiencies, streamlining, and accountability in the vaccine development space, while testing a new approach of funding late-stage clinical trials in a targeted manner. When viewed from the investors' perspective, the attractiveness of Option 1 becomes even more apparent – its BCR is much higher than the BCR of Options 2 and 3.

Overall, Option 1 promises a pragmatic but also ambitious approach to strategically address the weaknesses in the global R&D ecosystem through coordinated funding for late-stage clinical trials. If the WHO is successful in rolling out a new streamlined approach to supporting product development (including pre-qualification, essential medicines list, etc.), products funded by this aggregator could potentially be fed into a pilot of the streamlined approach, which could smooth the product's pathway to scale-up. Option 1 could serve as a proof of concept and become a stepping stone for Option 2. While Option 1 will probably require the launch of a new mechanism, CEPI seems to be potentially open to the possibility of expanding its portfolio. If this is the case, the aggregator could initially be "incubated" in CEPI, and – if it turns out to be successful – a new mechanism (independent of CEPI) could be put in place that covers a larger set of diseases and product types (Option 2).

It will also be critical for the aggregator to support tech transfer and local manufacturing. Such benefits would incentivize both LMICs and high-income country donors to participate. The COVID-19 pandemic has shown the critical need to globalize manufacturing capacity for medicines, vaccines, and diagnostics. Globalizing such capacity could help to (a) bring down the price of these control tools, (b) ensure that these tools are more readily available in LMICs, and (c) boost economic growth.

We believe that the COVID-19 pandemic, and the current urgency to fund COVID-19 control tools, is not a threat to launching an aggregator for PRNDs but rather the opposite: it opens a window of opportunity. It is true that the funds needed for the development, manufacturing, deployment, and delivery of COVID-19 technologies could end up being diverted from funding from PRND product development. Nevertheless, the conversations that are now happening at the highest political levels—e.g., on mobilizing funds for R&D, scaling up and globalizing manufacturing capacity, creating trial networks in the Global South, and establishing fair pricing and fair allocation—are setting the terms for new forms of governance in global health R&D. They are creating a clear window of opportunity to establish a new system for funding a *broader range* of technologies for neglected diseases, not just for EIDs. In addition, the COVID-19 pandemic has led to an increased awareness of vaccines and global health more broadly (i.e., of the inter-connectedness of nations) and of the

need for global health R&D. It will be critical to make the case that we need to invest in a set of high priority diseases, not just one. If we can establish a proper prioritization mechanism, then of course COVID-19 would rise to the top right now, but other diseases would also be high on the list, including TB (the world's number one infectious disease killer), HIV, and malaria.

Although we have argued that the launch of an aggregator focusing on vaccines for an initially narrow set of diseases is feasible, we recognize that getting any new initiative off the ground is challenging—both financially and in its governance. We estimate that Option 1 would cost around US$2.6 billion over 11 years, a price tag that in theory at least should not cause "sticker shock" among funders. However, the fact that the ACT Accelerator faces a massive funding gap (it has raised only about 10% of what it needs) suggests that resource mobilization for a PRNDs aggregator will not necessarily be straightforward. Despite this caveat, our study suggests that the timing is right for launching an aggregator that funds late-stage trials of candidate products to control PRNDs.

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ANNEXES

Annex 1. Semi-structured interview questionnaire

High-income countries (HICs)

1) From your perspective, what are the main barriers inhibiting the development of new technologies for poverty-related and neglected diseases (PRNDs)?
   a) And, to what extent are barriers to late-stage clinical trials a significant contributor to delays in the development and lack of new technologies for PRNDs? If so, why?

2) To what extent could this global financing mechanism help to overcome existing barriers for late-stage clinical trials for PRNDs?
   a) Do you see any advantages of a new financing mechanism for late-stage clinical trials?
   b) Do you see any disadvantages and/or unintended negative effects?

3) How would you assess the potential of regional financing mechanisms for late-stage clinical trials? Do you want regional mechanisms instead of a global mechanism or would you want both (and why)?

4) Would your country/organization support the development of a financing mechanism for late-stage clinical trials for PRNDs? If so, how?

5) How do you assess the overall political appetite for the creation of a financing mechanism for late-stage clinical trials for PRNDs?
   a) Which countries/organizations would likely be key supporters and potentially champions of a global/regional financing mechanism for late-stage clinical trials?
   b) Which countries/organizations will likely be reluctant to support a new mechanism, and why?

6) What should the design of the new financing mechanism ideally look like?
   a) Which structures should be created (e.g., a board, scientific committee, secretariat)?
   b) Which bodies decide about priorities and who makes financial decisions? Who needs to be on the main decision-making body?
   c) How should the available funding for late-stage clinical trials be allocated across recipients? And, based upon what criteria (e.g., likely health impact, scientific promise, priority disease, type of tool, likelihood of success, other)?
   d) Which resources could low- and middle-income countries best bring to the table in support of the mechanism (e.g., infrastructure, human resources, financing)?

7) What capacity building goals should be pursued (if any)? For example, how do you rate the importance of human resources, trial networks, manufacturing capacity, and infrastructure? (For industry: what is important for you in terms of the capacity that you would need?)

8) How would you suggest handling the following issues?
   a) ownership of intellectual property, pricing, licensing, and trial data
   b) local manufacturing
   c) technology transfer

9) Do you have any other comments and advice?

10) Whom else should we contact to inform our research?

Additional questions for finance stakeholders (e.g., ministries of finance, treasuries, parliamentarians)

1) Do you think that your government would provide new and additional financing for a new mechanism in support of late-stage clinical trials?
2) Are there examples of where you have funded a similar initiative? If yes, please tell us about that.

Additional questions for HIC domestic health agencies (e.g., departments of health)

1) Are you involved in any issues that have developing country overlap (e.g., TB control, Ebola, etc.)? If yes, what are they?
2) Would you be interested in integrating with a global effort?

Additional questions for HIC domestic industry (e.g., departments of industry and innovation)

1) Do you fund companies or innovators that are working on any issues that have developing country overlap (e.g., TB control, Ebola, etc.)? If yes, what are they?
2) Would you be interested in integrating with a global effort?

Additional questions for HIC regulatory agencies (e.g., FDA)

1) If there is a financing mechanism, should it include a regulatory component? If so, why and what should it look like?
2) Would you be interested in integrating with a global effort?

Middle-income countries (MICs)

1) From your perspective, what are the main barriers inhibiting the development of new technologies for poverty-related and neglected diseases (PRNDs)?
   a) And, to what extent are barriers to late-stage clinical trials a significant contributor to delays in the development and lack of new technologies for PRNDs? If so, why?
2) To what extent could a global (or a regional) financing mechanism help to overcome existing barriers for late-stage clinical trials for PRNDs?
   a) What opportunities and benefits would a new financing mechanism for late-stage clinical trials create for your country?
   b) Do you see any disadvantages and/or unintended negative effects?
3) What is your own country's current capacity for regulatory-standard late-stage clinical trials?
   a) Are there any areas/diseases where particularly good capacities/skills exist? If so, which?
   b) Which specific areas need capacity-strengthening to benefit from an aggregator financing model (e.g., human, health system, trial networks, manufacturing capacity, regulatory)?
   c) To what extent does your regulatory authority have the capacity to regulate clinical trials? Are ethical reviews of clinical trials straightforward?
4) Who are the main (inter-)national partners for late-stage clinical trials in your country?
5) To what extent would your country be interested to get involved in a new mechanism?
6) From your perspective, how would your country get involved?
   a) What area do you think your country would be most interested in supporting?
7) What should the design of the new financing mechanism ideally look like?
   a) Which structures should be created (e.g., a board, scientific committee, secretariat)?
   b) Which bodies decide about priorities and who makes financial decisions? Who needs to be on the main decision-making body?

c) How would the available funding for late-stage clinical trials be allocated across recipients? And based upon what criteria (e.g., likely health impact, scientific promise, likelihood of success, other)?
d) Which resources should low- and middle-income countries bring to the table in support of the mechanism (e.g., infrastructure, human resources, financing)?

8) How would you suggest handling the following issues?
   a) ownership of intellectual property, pricing, licensing, and trial data
   b) local manufacturing
   c) technology transfer

9) Do you have any other comments and advice?

10) Whom else should be contact to inform our research?

Additional questions for MIC finance stakeholders (e.g., ministries of finance, treasuries, parliamentarians, central bank)

1) Do you think that your government would provide new and additional financing for a new mechanism in support of late-stage clinical trials?

2) Are there examples of where you have funded a similar initiative? If yes, please tell us about that.

Additional questions for MIC domestic industry (e.g., departments of industry and innovation)

1) Do you fund companies or innovators that are working on any neglected disease products? If yes, why?
   a) biotech
   b) local manufacturing

2) Would you be interested in integrating with a global effort to support this?

Annex 2. Detailed methods and assumptions used to estimate costs and benefits of an aggregator

Tables 2A, 2B, 2C, and 2D provide details of the model variables and parameters used for our analyses. We had two goals for our modeling exercise. The first was to project the required phase III investment and expected product launches based on the aggregator design options identified through our analysis of the key informant interviews and literature review. The second was to estimate the long-term health and economic benefits of these successful launches over the period 2021 to 2035. In this methods annex, we include the specific equations that we used in estimating these costs and benefits.

Baseline disease profile

The baseline DALYs were calculated as the sum of the baseline years of life lost (YLL) and years lived with disability (YLD) (**Equations 1 and 2**). To calculate YLLs and YLDs, we first used data from the United Nations World Population Prospects to identify life expectancy at birth and life expectancy at age x. Then, we reviewed the literature and the databases of the Institute of Health Metrics and Evaluation (IHME) to identify the baseline prevalence, incidence, annual number of deaths by age group, and disability weights for different diseases and disease states. 2017 data were used.

Equation 1: Years of Life Lost (YLL) for population

$$YLL = D_i * YLL_i$$

Where YLL_i is the average YLL per individual case (see **Equation 3**), and D_i is the total number of deaths from disease i in all age groups.

Equation 2: Years Lived with Disability (YLD) for population

$$YLD = (I_b * C_b * YLD_{ti}) + (I * YLD_i) * (1 - C_b)$$

Where I_b is the baseline incidence, C_b is the baseline treatment coverage, YLD_{ti} is the YLD per individual case with treatment, and YLD_i is the YLD per individual case without treatment.

Equation 3: Years of Life Lost from Disease *i* (YLL_i) by individual

$$YLL_i = \frac{\sum_{a=1}^{n} d_{ai} * L_a * R}{D_{ti}}$$

Where d is the number of deaths in age group a from disease i, L is the average life expectancy at age a, and d_{ai} is the total number of deaths from disease i in age group a. R is treatment mortality reduction if with treatment and 1 otherwise, and D_{ti} is the total number of deaths from disease i and treatment status t.

Equation 4: Years Lived with Disability for disease i (YLD_i) by individual

$$YLD_i = \frac{\sum_{a=1}^{n} I_{ai} * T_{ai} * DW_i}{I_i}$$

Where I_{ia} is the incidence of disease i in age group a, DW_i is the disability weight for disease i, T_{ia} is the duration of illness for disease i in age a for treatment status t.

For chronic diseases with multiple disease states and a very long duration of illness (e.g., HIV and Chagas disease), we multiplied the duration spent in each disease state by the corresponding disability weight for that

disease state. Detailed disability weights assumptions, incidence, prevalence, number of death inputs, and YLLs/ YLDs result tables are available in **Tables 2C and 2D** below.

Equation 5: Number of cases (i.e., illness episodes) averted

$$Cases\ averted = I_b - I_v$$

Where I_v is the incidence (i.e., number of cases) with vaccination at a given year x, and I_b is the incidence at baseline without vaccination.

Equation 6: Deaths averted

$$Deaths\ averted = [((I_b * C_b * CFR_t) + ((1 - C_b) * CFR_0)) - ((I_v * C_b * CFR_t) + ((1 - C_b) * CFR_0))]$$

Where, CFR_0 is the case fatality rate without treatment, and CFR_t is the case fatality rate with treatment, I_v is the incidence (i.e., number of cases) with vaccination at a given year x, and I_b is the incidence at baseline without vaccination.

Equation 7: Disability Adjusted Life Years (DALYs) averted

$$DALYs\ averted = Baseline\ DALYs - DALYs\ with\ vaccine$$

Treatment costs averted: The treatment costs averted were the product of the number of cases averted and the average treatment cost per case (Table 2B). Since treatment costs vary significantly by disease state (e.g., MDR-TB vs. drug-sensitive TB) and severity (HIV with a CD4 count > 500 vs < 200), we took a weighted average cost for different disease states.

Model variables, parameters and assumptions

Table 2A. Assumptions for the product pipeline development model

Archetype	Cost per phase (US $million)				Length of phase				Probability of success			
	Preclinical	P 1	P 2	P 3	Preclinical	P 1	P 2	P 3	Preclinical	P 1	P 2	P 3
Vaccine-simple	$6.66	$2.25	$ 13.22	$ 111.10	3.36	1.57	2.23	2.33	41.0%	68.4%	45.9%	70.8%
Vaccine-complex	$16.63	$2.47	$ 13.88	$ 133.32	3.33	1.97	3.71	3.50	41.0%	50.0%	21.6%	63.6%
NCE-simple	$5.00	$2.21	$5.81	$32.82	2.49	1.80	3.38	3.18	65.0%	59.7%	38.8%	69.1%
NCE-complex	$10.00	$7.44	$6.39	$36.10	2.87	1.93	3.51	2.80	55.0%	57.2%	19.7%	40.3%
Drug repurposed-simple	-	-	$5.81	$17.61	-	-	2.14	2.14	-	-	45.7%	68.1%
Drug repurposed-complex	$5.00	$2.21	$5.81	$17.61	-	-	2.14	2.14	75.0%	58.5%	45.7%	68.1%
Biologic-simple	$10.79	$2.41	$7.53	$54.12	3.29	1.62	2.47	2.10	75.0%	66.2%	44.3%	70.9%
Biologic-complex	$21.59	$7.65	$8.28	$59.53	3.24	1.49	4.16	3.38	77.0%	69.6%	32.2%	62.5%
Diagnostic-assay dev.	$3.00	$2.00	$3.50	-	1.00	1.25	1.33	-	50.0%	100%	100%	-
Diagnostic-simple platform dev.	-	$100	$3.50	-	-	2.50	2.00	-	-	75%	100%	-

Table 2B. Treatment costs data

Disease	Treatment cost ($US)	Notes	Reference
HIV	$336.00	Average ART cost per person year across different disease states (CD4 >500 to <200)	Ross JM, Ying R, Celum CL, et al. Modeling HIV disease progression and transmission at population-level: The potential impact of modifying disease progression in HIV treatment programs. *Epidemics*. 2018;23:34-41. doi:10.1016/j.epidem.2017.12.001
Tuberculosis	$1,251.00	Weighted average of treatment cost per case for drug sensitive TB and MDR-TB	WHO: Global TB Report 2019
Malaria	$72.00	Weighted average of treatment cost of moderate malaria and severe malaria	White MT, Conteh L, Cibulskis R, Ghani AC. Costs and cost-effectiveness of malaria control interventions--a systematic review. *Malar J*. 2011;10:337. Published 2011 Nov 3. doi:10.1186/1475-2875-10-337
Pneumonia	$81.00	n/a	Anh, Dang Duc, et al. "Treatment costs of pneumonia, meningitis, sepsis, and other diseases among hospitalized children in Viet Nam." Journal of health, population, and nutrition 28.5 (2010): 436. Tichopad, Ales, et al. "Clinical and economic burden of community-acquired pneumonia among adults in the Czech Republic, Hungary, Poland and Slovakia." PLoS One 8.8 (2013).
Chagas disease	$286.00	Average cost per person year across different disease states	Wilson LS, Strosberg AM, Barrio K. Cost-effectiveness of Chagas disease interventions in latin america and the Caribbean: Markov models. Am J Trop Med Hyg. 2005;73(5):901-910.
Schistosomiasis	$4.40	Cost per person	Salari P, Fürst T, Knopp S, Utzinger J, Tediosi F. Cost of interventions to control schistosomiasis: A systematic review of the literature. PLoS Negl Trop Dis. 2020;14(3):e0008098. Published 2020 Mar 30. doi:10.1371/journal.pntd.0008098
Leishmaniasis	$150.93	Average cost per person across different treatment strategies	Meheus F, Balasegaram M, Olliaro P, et al. Cost-effectiveness analysis of combination therapies for visceral leishmaniasis in the Indian subcontinent. PLoS Negl Trop Dis. 2010;4(9):e818. Published 2010 Sep 7. doi:10.1371/journal.pntd.0000818
Dengue	$263.00	Average cost per patient for moderate dengue and severe dengue	Lee JS, Mogasale V, Lim JK, et al. A multi-country study of the economic burden of dengue fever: Vietnam, Thailand, and Colombia. PLoS Negl Trop Dis. 2017;11(10):e0006037. Published 2017 Oct 30. doi:10.1371/journal.pntd.0006037
Leprosy	$309.70	Cost of treatment per person per year	Xiong M, Li M, Zheng D, et al. Evaluation of the economic burden of leprosy among migrant and resident patients in Guangdong Province, China. BMC Infect Dis. 2017;17(1):760. Published 2017 Dec 11. doi:10.1186/s12879-017-2869-8
Shigellosis	$1.11	Outpatient treatment cost for diarrheal disease	Baral, Ranju, et al. "Cost of illness for childhood diarrhea in low-and middle-income countries: a systematic review of evidence and modelled estimates." BMC Public Health 20 (2020): 1-13.
Ebola	$915.35	Extensive supportive care EVD treatment and PPE costs per case	Bartsch, Sarah M., Katrin Gorham, and Bruce Y. Lee. "The cost of an Ebola case." Pathogens and global health 109.1 (2015): 4-9.
Hepatitis C	$980.00	12-week course of sofobuvir for countries like Mongolia, Egypt, Pakistan.	Iyengar, Swathi, et al. "Prices, costs, and affordability of new medicines for hepatitis C in 30 countries: an economic analysis." PLoS medicine 13.5 (2016): e1002032.
Enterotoxigenic E. coli	$36.56	Outpatient treatment cost for diarrheal disease	Baral, Ranju, et al. "Cost of illness for childhood diarrhea in low-and middle-income countries: a systematic review of evidence and modelled estimates." BMC Public Health 20 (2020): 1-13.
Non-typhoidal salmonella	$20.91	Cost per treatment per case (USD 2016). We used estimates for typhoidal salmonella	Luthra K, Watts E, Debellut F, Pecenka C, Bar-Zeev N, Constenla D. A Review of the Economic Evidence of Typhoid Fever and Typhoid Vaccines. Clin Infect Dis. 2019;68(Suppl 2):S83-S95. doi:10.1093/cid/ciy1122
Sleeping Sickness (HAT)	$845.99	Average total cost of Elfornithine administration.	Keating, Joseph, et al. "Human African trypanosomiasis prevention, treatment and control costs: a systematic review." Acta tropica 150 (2015): 4-13.
Onchocerciasis	$38.80	One dose of ivermectin	Keating, Joseph, et al. "Lymphatic filariasis and onchocerciasis prevention, treatment, and control costs across diverse settings: a systematic review." Acta tropica 135 (2014): 86-95.
Cholera	$34.04		Ilboudo, Patrick G., et al. "Cost-of-illness of cholera to households and health facilities in rural Malawi." PloS one 12.9 (2017).

			Schaetti, Christian, et al. "Costs of illness due to cholera, costs of immunization and cost-effectiveness of an oral cholera mass vaccination campaign in Zanzibar." PLoS neglected tropical diseases 6.10 (2012). Sarker, Abdur Razzaque, et al. "Cost of illness for cholera in a high risk urban area in Bangladesh: an analysis from household perspective." BMC infectious diseases 13.1 (2013): 518.
Hookworm	$0.31	Cost per round of treatment for pre school-age child	Hall A, Horton S, de Silva N (2009) The Costs and Cost-Effectiveness of Mass Treatment for Intestinal Nematode Worm Infections Using Different Treatment Thresholds. PLOS Neglected Tropical Diseases 3(3): e402. https://doi.org/10.1371/journal.pntd.0000402
Meningitis	$1,749.17	Average treatment cost per infection across 144 LMICs (2012 USD)	Portnoy A, Jit M, Lauer J, et al. Estimating costs of care for meningitis infections in low- and middle-income countries. Vaccine. 2015;33 Suppl 1:A240-A247. doi:10.1016/j.vaccine.2014.11.061
Rheumatic Fever	$15,081.73	RHD admission +RHD valve surgery + RHD medical management	Irlam, James, et al. "Primary prevention of acute rheumatic fever and rheumatic heart disease with penicillin in South African children with pharyngitis: a cost-effectiveness analysis." Circulation: Cardiovascular Quality and Outcomes 6.3 (2013): 343-351.
Multiple diarrhoeal diseases	$36.56	Used outpatient cost of illness for diarrheal diseases	Baral, Ranju, et al. "Cost of illness for childhood diarrhea in low-and middle-income countries: a systematic review of evidence and modelled estimates." BMC Public Health 20 (2020): 1-13.
Buruli Ulcer	$4,058.30	Buruli Ulcer (severity NR)	Omansen, Till F., et al. "Global Epidemiology of Buruli Ulcer, 2010–2017, and Analysis of 2014 WHO Programmatic Targets." Emerging infectious diseases 25.12 (2019): 2183. Drummond, Christina, and James RG Butler. "Mycobacterium ulcerans treatment costs, Australia." Emerging infectious diseases 10.6 (2004): 1038. Asiedu, Kingsley, and Samuel Etuaful. "Socioeconomic implications of Buruli ulcer in Ghana: a three-year review." The American journal of tropical medicine and hygiene 59.6 (1998): 1015-1022.
Trachoma	$35.29	Cost per patient of targeted azythromycin treatment in regions of Africa with high adult mortality and high child mortality.	Baltussen RM, Sylla M, Frick KD, Mariotti SP. Cost-effectiveness of trachoma control in seven world regions. Ophthalmic Epidemiol. 2005;12(2):91-101. doi:10.1080/09286580590932761
Typhoid and Paratyphoid	$20.91	Cost per treatment per case (USD 2016)	Luthra K, Watts E, Debellut F, Pecenka C, Bar-Zeev N, Constenla D. A Review of the Economic Evidence of Typhoid Fever and Typhoid Vaccines. Clin Infect Dis. 2019;68(Suppl 2):S83-S95. doi:10.1093/cid/ciy1122
Cryptosporadiosis	$24.77	Symptomatic cryptospordiosis	Rafferty, Ellen R., et al. "Pediatric cryptosporidiosis: an evaluation of health care and societal costs in Peru, Bangladesh and Kenya." PloS one 12.8 (2017).
Multiple salmonella infections	$20.91	Cost per treatment per case (USD 2016)	Luthra K, Watts E, Debellut F, Pecenka C, Bar-Zeev N, Constenla D. A Review of the Economic Evidence of Typhoid Fever and Typhoid Vaccines. Clin Infect Dis. 2019;68(Suppl 2):S83-S95. doi:10.1093/cid/ciy1122
Hepatitis B	$34.84	Median cost per patient per year of tenofovir treatment in 2016.	https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
Herpes Simplex 2	$11.74	Average cost per treatment across LMICs (Acyclovir 400 mg).	Korenromp EL, Wi T, Resch S, Stover J, Broutet N. Costing of National STI Program Implementation for the Global STI Control Strategy for the Health Sector, 2016-2021. PLoS One. 2017;12(1):e0170773. Published 2017 Jan 27. doi:10.1371/journal.pone.0170773
Gonorrhea	$11.38	Average cost per treatment across LMICs (Ceftriaxone 250 mg)	Korenromp EL, Wi T, Resch S, Stover J, Broutet N. Costing of National STI Program Implementation for the Global STI Control Strategy for the Health Sector, 2016-2021. PLoS One. 2017;12(1):e0170773. Published 2017 Jan 27. doi:10.1371/journal.pone.0170773
Chlamydia	$11.63	Average cost per treatment across LMICs (Azithromycine 500 mg)	Korenromp EL, Wi T, Resch S, Stover J, Broutet N. Costing of National STI Program Implementation for the Global STI Control Strategy for the Health Sector, 2016-2021. PLoS One. 2017;12(1):e0170773. Published 2017 Jan 27. doi:10.1371/journal.pone.0170773

Table 2C. Disease disability weights.

Disease	Health state	Disability weight (DW)	Notes
HIV	Acute HIV (entry)	0.012	Used DW for early HIV without anemia
	CD4 > 500	0.078	Used DW for HIV/AIDS with antiretroviral treatment without anemia
	CD4 500-350	0.274	Used DW for symptomatic HIV without anemia
	CD4 350-200	0.582	AIDS without anemia
	CD4 <200	0.582	AIDS without anemia
Tuberculosis	Drug-susceptible tuberculosis	0.333	Used DW for drug-susceptible TB
	Multidrug-resistant tuberculosis without extensive drug resistance	0.333	Used DW for multidrug-resistant TB
	Extensively drug-resistant tuberculosis	0.333	Used DW for extensively drug-resistant TB
Malaria	Mild malaria	0.006	n/a
	Moderate malaria	0.051	n/a
	Severe malaria	0.133	n/a
	Severe motor impairment due to malaria	0.402 (0.268-0.545)	n/a
Pneumonia	Moderate lower respiratory infections	0.051 (0.032-0.074)	n/a
	Severe lower respiratory infections	0.133 (0.088-0.190)	n/a
Chagas disease	Asymptomatic Chagas disease	n/a	n/a
	Acute Chagas disease	0.051 (0.032-0.074)	n/a
	Moderate chronic digestive disease due to Chagas disease	0.114 (0.078-0.159)	n/a
	Moderate heart failure due to Chagas disease	0.072 (0.047-0.103)	n/a
	Severe heart failure due to Chagas disease	0.179 (0.122-0.251)	n/a
	Treated heart failure due to Chagas disease	0.049 (0.031-0.072)	n/a
	Mild heart failure due to Chagas disease	0.041 (0.026-0.062)	n/a
Schistosomiasis	Severe anemia due to schistosomiasis	0.149 (0.101-0.209)	n/a
	Moderate anemia due to schistosomiasis	0.052 (0.034-0.076)	n/a
	Bladder pathology due to schistosomiasis	0.011 (0.005-0.021)	n/a
	Hydronephrosis due to schistosomiasis	0.011 (0.005-0.021)	n/a
	Hepatomegaly due to schistosomiasis	0.011 (0.005-0.021)	n/a
	Hematemesis due to schistosomiasis	0.325 (0.209-0.462)	n/a
	Ascites due to schistosomiasis	0.114 (0.078-0.159)	n/a
	Mild diarrhea due to schistosomiasis	0.074 (0.049-0.104)	n/a
	Mild schistosomiasis	0.006 (0.002-0.012)	n/a
	Mild anemia due to schistosomiasis	0.004 (0.001-0.008)	n/a
Leishmaniasis	Severe visceral leishmaniasis	0.133 (0.088-0.190)	n/a
	Moderate visceral leishmaniasis	0.051 (0.032-0.074)	n/a
	Cutaneous and mucocutaneous leishmaniasis	0.067 (0.044-0.096)	n/a
Dengue	Moderate dengue	0.051 (0.032-0.074)	n/a
	Severe dengue	0.133 (0.088-0.190)	n/a
Leprosy	Disfigurement level 1 due to leprosy	0.011 (0.005-0.021)	n/a
	Disfigurement level 2 due to leprosy	0.067 (0.044-0.096)	n/a
Buruli Ulcer	Mild decubitus ulcer	0.027 (0.015-0.042)	

	Moderate decubitus ulcer	0.188 (0.125-0.267)	Used decubitis ulcer as proxy for buruli ulcer. Used average of all sequelae
	Severe decubitus ulcer	0.576 (0.401-0.731)	
Cholera	Mild diarrheal diseases	0.074 (0.049-0.104)	n/a
	Severe diarrheal diseases	0.247 (0.164-0.348)	n/a
	Moderate diarrheal diseases	0.188 (0.125-0.264)	n/a
Cryptosporadiasis	Mild diarrheal diseases	0.074 (0.049-0.104)	n/a
	Severe diarrheal diseases	0.247 (0.164-0.348)	n/a
	Moderate diarrheal diseases	0.188 (0.125-0.264)	n/a
Ebola	Ebola cases	0.133 (0.088-0.190)	n/a
Enterotoxigenic E. coli	Mild diarrheal diseases	0.074 (0.049-0.104)	n/a
	Severe diarrheal diseases	0.247 (0.164-0.348)	n/a
	Moderate diarrheal diseases	0.188 (0.125-0.264)	n/a
Sleeping Sickness (HAT)	Sleeping sickness due to Trypanosoma brucei rhodesiense	0.542 (0.374-0.702)	n/a
	Skin disfigurement due to Trypanosoma brucei rhodesiense	0.027 (0.015-0.042)	n/a
	Sleeping sickness due to Trypanosoma brucei gambiense	0.542 (0.374-0.702)	n/a
	Skin disfigurement due to Trypanosoma brucei gambiense	0.027 (0.015-0.042)	n/a
Hepatitis C	Severe acute hepatitis C	0.133 (0.088-0.190)	n/a
	Moderate acute hepatitis C	0.051 (0.032-0.074)	n/a
	Terminal phase of liver cancer due to hepatitis C	0.540 (0.377-0.687)	n/a
	Controlled phase of liver cancer due to hepatitis C	0.049 (0.031-0.072)	n/a
	Cirrhosis and other chronic liver diseases due to hepatitis C, decompensated	0.178 (0.123-0.250)	n/a
Hookworm	Heavy infestation of hookworm	0.027 (0.015-0.043)	n/a
	Severe wasting due to hookworm disease	0.128 (0.082-0.183)	n/a
	Moderate anemia due to hookworm disease	0.052 (0.034-0.076)	n/a
	Severe anemia due to hookworm disease	0.149 (0.101-0.209)	n/a
Meningitis			n/a
Multiple diarrhoeal diseases	Mild diarrheal diseases	0.074 (0.049-0.104)	n/a
	Severe diarrheal diseases	0.247 (0.164-0.348)	n/a

	Moderate diarrheal diseases	0.188 (0.125-0.264)	n/a
Multiple salmonella infections	Mild diarrheal diseases	0.074 (0.049-0.104)	n/a
	Severe diarrheal diseases	0.247 (0.164-0.348)	n/a
	Moderate diarrheal diseases	0.188 (0.125-0.264)	n/a
Non-typhoidal salmonella	Mild diarrheal diseases	0.074 (0.049-0.104)	n/a
	Severe diarrheal diseases	0.247 (0.164-0.348)	n/a
	Moderate diarrheal diseases	0.188 (0.125-0.264)	n/a
Onchocerciasis	Severe vision impairment due to onchocerciasis	0.184 (0.125-0.258)	n/a
	Blindness due to onchocerciasis	0.187 (0.124-0.260)	n/a
	Mild skin disease without itch due to onchocerciasis	0.011 (0.005-0.021)	n/a
	Moderate skin disease due to onchocerciasis	0.188 (0.125-0.267)	n/a
	Mild skin disease due to onchocerciasis	0.027 (0.015-0.042)	n/a
	Moderate vision impairment due to onchocerciasis	0.031 (0.019-0.049)	n/a
Rheumatic Fever	No sequelae listed	0.685 (0.592-0.769)	Ock M, Lee JY, Oh IH, Park H, Yoon SJ, Jo MW. Disability Weights Measurement for 228 Causes of Disease in the Korean Burden of Disease Study 2012. J Korean Med Sci. 2016;31 Suppl 2(Suppl 2):S129-S138.doi:10.3346/jkms.2016.31.S2.S129"
Shigellosis	Mild diarrheal diseases	0.074 (0.049-0.104)	n/a
	Severe diarrheal diseases	0.247 (0.164-0.348)	n/a
	Moderate diarrheal diseases	0.188 (0.125-0.264)	n/a
Trachoma	Moderate vision impairment due to trachoma	0.031 (0.019-0.049)	n/a
Typhoid and Paratyphoid	Acute typhoid infection	0.051 (0.032-0.074)	n/a
	Severe typhoid fever	0.133 (0.088-0.190)	n/a
	Intestinal perforation due to typhoid	0.324 (0.220-0.442)	n/a
	Gastrointestinal bleeding due to typhoid	0.325 (0.209-0.462)	n/a
Hepatitis B	Severe acute hepatitis B	0.133 (0.088-0.190)	n/a

	Terminal phase of liver cancer due to hepatitis B	0.540 (0.377-0.687)	n/a
	Controlled phase of liver cancer due to hepatitis B	0.049 (0.031-0.072)	n/a
	Cirrhosis and other chronic liver diseases due to hepatitis B, decompensated	0.178 (0.123-0.250)	n/a
Herpes Simplex 2	Moderate infection due to initial genital herpes episode	0.051 (0.032-0.074)	n/a
	Symptomatic genital herpes	0.006 (0.002-0.012)	n/a
Gonnorhea	Moderate pelvic inflammatory diseases due to gonococcal infection	0.114 (0.078-0.159)	n/a
	Mild gonococcal infection	0.006 (0.002-0.012)	n/a
	Secondary infertility due to gonococcal infection	0.005 (0.002-0.011)	n/a
	Primary infertility due to gonococcal infection	0.008 (0.003-0.015)	n/a
Chlamydia	Epididymo-orchitis due to chlamydial infection	0.128 (0.086-0.180)	n/a
	Moderate pelvic inflammatory diseases due to chlamydial infection	0.114 (0.078-0.159)	n/a
	Severe pelvic inflammatory diseases due to chlamydial infection	0.324 (0.220-0.442)	n/a
	Mild chlamydial infection	0.006 (0.002-0.012)	n/a
	Secondary infertility due to chlamydial infection	0.005 (0.002-0.011)	n/a
	Primary infertility due to chlamydial infection	0.008 (0.003-0.015)	n/a

Source: IHME

Table 2D. Baseline disease burden

Disease	Point prevalence	Incidence	Annual number of deaths	Year	Source
HIV/AIDS	36,822,237	1,942,071	954,492	2017	IHME, GBD results tool
Malaria	136,085,123	208,768,201	619,827	2017	IHME, GBD results tool
Tuberculosis	1,929,208,623	8,965,814	1,183,672	2017	IHME, GBD results tool
Pneumonia	n/a	471,825,514	2,558,606	n/a	IHME, GBD results tool
Chagas disease	6,196,959	162,470	7,853	2017	IHME, GBD results tool
Schistosomiasis	142,788,542	71,385,000	8,837	2016	GBD 2016
Leishmaniasis	4,130,197	669,058	7,527	2017	IHME, GBD results tool
Dengue	6,267,410	104,771,911	40,467	2017	IHME, GBD results tool
Leprosy	518,527	48,477	4,000	2017	IHME, GBD results tool Engers H, Morel CM. Leprosy. Nat Rev Microbiol. 2003;1(2):94-95. doi:10.1038/nrmicro764
Shigellosis	NA	269,191,131	212,438	2016	Khalil IA, Troeger C, Blacker BF, et al. Morbidity and mortality due to shigella and enterotoxigenic Escherichia coli diarrhoea: the Global Burden of Disease Study 1990-2016 [published correction appears in Lancet Infect Dis. 2018 Oct 30;:]. Lancet Infect Dis. 2018;18(11):1229-1240. doi:10.1016/S1473-3099(18)30475-4
Ebola	NA	20,200	7,905	2014	Cenciarelli O, Pietropaoli S, Malizia A, et al. Ebola virus disease 2013-2014 outbreak in west Africa: an analysis of the epidemic spread and response. Int

					J Microbiol. 2015;2015:769121. doi:10.1155/2015/769121
Hepatitis C	135,447,784	6,527,210	580,052	2017	IHME, GBD results tool
Enterotoxigenic E.coli (ETEC)	NA	222,637,561	51,186	2010	Khalil IA, Troeger C, Blacker BF, et al. Morbidity and mortality due to shigella and enterotoxigenic Escherichia coli diarrhoea: the Global Burden of Disease Study 1990-2016 [published correction appears in Lancet Infect Dis. 2018 Oct 30;:]. Lancet Infect Dis. 2018;18(11):1229-1240. doi:10.1016/S1473-3099(18)30475-4
Non-typhoidal Salmonella (NTS)	NA	534,595	120,281	2017	IHME, GBD results tool
HAT	4,896	3,322	1,364	2017	IHME, GBD results tool
Onchocerciasis	20,938,147	1,017,375	60,025	2017	IHME, GBD results tool
Cholera	NA	2,800,000	75,772	2017	IHME, GBD results tool
Hookworm	229,217,130	86,972,676	65,000	2016	Bartsch SM, Hotez PJ, Asti L, et al. The Global Economic and Health Burden of Human Hookworm Infection. PLoS Negl Trop Dis. 2016;10(9):e0004922. Published 2016 Sep 8. doi:10.1371/journal.pntd.0004922 Stanley Plotkin, David J. Diemert, Jeffrey M. Bethony, Peter J. Hotez, Hookworm Vaccines, Clinical Infectious Diseases, Volume 46, Issue 2, 15 January 2008, Pages 282–288, https://doi.org/10.1086/524070
Meningitis	10,572,886	5,045,411	288,021	2017	IHME, GBD results tool
Rheumatic fever	39,345,369	1,311,253	285,517	2017	IHME, GBD results tool
Multiple diarrhoeal diseases	93,472,768	6,292,936,672	1,569,556	2017	IHME, GBD results tool
Buruli Ulcer	NA	2,708	14	2017	Global Health Observatory Data Repository
Trachoma	3,818,880	2,034,879	50,870	2017	Gouda H, Powles J, Barendregt J, Emerson P, Ngondi J. The burden of trachoma in South Sudan: assessing the health losses from a condition of graded severity. PLoS Negl Trop Dis. 2012;6(3):e1538. doi:10.1371/journal.pntd.0001538 WHO Alliance for the Global Elimination of Trachoma by 2020: progress report on elimination of trachoma, 2014–2016
Typhoid & paratyphoid	387,451	14,321,147	135,922	2017	IHME, GBD results tool
Cryptosporidiosis	NA	64,003,709	27,553	2010	Kirk MD, Pires SM, Black RE, et al. World Health Organization Estimates of the Global and Regional Disease Burden of 22 Foodborne Bacterial, Protozoal, and Viral Diseases, 2010: A Data Synthesis [published correction appears in PLoS Med. 2015 Dec;12(12):e1001940]. PLoS Med. 2015;12(12):e1001921. Published 2015 Dec 3. doi:10.1371/journal.pmed.1001921
Multiple salmonella infections	NA	25,811,160	178,215	2010	Kirk MD, Pires SM, Black RE, et al. World Health Organization Estimates of the Global and Regional Disease Burden of 22 Foodborne Bacterial, Protozoal, and Viral Diseases, 2010: A Data Synthesis [published correction appears in PLoS Med. 2015 Dec;12(12):e1001940]. PLoS Med. 2015;12(12):e1001921. Published 2015 Dec 3. doi:10.1371/journal.pmed.1001921
Hepatitis B	448,571,213	147,666,509	799,009	2017	IHME, GBD results tool
Herpes Simplex-2	955,894,784.19	77,696,683.76		2017	IHME, GBD results tool
Gonorrhea	47,269,180.69	137,221,507.51	3,019.11	2017	IHME, GBD results tool
Chlamydia	109,822,037.14	297,131,257.70	1,050.55	2017	IHME, GBD results tool

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Annex 3. Number of candidates in phase II

The table below shows the number of candidates in the current pipeline.

All diagnostics (N = 168) were excluded. The total number of candidates is 522; if diagnostics were included, the total number of candidates would be 690. The paper by Bandara et al. also includes an expanded list of diseases with 754 candidates in the pipeline (not shown here).[5]

Pipeline	Number of Candidates in phase II	Total	Percentage
2019 study (# for direct comparison with 2017 results; see Bandara et al. for more details[5])	103	522	19.73%

Annex 4. Product candidates in the 2017 and the complete 2019 pipelines categorized by disease

	Number of candidates		Changes due to	
Disease	2017	2019	Pipeline expansion	Scope expansion
Buruli Ulcer	4	6	2	0
Chagas	18	16	-2	0
Chlamydia	Not in scope	5	0	5
Cholera	3	2	-1	0
Cryptococcal meningitis	1	3	2	0
Cryptosporidiasis	0	1	1	0
Dengue	7	9	2	0
Ebola	20	82	62	0
Enterotoxigenic E.coli (ETEC)	8	6	-2	0
Giardia	1	1	0	0
Gonorrhea	Not in scope	11	0	11
HAT (Sleeping sickness)	6	4	-2	0
Hepatitis B	Not in scope	8	0	8
Hepatitis C	16	15	-1	0
Herpes Simplex-2	Not in scope	7	0	7
HIV/AIDS	99	105	-10	16
HPV- Cervical Cancer	Not in scope	1	0	1
Hookworm	2	3	1	0
Leishmaniasis	14	19	5	0
Leprosy	2	3	0	1
Leptospirosis	1	6	5	0
Lymphatic filariasis	2	2	0	0
Malaria	109	127	18	0
Meningitis	2	11	9	0
Multiple diarrhoeal diseases	1	2	1	0
Multiple Diseases	0	1	0	1
Multiple salmonella infections	0	1	1	0
Multiple vector borne diseases	1	4	3	0
Mycetoma	Not in scope	1	0	1
Non-typhoidal Salmonella (NTS)	7	4	-3	0
Onchocerciasis	4	6	2	0
Pneumonia	8	12	4	0
Reproductive Health	59	100	28	13
Rheumatic fever	2	4	2	0
Rotavirus	5	11	6	0
Schistosomiasis	16	9	-7	0
Shigellosis	13	14	1	0
Trachoma	2	2	0	0
Trichuriasis	1	1	0	0
Tuberculosis	98	120	22	0
Typhoid & paratyphoid	6	9	3	0
Total	**538**	**754**	**152**	**64**

Annex 5. Expected launches by disease based on the 2017 and the complete 2019 pipelines

Disease	Expected launches		Difference in launches due to		
	2017	Complete 2019 pipeline	Changes in the pipeline	Scope expansion	Classification changes
Buruli Ulcer	2	3	1		
Chagas	3	3	0		
Chlamydia	Not in scope	3	0	3	
Cholera	1		-1		
Dengue	2	3	1		
Ebola	2	20	18		
Enterotoxigenic E.coli (ETEC)	1	1	0		
Gonorrhea	Not in scope	2	0	2	
HAT (Sleeping sickness)	2	3	1		
Hepatitis B	Not in scope	1	0	1	
Hepatitis C	8	12	3		1
HIV/AIDS	23	20	-4	1	
Leishmaniasis	3	6	3		
Leprosy	0	1	1		
Leptospirosis	1	6	5		
Lymphatic filariasis	1	2	1		
Malaria	27	39	11		1
Meningitis	0	5	5		
Multiple vector borne diseases	0	1	1		
Pneumonia	1	3	2		
Reproductive Health	8	15	6	1	
Rotavirus	2	3	1		
Schistosomiasis	3	2	-1		
Shigellosis	2	2	0		
Trachoma	0	1	1		
Tuberculosis	35	49	13		1
Typhoid & paratyphoid	1	1	0		
Total	**128**	**207**	**68**	**8**	**3**

Annex 6. Cost by phase to move product candidates through the pipeline to launch for the 2019 direct comparison pipeline and the complete 2019 pipeline

Phases	2019 direct comparison pipeline ($US million)	Percent of the total	Complete 2019 pipeline ($US million)	Percent of the total
Pre-Clinical	2,334.98	11.75	2,456.86	11.68
Phase I	833.10	4.19	921.84	4.38
Phase II	4,992.70	25.13	4,715.76	22.43
Phase III	11,709.20	58.93	12,932.71	61.50
Total	**19,869.98**	**100.00**	**21,027.18**	**100.00**

As described in Section 3, we amended the list of diseases included in the costing to compare the costs for moving product candidates through the pipeline with the disbursements from the 2019 G-FINDER 2019 report.[4] The table below shows the costs per phase; a total of US$9.9 billion is needed for phase III trials according to this modeling.

Phases	Total costs ($US million)	Percentage of the total
Preclinical	1,344.87	8.465868202
Phase I	644.88	4.059473438
Phase II	4,017.84	25.29198698
Phase III	9,878.23	62.18267138
Total	**15,885.83**	**100**

Annex 7. Summary table of major PDPs and intermediaries in PRNDs R&D

Funding Mechanism	Type	Partners	Description	Funds mobilized ($US)	Governance structure	Product/trial status to date
International AIDS Vaccine Initiative (IAVI)	PDP	USAID, PEPFAR, BMGF, EU, World Bank, DOD, UKAID, EDCTP, DTRA, CEPI, Wellcome Trust, and the governments of Denmark, India, Japan, Norway, and Ireland	Provides grants and scientific and technical support to advance vaccine and antibody candidates for HIV/AIDS. Shares best practices between high and middle-income countries through a network of clinical trial partners.	~$330 million from 2015-18	Governed by Board of Directors. The day-to-day operations are overseen by senior leadership.	33 vaccine candidates advanced to clinical trials across 11 countries. No products launched.
MMV	PDP	BMGF, UK DFID, USAID, Wellcome Trust, Netherlands Ministry of Foreign Affairs, and other private and public sector stakeholders	Provides grants, scientific and technical expertise to facilitate equitable access to quality antimalarials, and brings forward new tools for resistance and elimination of malaria.	~$281 million from 2015-18	Governed by Board of Directors. The Expert Scientific Advisory Committee helps to identify projects and monitor progress through an annual review. The Access & Product Management Advisory Committee advices on strategies to drive access. Global Safety Board reviews projects that are testing for the first time in humans.	9 products developed and registered and 4 products currently in phase III trials.
PATH	PDP	Government of the US, philanthropic institutions such as the Bill and Melinda Gates Foundation	Provides grants and technical expertise to bridge the gap between technologies of the developed world and family planning needs of developing nations with recent venture into malaria vaccines.	~$307 million from 2015-18	Governed by Board of Directors. The day-to-day operations are managed by an executive team.	No quantified pipeline data publicly available.
DNDi	PDP	UK DFID, BMGF, MSF, Wellcome Trust, EU, UNITAid, NIH/NIAID/USAID, and governments of	Provides grants to early-stage research and product registration,	~$196 million from 2015-18	Governed by Board of Directors. Regional entities are governed by regional	9 products developed and registered and 2 products currently

		Netherlands, Germany, Japan, Switzerland, France, and Spain	implementation and access for neglected diseases like leishmaniasis, sleeping sickness, and Chagas disease.		boards. The Scientific Advisory Committee advises the Board regarding project funding and decisions. The day-to-day operations are managed by an executive team.	undergoing regulatory review.
TB Alliance	PDP	Australian Aid, BMGF, Cystic Fibrosis Foundation, EDCTP, GHIT, Indonesia Health Fund, Irish Aid, Medical Research Council, NIAID, USAID, Rockefeller Foundation, and the governments of Netherlands, Germany, and UK	Provides grants and technical expertise to evaluate novel combinations of TB drugs, and promotes market access by working with partner manufacturers, distributors, and purchasers to ensure consistent product supply.	~$233 million from 2015-18	Governed by Board of Directors. The Board is advised by four committees that include: Scientific (technical expertise on drug research and development), Stakeholder (advises on R&D activities, market adoption techniques, and dissemination and sharing of global information), Access (advises on strategies to achieve adoption, availability, and affordability of new treatments), and Pediatric (provides strategic guidance on pediatric TB issues/concerns).	3 products developed and registered.
EDCTP	Intermediary	EU and EU member states	Provides grants, capacity building, and technical expertise to support collaborative research that accelerates the clinical development of new or improved interventions for HIV/AIDS, Malaria, TB, and NTDs.	~$650 million since 2014 (EDCTP2)	The General Assembly provides oversight with representatives from African and EU member states and representatives from EU, WHO, and the African Union. The Scientific Advisory Committee is comprised of EU and African scientists and advises the General Assembly on technical matters. The day-to-day operations are managed by the Secretariat.	Funded more than 100 clinical trials for drugs, vaccines, and diagnostics primarily in the early stages.
GHIT	Intermediary	Government of Japan, Japanese Pharmaceutical Companies, BMGF,	Invests in discovery, preclinical, and other development	$145 million since 2013 with additional	The Board of Directors approves major rules, strategic plans, and annual budget.	11 products in clinical trials with 1 in Phase III and 1 in

		Wellcome Trust, and UNDP	phases of neglected disease projects including HIV/AIDS, Malaria, TB, and NTDs, and also provides a drug screening and discovery service to PDPs/Pharma.	$200 million for 2018-20	The Selection Committee evaluates investment proposals and reports from development partners and provides investment recommendations to the Board of Directors. No private company representatives are represented on the Selection Committee to allow for investments into pharmaceutical products. The day-to-day operations are managed by a leadership team.	product registration phase.
CEPI	Other	BMGF, Wellcome Trust, WEF, EC, and governments of Australia, Belgium, Canada, Germany, India, Japan, and Norway	Focuses on pre-outbreak vaccine development for priority diseases from the WHO R&D Blueprint for Action to Prevent Epidemics.	$630 million raised since 2016	Governed by the Board of Directors. The Scientific Advisory Committee provides recommendations on priority pathogens and development partners. CEPI Investment Council members engage in resource mobilization efforts and serve on the Board of Directors. The Joint Coordination Group also advises the organization, which is a roundtable of independent institutions that play roles in R&D for vaccines.	7 products in clinical trials with 1 in phase III.
GHIF	Other	BMGF, JP Morgan, Swedish IDA, CIFF, KFW, GSK, Merck, Pfizer, Equitable Investment Managers, and IFC	Mobilizes capital from high-net worth individuals and institutions to fund late-stage innovations for neglected diseases seeking social impact and a return on investment.	$108 million since 2013	The Investment Committee and Charitability Oversight Committee monitor and approve investments. This fund leverages expertise of the investor base via an Investor Advisory Committee and a Scientific Advisory Committee, which both provide investment reviews for companies.	11 products in late-phase clinical development across more than 7 diseases.

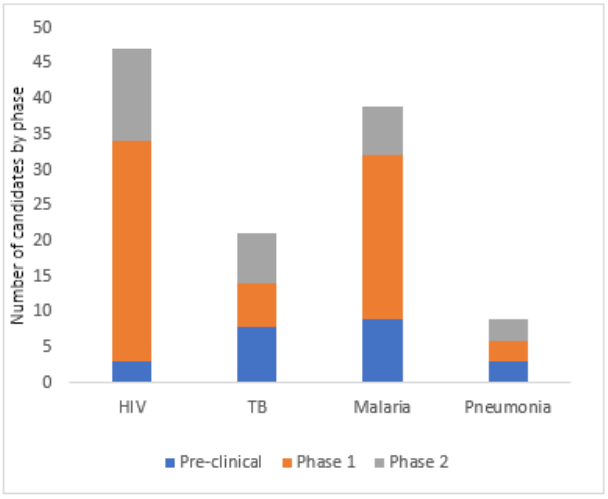
GARDP	Other	BMGF, Leo Model Foundation, MSF, UK DFID, Wellcome Trust, and the governments of UK, South Africa, Netherlands, Monaco, Luxembourg, and Germany	Identifies gaps in the antibiotic pipeline and partners with research institutions and pharmaceutical companies to advance product development—particularly new therapeutics.	$65 million pledged since 2016	Governed by a Board of Directors that determines its strategic goals and ensures that milestones are met. The Scientific Advisory Committee advises the Board of Directors on scientific objectives and strategies.	4 products developed and in registration and 1 candidate in Phase IIb/III
CARB-X	Other	BARDA, Wellcome Trust, BMBG, UK Department of Health and Social Care, BMGF, NIAID, and Boston University	Provides grants as well as scientific and business support to advance the early stages of innovative antibiotics and other therapeutics, vaccines, rapid diagnostics, and devices to address drug-resistant bacterial infections with primary focus on preclinical and early-stage.	$500 million from 2016-21	The Joint Oversight Committee acts as the Board of Directors with full oversight of operational and financial activities. The Advisory Board provides recommendations on research investment decisions.	Graduated six products to Phase I clinical trials. No products registered.
UNITAID	Other	BMGF and the governments of France, UK, Norway, Brazil, Spain, Republic of Korea, and Chile	Provides grants to scale up access to treatment for HIV/AIDS, Malaria, and Tuberculosis by leveraging price reductions of quality drugs and diagnostics and creates a network of innovators who produce high-quality health products.	~$680 million from 2015-18	The Executive Board determines the organization's objectives and monitors progress. The Finance & Accountability Committee and Policy & Strategy Committee advise the Executive Board. The Proposal Review Committee is an independent, impartial team of experts who provide scientific, market dynamics, health economics, and implementation expertise to UNITAID on proposals and draft grant agreement development documents.	1 approved pediatric TB drug. Project status for other treatment areas unavailable.

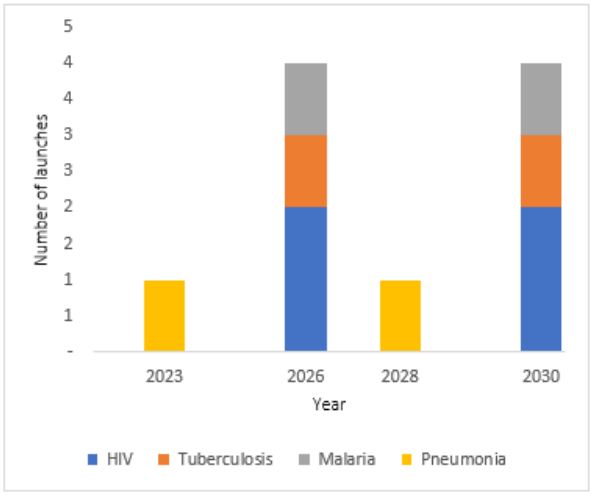
As of May 2020

Annex 8. Detailed results of the modeling on costs and benefits

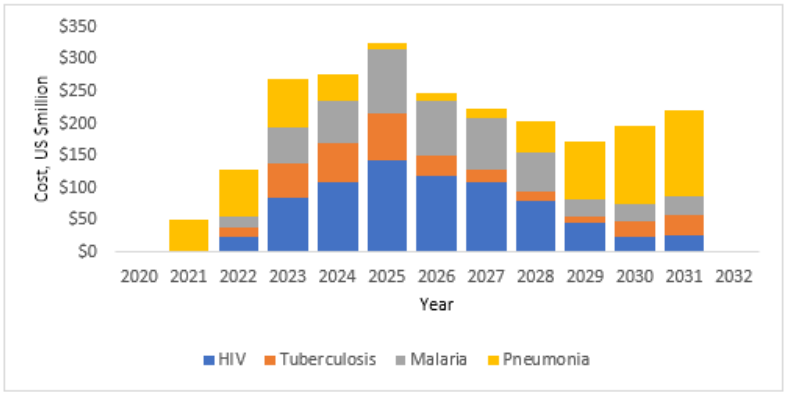
Required investments and expected launches

Option 1: We reviewed the pipeline of product candidates for PRNDs as of August 31, 2019 (see https://f1000research.com/articles/9-416) and found a total of 116 vaccine candidates in the early stages of development (defined as advanced pre-clinical, phase I, and phase II) for HIV, TB, malaria, and pneumonia (**Panel 1A**). Of these 116 vaccine candidates, 23 (20%) were in the advanced pre-clinical phase, 63 (54%) were in phase I, and 30 (26%) were in phase II. We assumed that the pipeline will be replenished through entry of new candidates into the advanced pre-clinical phase at a rate of 10 new candidates per disease condition per year. Based on this portfolio, about 16 vaccine candidates will make it to phase III between 2022 and 2029. Of these 16 candidates, 3 will be simple vaccine candidates for pneumonia and 13 will be complex candidates for HIV, TB, malaria, and pneumonia. With a phase III investment of around US$2.8 billion over 11 years, 10 vaccine launches are expected between 2023 and 2029. The first expected success is a pneumonia vaccine in 2023, followed by HIV, TB, and malaria vaccines (in 2026) and further vaccine launches after that (**Panel 1B**). **Panel 1C** shows the needed phase III funding by year. Assuming a start-up cost of US$36 million and an annual running cost of US$25 million, the total operational cost over 10 years for Option 1 is US$249.5 million. With an additional US$50 million annually over five years for health system strengthening activities, the total needed investment increases to US$2.8 billion.





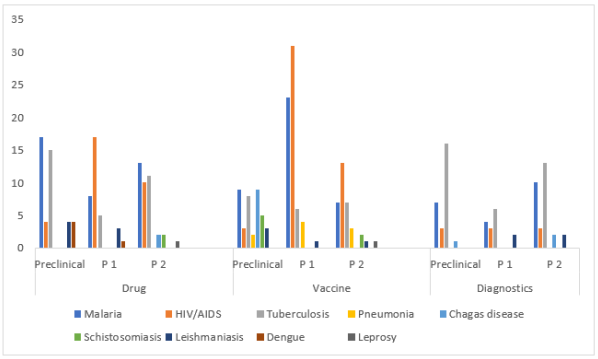
Panel 1.A. number of vaccine candidates in early stages of development. 2(**Panel 1.B.** Expected launches by year



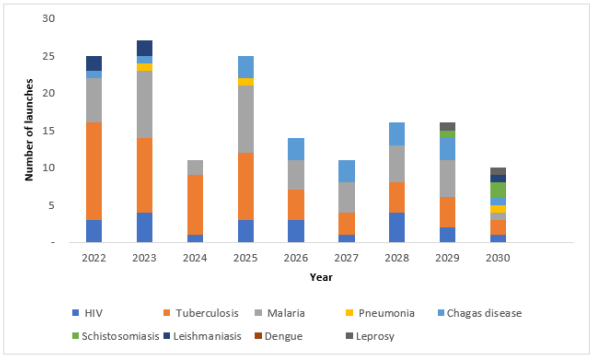
Panel 1.C. needed phase 3 funding by year (US $million).

Panel 1. Number of vaccine candidates in early stages of development (1A), expected launches by year (1B), and needed phase III funding by year (1C) for Option 1

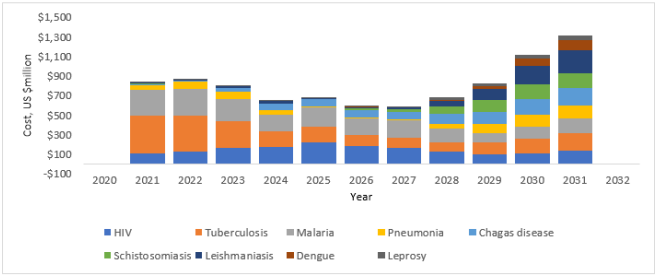
Option 2: For Option 2, we identified a total of 327 product candidates (therapeutics, vaccines, and diagnostics) in early stage development (**Panel 2A**). Of these, 272 (83%) were candidate products for HIV, TB, and malaria; 16 (5%) were for visceral leishmaniasis, 14 (4%) were for Chagas disease, 9 (3%) were for pneumonia, 9 (3%) were for schistosomiasis, 5 were for dengue, and 2 were for leprosy. As with Option 1, we assumed that the pipeline will be replenished through entry of new candidates into the advanced pre-clinical phase at a rate of 10 new candidates per disease condition per year. The total investment needed for phase III is US$8.96 billion, which is expected to result in 155 product launches between 2021 and 2031 (**Panel 2B**). **Panel 2C** shows the needed phase III funding by year. Assuming an annual running cost of US$40 million, a startup investment of US$58 million in year 0, and an additional US$100 million annually for health system strengthening activities, the total needed investment for Option 2 is US$9.84 billion.



Panel 2.A. design option 2 number of products in early stages of development



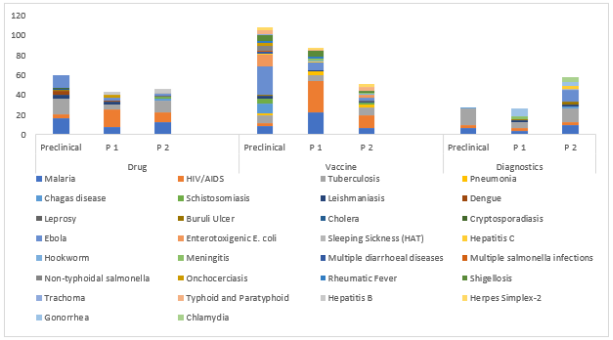
Panel 2.B. expected launches by year from design option 2



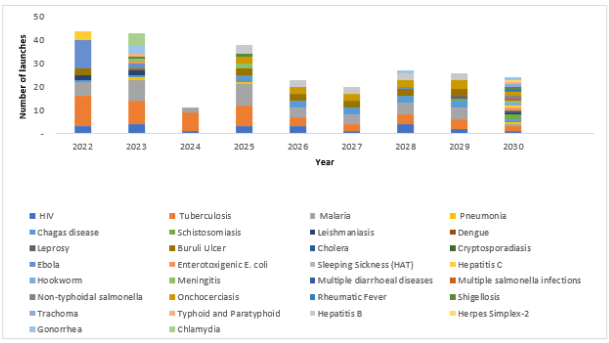
Panel 2.C. design option 2 needed phase 3 funding by year (US $ million)

Panel 2. Number of product candidates in early stages of development (2A), expected launches by year (2B), and needed phase III funding by year (2C) for Option 2

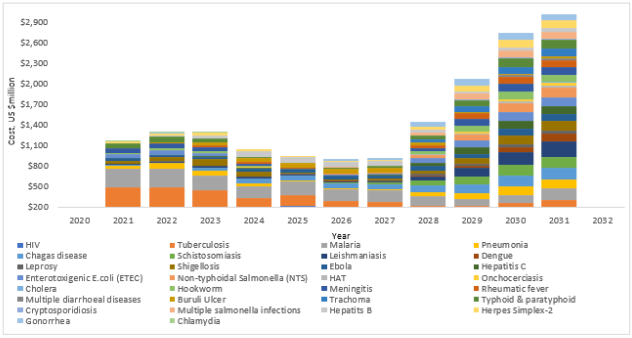
Option 3: For Option 3, we included an additional 21 disease conditions to those included in option 2. We identified 179 product candidates in addition to those included in option 2. The total number of candidates in early stage of development is 506. (**Panel 3A**). The highest number of candidates were for malaria (98), tuberculosis (87), HIV (87), and Ebola (70). Combined, products for neglected tropical diseases represented only 11.5%, where all except Chagas disease, and leishmania have less the 10 candidates. Similar to the other options, we assumed that the pipeline will be replenished through entry of new candidates into the advanced pre-clinical phase at a rate of 10 new candidates per disease condition per year. The total investment needed for phase III is US$16.83 billion, which is expected to result in 256 product launches between 2021 and 2031 (**Panel 3B**). **Panel 3C** shows the needed phase III funding by year. Assuming an annual running cost of US$60 million, a startup investment of US$87 million in year 0, and an additional US$250 million annually for health system strengthening activities, the total needed investment for Option 3 is US$18.61 billion.



Panel 3.A. design option 2 number of products in early stages of development



Panel 3.B. expected launches by year from design option 2

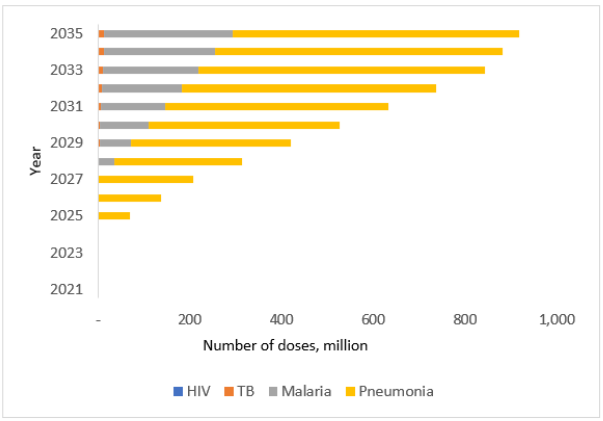


Panel 3.C. design option 2 needed phase 3 funding by year (US $ million)

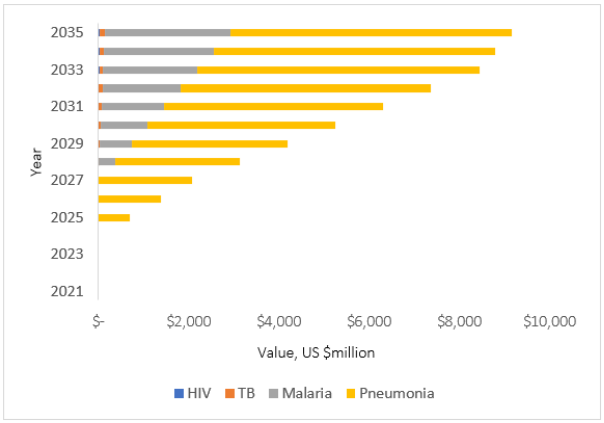
Panel 3. Number of product candidates in early stages of development (3A), expected launches by year (3B), and needed phase III funding by year (3C) for Option 3

Estimating post-launch demand for vaccines, therapeutics, and procurement costs

The primary benefits from vaccines derive from their effect on reducing the annual incidence of a disease, while benefits from therapeutics could arise either from an increase in treatment coverage (e.g., from the development of a cheaper drug) or through increase in therapeutic effectiveness. Under vaccine efficacy assumptions of 75% (for HIV, TB, malaria, Chagas disease, schistosomiasis, and visceral leishmaniasis), and 85% for pneumonia (assuming a pneumonia vaccine will be at least as effective as PCV vaccine), and a target annual incidence reduction of 10 percentage point increments, a pneumonia vaccine will have the highest annual number of doses demanded. For example, our estimates show that the annual number of vaccine doses demanded for pneumonia in the first year of introduction will be 69 million, compared with 35 million for malaria and one million each for HIV and TB, respectively. At a vaccine price per course of US$10, the overall vaccine procurement cost for Option 1 ranged from US$61.7 million (HIV) to US$3.7 billion for pneumonia vaccine (**Panel 4**). Two factors contribute to the higher numbers for pneumonia: (i) the pneumonia vaccine will be the first to launch in 2023, and ii) pneumonia has the highest baseline incidence compared to all of the other diseases included in the model. At US$99.0 billion, the overall vaccine procurement cost in design Option 3 is the highest of the 3 options, compared to US$41.0 billion and US$40.3 billion for option 2 and 1, respectively.



Panel 4.A. number of needed doses for HIV, TB, Malaria, and pneumonia vaccines



Panel 4.B. projected total procurement costs for HIV, TB, Malaria, and pneumonia vaccines

Panel 4. Number of needed doses of HIV, TB, malaria, and pneumonia vaccines (4A) and projected total procurement costs (4B) to achieve incidence reduction targets for Option 1

For therapeutics, under the assumption that (a) the costs of new therapeutics will be similar to the costs of existing ones, and (b) there will be a 10% year-on-year increase in treatment coverage (as described earlier), the overall demand (for additional cases covered) over 11 years is valued at US$28.5 billion. The highest demand will be for malaria therapeutics (US$17.3 billion), followed by TB therapeutics (US$10.7 billion). The demand for additional HIV therapeutics will have a value of US$366.9 million. The value will be US$106.8 million, US$43.4 million, US$7 million, and US$2.1 million for schistosomiasis, Chagas disease, leishmaniasis, and leprosy therapeutics, respectively. It is important to note that the model stops at the year 2035, so if a product launch is expected to happen in 2031 (leprosy), only three years were modeled (2033-2035). Therefore, the demand for therapeutics will be different if the model is extended beyond 2035. Another factor that determines demand is the baseline treatment coverage. If the baseline coverage is high and the launch happens towards the end of the model time horizon, the resulting demand will be low. Lastly, if there was a successful launch of a vaccine and a therapeutic candidate for the same disease, the potential increase in demand for therapeutics will be partly or completely offset by the potential decrease in demand for treatment as a result of vaccine-induced reduction in incidence. For diagnostics, under the assumption that a new diagnostic would result in higher case detection, we measured the benefits from diagnostics as an increase in treatment coverage (of the new cases identified). We assumed a one-time 10% increase in treatment coverage in the year of introduction and maintain that level as the baseline treatment coverage in subsequent years. Further increases in treatment coverage can occur with new launches of therapeutics.

Net benefits

From a societal perspective, we estimated that Option 1 will avert 18.4 million deaths and 516 million DALYs over 10 years at a cost per death averted of US$2,341, and a cost per DALY averted of US$84. Option 2 will avert 23 million deaths and 674 million DALYs at a cost per death averted of US$2,217 and a cost per DALY averted of US$75. Option 3 will avert 26.9 million deaths and 1.03 billion DALYs at a cost of US$4,371 and US$114 per death averted and DALY averted, respectively. The incremental cost-effectiveness ratio (ICER) of Option 2 compared to Option 1 is US$27.55 per DALY averted. Fund investors' perspective only include costs incurred by the aggregator, thus from this perspective the cost effectiveness ratios are significantly better for all options (**Table 8A**)

Table 8A. Comparison of the cost-effectiveness of Options 1, 2 and 3

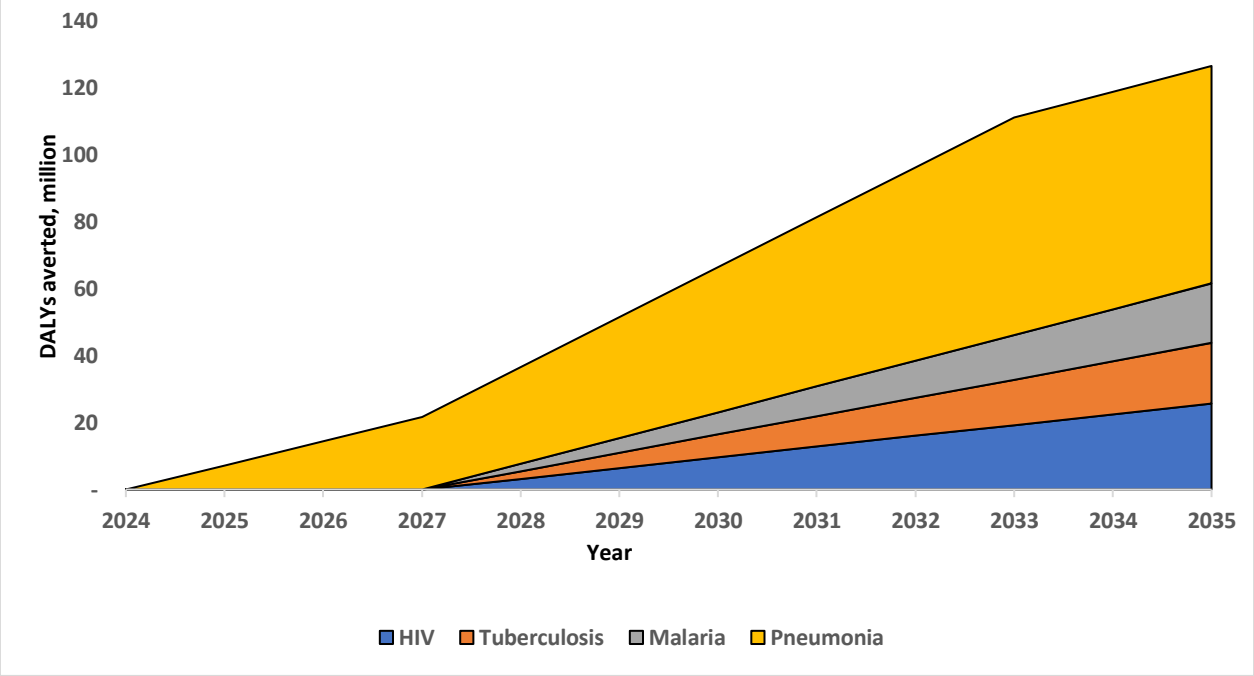
	Net cost (US$ billion)		DALYs averted over 10 years (in millions)	Cost per DALY averted		Deaths averted over 10 years (in millions)	Cost per Death averted	
	Societal	Fund investor		Societal	Fund investor		Societal	Fund investor
Design option 1	$43.07	$2.80	516	$84	$5.43	18.4	$2341	**$152**
Design option 2	$50.81	$9.84	674	$75	$14.60	22.9	$2217	**$429**
Design option 3	$117.64	$18.61	1,030	$114	$18.01	26.91	$4,371	**$692**
ICER (2 vs 1)				$48.94			$1,714	
ICER (3 vs 2)				$186			$16715	

Table 8B. Benefit cost ratios and net benefits: societal vs. investor's perspective

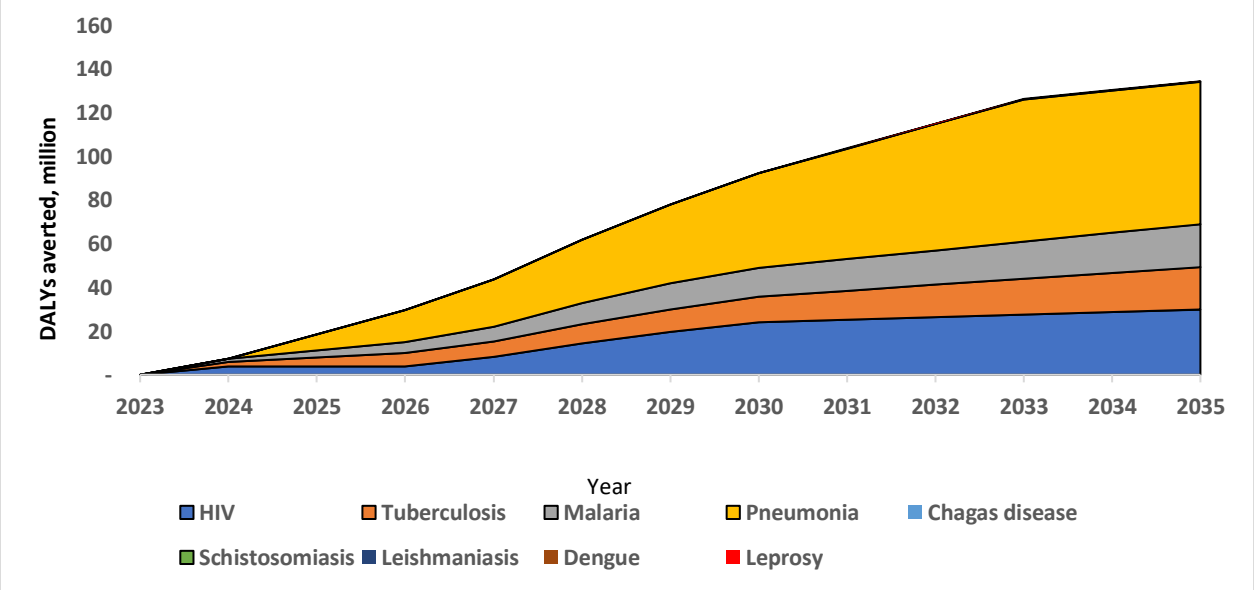
	Societal perspective			Fund investor's perspective		
	Net costs (US billion)	Net benefits	Benefit cost ratio	Net costs (US billion)	Net benefits	Benefit cost ratio
Option 1	$43.07	$238.4	5.53	$2.80	$198.11	70.78
Option 2	$50.81	$197.4	3.88	$9.8	$156.41	15.90
Option 3	$117.64	$286.67	2.52	$18.6	$197.61	10.62

For Option 1, more than half of the averted DALYs are from pneumonia vaccines (324.9 million DALYs) while an HIV vaccine will avert 79.6 million DALYs (15%). Tuberculosis and malaria vaccines will avert 56.2 million (11%), and 55.1 million (11%) DALYs, respectively (**Panel 5**). This design option is also projected to avert US$238.4 billion in treatment costs over the period of interest to 2035. With a net cost of US$43.07 billion, the estimated benefit cost ratio of Option 1 is 5.53 (**Table 8B**). For Option 2, 48% of the averted DALYs were from pneumonia products, 23%from HIV products, 15% from malaria products, 14% from TB products, and <1% was from other products to control other diseases (**Panel 6**). With a net cost of US$50.81 billion, the estimated benefit cost ratio of Option 2 is 3.88. For option 3, In addition to the DALYs from the products included in option 2, the majority of the DALYs averted were from hepatitis B products (175.5 million), meningococcal meningitis products (55.4 million), shigellosis products (34 million) and, typhoid and paratyphoid (17.9 million). (**Panel 7**) The net cost of design option 3 is US$117.6, and the benefit cost ratio is 2.52. We discounted costs and health benefits using an annual discount rate of 3%.

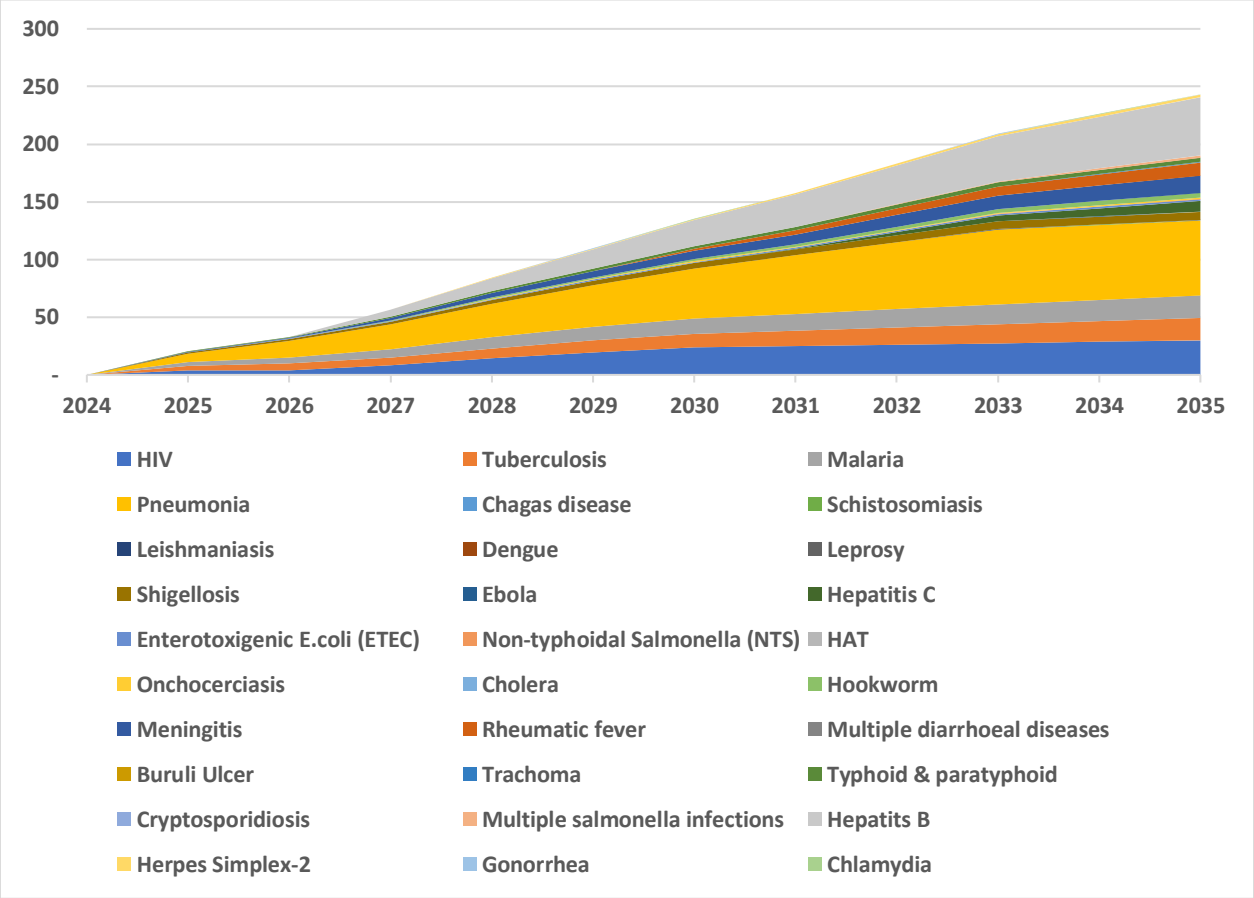
Overall, compared with Option 2, Option 1 has higher societal benefits as a result of the treatment costs averted due to vaccination. While Options 2 results in high averted medical costs due to vaccination, it also has additional medical costs as a result of increased treatment coverage. Thus, although the net health benefits (DALYs averted) of design Option 2 are higher than those of Option 1, the net economic benefits (treatment costs averted) are lower. Because of its large scope, option 3 has the highest net benefits, however, for the same reason, it has the highest cost and the lowest benefit cost ratio.



Panel 5. Projected health benefits (DALYs averted, million) over 10 years for Option 1



Panel 6. Projected health benefits (DALYs averted, million) over 10 years for Option 2



Panel 7. Projected health benefits (DALYs averted, million) over 10 years for Option 3

Efficiency gains

Efficiency gains arise from the aggregator's ability to use adaptive clinical trials. Benefits from adaptive clinical trials result from operational and statistical efficiencies that ultimately reduce trial costs and shorten lead times between trial phases. We modeled two scenarios. In the first scenario 50% of trials supported by the aggregator adopt an adaptive design, resulting in a 3-month reduction in phase length for all phases and a 7.5% reduction in late-stage trial costs. In the second scenario 100% of trials supported by the aggregator adopt an adaptive design, resulting in a 6-month reduction in phase length for all phases and a 15% reduction in late-stage trial costs. Both scenarios were compared to a baseline scenario in which 0% of trials supported by the aggregator adopt an adaptive design.

In our discrete event simulation (DES) model, products (vaccines, drugs, and diagnostics) were treated as entities with attributes specifying their unique phase length times and phase success probabilities. Trial phases (preclinical, phase I, phase II, and phase III) were treated as servers with an infinite capacity to handle entities. All entities generated were assigned four numbers randomly sampled from a uniform distribution ranging from 0 to 1. Each of these four numbers determined an entity's success in moving from one server to the next. An entity

was considered launched if it successfully exited the phase III server. The baseline model results were validated against the results from the portfolio to impact model. **Figure 8A** is a diagram of our DES for option 1.

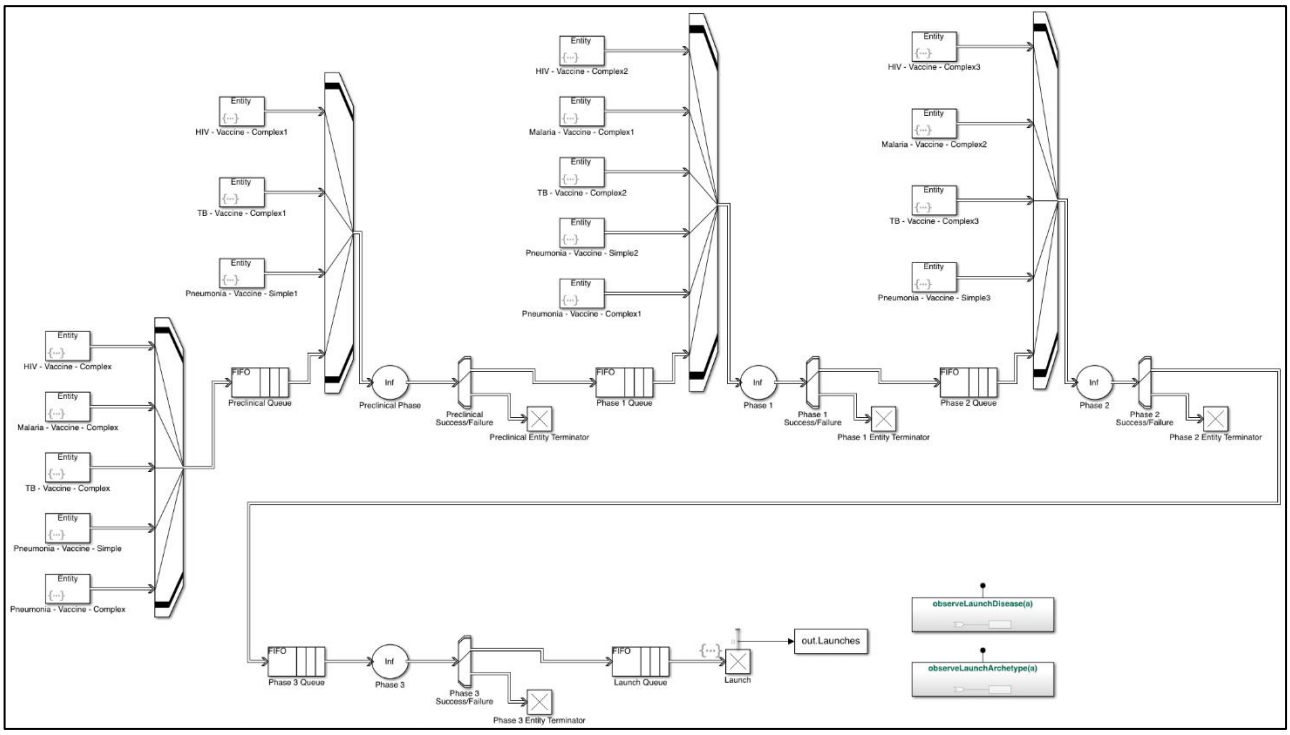


Figure 8A. Architecture of discrete event simulation model for Option 1 built with SimEvents (Matlab 2020Ra).

Given the probabilistic nature of our discrete event models that arises from random number generation, we used a Monte Carlo approach to synthesize results. Each of the three scenarios described above were simulated 100 times each. Product launches were averaged across all 100 simulations to obtain our final statistic: mean launches per entity per year. Results from all three scenarios are described in **Table 8C.**

Table 8C. Cost, DALYs Averted, Deaths Averted, and BCR for All Efficiency Scenarios.

Option 1			
	Business-as-usual (No improvements in efficiency)	**Feasible improvements in efficiency (50% adaptive trials)**	**Ambitious improvements in efficiency (100% adaptive trials)**
Net Cost	$43,070,968,662	$45,284,863,680	$50,055,372,038
Total DALYs Averted	515,780,177	565,965,737	617,465,617
Net Cost Per DALY Averted	$84	$80	$81
Total Deaths Averted	18,401,771	19,842,072	21,647,868
Net Cost Per Death Averted	$2,341	$2,282	$2,312
Benefit Cost Ratio	5.53	5.65	5.65
Option 2			
	Business-as-usual (No improvements in efficiency)	Feasible improvements in efficiency (50% adaptive trials)	Ambitious improvements in efficiency (100% adaptive trials)
Net Cost	$50,809,984,900	$52,886,955,917	$57,599,563,624
Total DALYs Averted	673,901,317	738,335,962	784,506,654
Net Cost Per DALY Averted	$75	$72	$73
Total Deaths Averted	22,915,217	24,655,929	26,296,865
Net Cost Per Death Averted	$2,217	$2,145	$2,190
Benefit Cost Ratio	3.88	4.06	4.18
Option 3			
	Business-as-usual (No improvements in efficiency)	**Feasible improvements in efficiency (50% adaptive trials)**	**Ambitious improvements in efficiency (100% adaptive trials)**
Net Cost	$117,643,715,881	$121,997,836,574	$137,792,068,261
Total DALYs Averted	1,033,172,193	1,156,616,145	1,292,684,784
Net Cost Per DALY Averted	$114	$105	$107
Total Deaths Averted	26,913,715	28,986,152	32,548,970
Net Cost Per Death Averted	$4,371	$4,209	$4,233
Benefit Cost Ratio	2.52	2.73	2.89