THE CENTER FOR POLICY IMPACT IN GLOBAL HEALTH

OPEN CONSULTANTS

Reforming the research and development ecosystem for neglected diseases, emerging infectious diseases, and maternal health

AUTHORS:

Marco Schäferhoff,[1] Gavin Yamey,[2] Osondu Ogbuoji,[2] Ayodamope Fawole[2], Armand Zimmerman,[2] Ipchita Bharali,[2] Shingai Machingaidze,[3] Ernesto J. Ortiz,[2] Mosa Moshabela,[4] Ming Xu[5]

1: Open Consultants, Berlin
2: Center for Policy Impact in Global Health (CPIGH), Duke University, Durham, North Carolina, USA
3: Global health consultant
4: School of Nursing and Public Health, University of KwaZulu-Natal, Durban, South Africa
5: Department of Global Health, School of Public Health & Institute for Global Health and Development, Peking University, Beijing, China

TABLE OF CONTENTS

Acknowledgements: We thank all key informants for generously sharing their expertise and relevant data. We also thank Luca Pusceddu from Open Consultants and Jane Claire Anderson from CPIGH for their editorial and organizational support in finalizing this study. We thank Agata Rocka from Rocka Design for graphic design of this report.

Funding: This study was funded by a research grant from the Bill & Melinda Gates Foundation.

ABBREVIATIONS

ACT-A	Access to COVID-19 Tools Accelerator
Africa CDC	Africa Centres for Disease Control and Prevention
AU	African Union
AMA	African Medicines Agency
AMRH	African Medicines Regulatory Harmonization
AI	Artificial intelligence
AMC	Advanced market commitment
APA	Advanced purchase agreement
AVAT	African Vaccine Acquisition Trust
AVAREF	African Vaccine Regulatory Forum
AVMA	African Vaccine Manufacturing Accelerator
ASEAN	Association of Southeast Asian Nations
CMA	Conditional marketing authorization
CEPI	Coalition for Epidemic Preparedness Innovations
CoGs	Cost of goods
CPP	Certificate of pharmaceutical product
CPIGH	Center for Policy Impact in Global Health, Duke University
DALYs	**Disability-adjusted life years**
DCTs	Decentralized clinical trials
DHTs	Digital health technologies
DHVI	Duke Human Vaccine Institute
EAC	East African Community
EDEN	Efficacy Discriminating Educated Network
EIDs	Emerging infectious diseases
EMA	European Medicines Agency
EUA	Emergency use authorization
FDA	US Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
FGHI	Future of Global Health Initiatives
Gavi	Gavi, the Vaccine Alliance
GAO	US Government Accountability Office
GBT	WHO Global Benchmarking Tool
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMP	Good Manufacturing Practice
HCTs	Human challenge trials
HECT	Highly Efficient Clinical Trials
HIC	High-income country
HPV	Human papillomavirus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
IRB	Institutional review board
KI	Key informant
KII	Key informant interview
LIC	Low-income country
LiST	Lives Saved Tool
LMICs	Low- and middle-income countries
mAbs	Monoclonal antibodies
MCM	Medical countermeasure
MH	Maternal health
ML	Maturity level
NCDs	Non-communicable diseases
NDs	Neglected diseases
NRA	National regulatory authority
PACs	Post-approval changes
PAVM	Partnership for African Vaccine Manufacturing
PE&E	Preeclampsia and eclampsia
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PPH	Postpartum hemorrhage
PPR	Pandemic preparedness and response
PRIME	PRIority MEdicines scheme
PQ	WHO prequalification of medicines
PRV	Priority review voucher
R&D	Research and development
REC	Regional economic community
RSV	Respiratory syncytial virus
RWD	Real world data
SCA	Synthetic control arm
SRA	Stringent regulatory authority
SSA	Sub-Saharan Africa
SADC-MRH	Southern African Development Community Medicines Regulatory Harmonization
SRH	Sexual and reproductive health
TB	Tuberculosis
TLD	Tenofovir, lamivudine, and dolutegravir
TLE	Tenofovir, lamivudine, and efavirenz
tWLA	Transitional WHO-listed authority
WHO	World Health Organization
WLA	WHO-listed authority

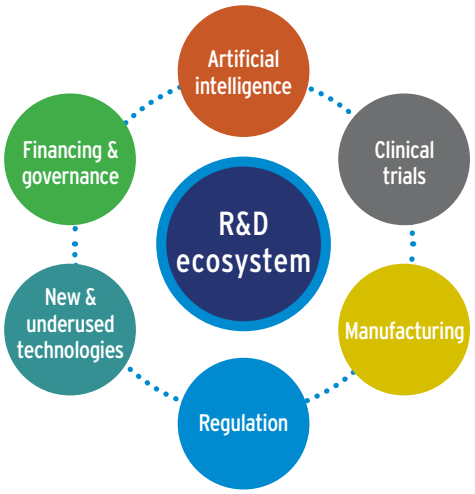
Aims, methods, and analytic framework

The long timelines, high attrition rates, and high costs of global health research and development (R&D) are impeding the development of new health technologies. This study examines the key shifts in the R&D ecosystem that could help overcome these problems and accelerate the discovery and development of new tools for neglected diseases (NDs), emerging infectious diseases (EIDs), and maternal health (MH) over the next 20 years. The analysis is based on insights and data from:

- **A workshop** with over 30 senior policy actors who are engaged in global health R&D policymaking, held in London on August 8-9, 2023, which had strong representation from low- and middle-income countries (LMICs). At this workshop, we shared and received feedback on our proposed study approach and elicited participants' views on the likely shifts in the R&D ecosystem that could drive efficiencies. A second virtual meeting was held in February 2024 to discuss our findings.
- **Key informant (KI) interviews** with over 60 key informants (KIs) worldwide, held between August 2023 and March 2024. We interviewed a broad range of KIs, including from academia, bilateral and multilateral health agencies, pharmaceutical companies, research funding agencies, regulatory agencies, product development partnerships, non-government organizations, foundations, and regional alliances. In addition, we organized regional consultations in Africa, Asia, and Latin America to better understand regional ecosystem needs. Over 60 additional stakeholders were consulted in this regional consultation process.
- **A review and synthesis** of the peer-reviewed and grey literature.

The analytic framework used for the study examined the R&D ecosystem across six key dimensions, which we validated with stakeholders at the London workshop (Figure ES1).

Figure ES1: Six key dimensions of the R&D ecosystem



Our study has three key limitations. First, the evidence on potential efficiency gains from ecosystem shifts is still nascent and some of it comes from high-income countries (HICs) and from studies on non-communicable diseases (NCDs). These findings cannot always be easily translated to NDs, EIDs, and MH in LMICs. Second, our paper does not address the transformations needed in R&D for NCDs in LMICs, even though the burden of NCDs will continue to grow in these countries over the next 20 years. Third, this report does not analyze delivery systems, which were beyond the scope of our study, but which are essential to ensure access to new health tools.

Key findings on efficiencies and their policy implications

APPLYING ARTIFICIAL INTELLIGENCE (AI) TO PRODUCT DEVELOPMENT

Given its potential to drive major efficiencies, there is huge interest in applying AI to global health R&D. AI has been applied across the whole product development spectrum, including new target identification, drug candidate selection, protein structure prediction, molecular compound design and optimization, and clinical trial design, conduct, and analysis. AI can accelerate discovery and preclinical research and reduce its costs. The standard time for screening, identifying, and validating target molecules is 3-5 years, with costs of up to US$10 million; with AI, the discovery phase can be shortened to less than 12 months. There are also examples of AI tools that have lowered

discovery costs by a factor of up to 50. Compared with traditional screening approaches, AI tools can improve screening and thus the quality of candidates, leading to less attrition during the clinical phase. AI tools have been used to identify truly novel compounds, which resulted in promising new drug candidates that are currently being tested in clinical trials. There is also a valuable role for AI platforms in drug repurposing and in identifying combination therapies; such platforms have identified optimal drug combinations (e.g., for COVID-19) faster and at lower cost compared with conventional approaches. AI platforms can predict trial success with high accuracy, which could reduce the costs of the clinical phase, e.g., one AI prediction tool, trained on 55,600 unique Phase 2 clinical trials over 7 years, predicted the probability of moving to Phase 3 with 79% accuracy.

However, AI has several limitations. If it is rolled out inequitably, AI could augment inequalities between LMICs and HICs. African researchers have therefore called for a research agenda on AI grounded in the African context to determine locally relevant strategies for its development and use. Most of the data feeding into AI tools comes from HICs and there is very little data on the use of AI for R&D for NDs.

Nevertheless, our analysis of the evidence, together with the experience of KIs interviewed for this project, shows that AI is *already* transforming the global health R&D ecosystem. While AI offers unprecedented opportunities for drug discovery, AI tools have the potential to optimize the entire product development process (from "end to end"), which could substantially reduce future R&D costs, accelerate R&D timelines, and lead to new medicines.

WE RECOMMEND FIVE KEY REFORMS:

1. Leverage the substantial efficiencies and benefits of AI in drug discovery and preclinical research: global health R&D funders should increase their investment in AI-based companies.
2. Expand the use of AI for epidemic and pandemic preparedness: use AI tools to predict protein structures for priority pathogens in a coordinated attempt to build a vaccine library.
3. Further assess and leverage the potential of AI in clinical research: using AI in the prediction of clinical trial outcomes, for example, can lead to cost savings.
4. Enable LMICs to meaningfully participate in AI-driven R&D and build respective capacity and expertise: Without such participation, existing inequalities in global health will be widened. Partnerships between AI companies—which are mostly based in HICs—and LMIC researchers will be important. Efforts to develop an African-led AI research agenda should be supported.
5. Significantly strengthen existing regulatory frameworks for AI in global health.

INNOVATIONS IN CLINICAL TRIAL CONDUCT

Clinical trials are essential in showing that a product is effective and safe. New health tools for NDs, EIDs, and MH should ideally be trialed in LMICs, where the burden of disease is highest, ensuring inclusive and representative selection of trial participants. Yet the vast majority of trials are conducted in HICs. In addition, traditional trial designs are expensive, lengthy, and have low success rates. The good news is that advances in trial conduct are now driving efficiencies and the COVID-19 pandemic validated many of these advances, e.g., trial networks were critical to the rapid development of vaccines, while platform trials like RECOVERY helped usher in COVID-19 therapies.

Innovations in trial conduct can be categorized into *technological innovations*, e.g., digital clinical trials (DCTs) and open source trials software; *innovative trial designs*, e.g., master protocols (such as platform trials) and real world evidence; and *trial networks*. There is good evidence—mostly from HICs—that DCTs can reduce trial costs, timelines, and the number of patients needed in a trial and can improve recruitment and retention of participants. It is unclear whether the findings can be generalized to LMICs. Platform trials can drive efficiencies by shortening trial duration, evaluating more treatments per trial, reducing the number of patients required per trial (by up to 70%), and increasing the proportion of programs that accurately recognize an effective treatment. Using real-world data and evidence can lead to savings of US$10 million to US$20 million per trial, depending on how much synthetic control arms are used to replace traditional control arms. Clinical trial networks can drive efficiencies by using existing sites instead of creating new ones, recruiting patients more quickly and reliably, and reducing the number of patients needed by sharing control groups with other trials. Furthermore, the ability to rapidly test product candidates during outbreaks relies on the existence of effective and inclusive regional clinical trial networks that are kept "warm" in between infectious disease outbreaks.

Capacity for conducting even traditional trials is currently limited in LMICs, and there are barriers to rolling out trial innovations in these settings (e.g., the high complexity of platform trials and maintaining data quality and privacy in DCTs). Nevertheless, we believe capacity building efforts *should* include innovative approaches.

WE RECOMMEND TWO KEY REFORMS:

1. Research funders and agencies should support sustained, long term efforts to build clinical trial networks that have the capacity to adopt innovative approaches, leveraging capacities already built. These networks need be kept active in between epidemics/pandemics.
2. Adoption of platform trials and other master protocols in low-resource settings will require funding agencies, institutional review boards (IRBs), data safety boards, and regulators to become familiar with these designs. As innovative trial designs become more widespread in LMICs, operational lessons need to be shared so that implementation barriers can be tackled and best practices adopted.

BUILDING MANUFACTURING CAPACITY IN LMICs

Multiple high-level regional efforts, such as the Partnership for African Vaccine Manufacturing (PAVM), are now underway to increase manufacturing capacity in LMICs and enable these countries to become self-sufficient in making their own health products. Building such capacity has taken on new urgency to ensure that LMICs can manufacture medical countermeasures (MCMs) in the next pandemic rather than relying on donations from HICs. In addition, diagnostics experts interviewed for this study highlighted the lack of production capacity for diagnostics in LMICs and noted that the market for diagnostics is dominated by just a few major players.

Traditional manufacturing is expensive. Innovative modular manufacturing approaches and optimized production processes for mRNA technologies could help to drive these costs down, speed up production, and globalize manufacturing. Modular facilities have a small footprint, so capital costs are much lower compared to traditional manufacturing sites. Optimized production processes for mRNA technologies have much lower operational costs because of high yields, reduced reagent use, and efficient design. Optimized mRNA production processes can save over 60% (about US$70 million) of the annual cost of goods for the production of 100 million vaccine doses compared to conventional mRNA manufacturing. These savings could lower mRNA vaccine production costs to US$0.5 per dose. An optimized mRNA production process offers several other advantages—the flexibility to quickly switch from making one vaccine to another, scalable production, and integration of product development with large-scale manufacturing. Such integration is especially useful during pandemics, supporting a rapid response in line with the target of the Coalition for Epidemic Preparedness Innovations (CEPI) to develop a vaccine against the next Disease X within 100 days ("100 days mission").

These savings could lower mRNA vaccine production costs to US$0.5 per dose.

While modular mRNA sites offer substantial benefits compared with traditional manufacturing, their full potential for LMICs still needs to be tested over the coming years. And there are several financial, political, and technical challenges to be addressed in creating sustainable markets and local demand. Despite these challenges, we believe that **investments in regional and sub-regional manufacturing in LMICs accompanied by regulatory strengthening would have a substantial public health impact and is a critical component of global pandemic preparedness and response (PPR)**.

WE RECOMMEND FOUR KEY REFORMS:

1. Donors need to support the creation of manufacturing capacity in LMICs over the long term. Building such capacity is part of planning for sustainable business models and creating market demand for routine immunization. Gavi, the Vaccine Alliance (Gavi) recently launched the African Vaccine Manufacturing Accelerator (AVMA), which will provide up to US$1 billion for creating sustainable vaccine production capacity on the African continent. Other funders must also be willing to subsidize manufacturing in LMIC regions and to guarantee procurement from LMIC manufacturers to create sustainable markets. They should make financial commitments and set concrete purchasing targets to enable the creation of sustainable production across regions, including Africa.
2. LMICs should also commit to buying products manufactured by LMICs, such as through advanced purchase agreements, to help create sustainable markets.
3. The multiple benefits of optimized mRNA production processes and modular production need to be leveraged. Such production approaches can be established faster and produce vaccines at much lower cost than conventional approaches. Nevertheless, supply chain problems (e.g., with reagents and other inputs) still need to be resolved.
4. While the construction of mRNA-based production sites should continue, diversified manufacturing is needed to enable production of existing licensed products across regions, including routine non-mRNA vaccines, drugs, and diagnostics. Building this capacity will also require a stronger focus on technology transfer, licensing agreements, and sharing of intellectual property (IP).

INCREASING THE USE OF NEW AND UNDERUSED HEALTH INNOVATIONS

Our analysis of new and underused innovations focused on mRNA and monoclonal antibodies (mAbs).

The COVID-19 pandemic validated two platform technologies for vaccines that were based on decades of prior research. The first was the mRNA platform, used by Moderna and Pfizer-BioNTech to develop their COVID-19 vaccines, and the second was the viral vector platform, used by Oxford University/AstraZeneca and Johnson & Johnson in developing their COVID-19 vaccines. During the pandemic, these platforms received large amounts of funding and streamlined regulatory approval. KIs argued that mRNA is now garnering the most attention given its potential applications towards a range of diseases, including NDs, EIDs, and certain cancers. mRNA platforms are suited for speed and are highly versatile, which is especially valuable during pandemics. They can be proactive rather than reactive to a pathogen, and have been successfully applied to a previously unknown pathogen. mRNA vaccines could potentially help overcome delivery challenges for NDs and EIDs by being thermostable, single dose, or delivered nasally, though this will require intensified R&D. As mentioned above, there are now multiple attempts to build regional self-sufficiency in mRNA manufacturing capacity. However, mRNA is not a panacea—the chances of developing mRNA vaccines against some pathogens are low.

mAbs have come of age in clinical medicine, with more than 100 mAbs licensed over the past 30 years to treat, prevent, and cure NCDs. However, only seven mAbs have been licensed for infectious diseases. Developing mAbs for EIDs would offer many benefits, including (i) primary prophylaxis while waiting for vaccines to be developed; (ii) immediate protection during the time it takes for an individual to mount a response after vaccination; (iii) passive immunity to patients who do not mount an adequate immune response to vaccines or who are vaccine hesitant; (iv) reducing transmission by reducing viral load; and (v) the potential for stockpiling.

WE RECOMMEND FOUR KEY REFORMS:

1. Given that mRNA platforms have significant comparative advantages over more traditional technologies, investments should be scaled up in mRNA technologies for NDs, EIDs, and MH.

2. It is critical for LMICs to be able to produce their own mRNA technologies. The global health community needs to further strengthen its ongoing support to strengthen mRNA production capacity in LMICs. The patent holders for many of the production inputs needed for mRNA are mostly in HICs, which contributes to existing equity gaps. Addressing this barrier requires a combination of stronger sharing of IP and technology transfer agreements. A major barrier facing LMICs in making mRNA vaccines is the IP constraints attached to lipid nanoparticles, a critical component of the technology—a lipid needs to be available without the IP constraints.

3. New approaches are needed to bring down the production costs of mAbs, e.g., by linking discussions of building manufacturing capacity for mRNA to mAb production in LMICs.

4. There is no example of scaled up mAbs in LMICs, yet we saw with antiretroviral therapies that it is possible to introduce expensive drugs in a relatively fast manner and see costs fall quickly. While the financial environment for mAbs is currently severely constrained, there is an opportunity to pilot their wide-scale introduction; COVID-19 was a missed opportunity to do so. RSV mAbs could be a game changer—a low-cost RSV mAb is believed to be under development—and could serve as a product for the global community to rally around.

In parallel, the case for using mAbs in LMICs needs to be further assessed. From an equity perspective, there needs to be a strong push for developing, producing, and using mAbs in LMICs and for generating evidence on effectiveness and cost effectiveness in different settings.

ACCELERATING REGULATORY REFORMS

Poor regulatory systems are a major barrier to providing safe, high quality, effective tools for NDs, EIDs, and MH. Globally, only 57 countries (around 3 in 10) have regulatory systems that are strong enough to perform core functions. Weak regulatory capacity is a key reason for the large time gap in market authorization of health products between LMICs and HICs. One study estimated that there is lag of 4 to 7 years between first submission for regulatory approval, which is usually to a regulator in a HIC, and final approval in Sub-Saharan Africa (SSA). The study found that the World Health Organization (WHO) prequalification of medicines

Globally, only 57 countries have regulatory systems that are strong enough to perform core functions.

(PQ) processes and national regulatory authorities (NRAs) often repeated assessments of quality, safety, and efficacy already performed by stringent regulatory authorities and that manufacturers did not prioritize market access in LMICs, slowing down rapid access.

Three sets of regulatory reforms have helped to accelerate introduction of new, quality-assured, effective health tools in LMICs. The first was regulatory harmonization and reliance. Second, there were efforts to strengthen regional and national regulatory capacity. The third was a set of regulatory reforms triggered by the COVID-19 pandemic, such as rapid scientific advice and review (in Europe, such advice and review was reduced from 40-70 days to 20 days), rolling reviews, and accelerated marketing authorization.

Multiple studies have shown that harmonization and reliance mechanisms, such as the use of reference agencies and joint reviews, can accelerate market authorization by limiting duplicative assessments. But KIs emphasized the lack of legislation for reliance in countries that also do not have capacity to fulfill the range of regulatory functions; in addition, the implementation of reliance is often done poorly. There is substantial potential to further deepen the collaboration between NRAs.

WE RECOMMEND THREE KEY REFORMS:

1. Regulatory capacity gaps need to be gradually and strategically addressed. LMICs should assess their current regulatory systems using the WHO benchmarking tool and allocate more funding to these systems. HICs should provide technical and financial support to national and regional regulatory agencies to ensure that these agencies can effectively perform core regulatory functions. Partnerships between regulatory authorities in HICs and those in LMICs, such as twinning or joint assessments, will also be critical to building capacity and achieving efficiency gains. African countries with more advanced NRAs should support less advanced countries. For example, Tanzania, a country with a regulatory system that has reached maturity level (ML) 3, has supported Rwanda's NRA in recent years.

2. Any efforts to strengthen manufacturing capacity need to be accompanied by investments in regulatory systems.

3. WHO PQ of medicines was introduced at a time when regulatory systems were very weak, but this situation has changed to a certain degree; while the WHO PQ system is currently still needed, there should be more flexibilities. Countries and global procurement agencies should increasingly accept reviews from WHO-Listed Authorities (WLAs) and/or transitional WLAs (tWLAs) as an alternative to WHO PQ.

IMPROVING THE FINANCE AND GOVERNANCE OF R&D FOR NDs, EIDs, AND MH

Product development for NDs, EIDs, and MH faces a constrained funding environment. Our previous research, in 2020, found a substantial funding gap for ND R&D (about US$2.6 billion per year), and our new research points to persisting R&D funding gaps.[1] Policy Cures Research found that funding for ND R&D declined in recent years. Industry only accounted for 13% of funding for ND R&D between 2007 and 2022, and funding from LMICs remained highly limited in this timeframe. Furthermore, even after the worst pandemic in a century, donors did not provide the US$3.5 billion requested by CEPI for its "100 days mission" at its 2022 replenishment. While funding for sexual and reproductive health R&D grew from 2018 to 2021 (totaling US$593.7 million in 2021), only a small share of this funding was for MH tools and the share declined over time.

WE RECOMMEND FOUR KEY REFORMS:

1. A priority review voucher (PRV) should be created in Europe, hosted by the European Medicines Agency. Introduced in 2007, the US PRV program awarded more than 60 vouchers by 2024, contributing to the development of new medicines for neglected diseases, such as Chagas and tuberculosis. US vouchers were sold for US$100 million each, creating a substantial though insufficient financial incentive for developers. An EU voucher would provide an additional incentive of US$100 million to US$200 million, which investors say would be a meaningful stimulus. The introduction of the voucher could have a substantial impact, especially if it is part of a larger strategy for neglected disease research and is integrated with other EU mechanisms, such as PRIME (the PRIority MEdicines scheme).

2. Volume guarantees should remain a key mechanism to promote access to new health tools. There needs to be thinking on how to best expand the use of these guarantees while managing associated risks (overreliance on such guarantees can create a moral hazard).

3. Rather than targeting individual research projects, such as individual clinical trials, R&D funders also need to invest in the underlying research ecosystem. A system-wide approach would include investments in clinical trial infrastructure, capacities for discovery and preclinical research, and local manufacturing.

4. LMIC governments need to increase their own funding for health R&D. This will be important to advance product development for NDs, EIDs, and MH.

5. The overarching R&D ecosystem would be improved by stronger regional priority setting and the creation of regional and sub-regional hubs for clinical trials, regulatory systems, and product manufacturing.

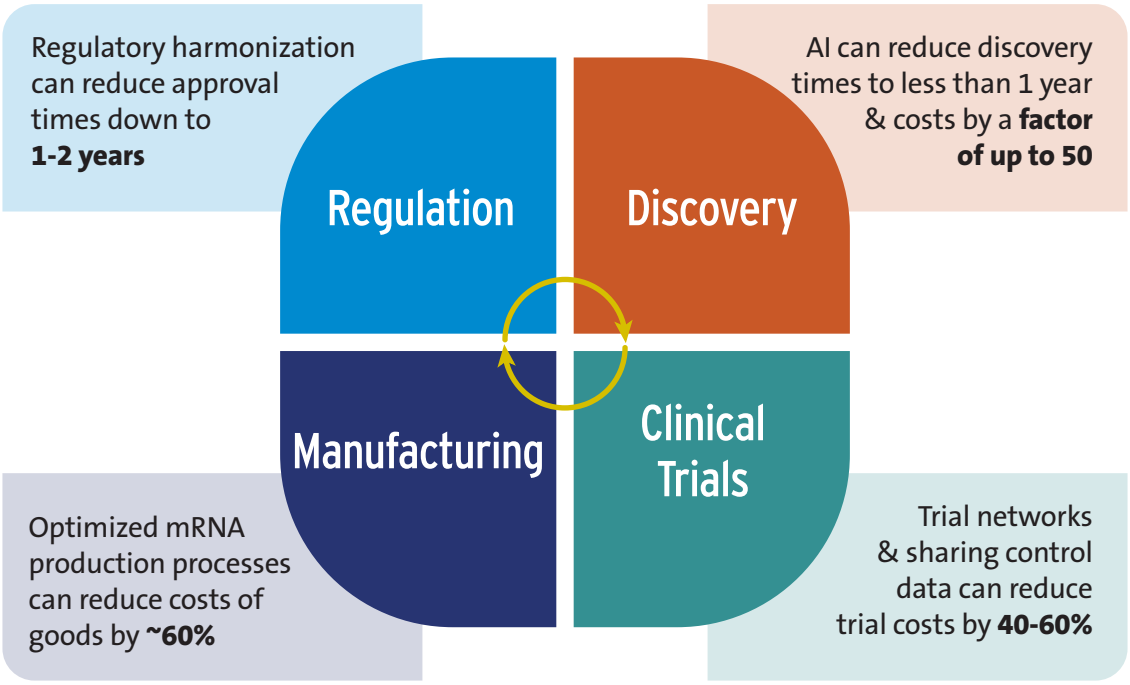
Conclusions: towards a reformed R&D ecosystem

Our analysis of key shifts and innovations across six major domains of the R&D ecosystem for NDs, EIDs, and MH found that many of these advances hold great potential for accelerating R&D, lowering its costs, and reducing attrition rates (Figure ES2). Changes in the ecosystem could also reduce manufacturing costs and speed up regulatory approval. Bringing new products to market at a faster pace and at lower cost could also help to relieve financial pressures on global health funders both upstream and downstream.

Our second working paper models the impact of these efficiencies in the R&D ecosystem.[1] In that second paper, we apply the Portfolio to Impact (P2I) modeling tool to the product candidate pipeline for NDs, EIDs, and MH to estimate the likely launches and the development costs and timelines of these launches. The P2I model is based on standard, historical attrition rates, cycle times, and costs per phase for a range of different product types (archetypes), such as simple and complex vaccines, new chemical entities, and repurposed drugs. In addition to the P2I modeling, we estimate the public health and economic impact resulting from these product launches. In our modeling, we first assumed that R&D uses traditional approaches (i.e., without the kinds of efficiencies that ecosystem shifts can bring). Second, we repeated the modeling but changed the model parameters (e.g., cycle times, costs per phase) to reflect the efficiency gains of ecosystem changes and innovations.

Finally, we believe that investments in R&D for LMICs should be driven by the disease and health priorities that these nations and regions set themselves. The shifts identified above must link to these priorities if we are to move in the direction of equity. Such shifts in R&D must be accompanied by increased ownership by LMICs and increased investments from LMIC governments, as well as from the private sector and industry players.

Figure ES2: Potential efficiency gains from shifts in the R&D ecosystem



SECTION

1

INTRODUCTION

INTRODUCTION

Investing in new health technologies is critical to reducing preventable illness, suffering, and death worldwide. Such technologies have saved tens of millions of lives. A new study by the WHO, for example, suggests that vaccines have saved 154 million lives over the past 50 years, of which 101 million were infant lives saved.[2] And a study by Jamison et al found that about 80% of the decline in the under-5 mortality rate from 1970-2000 across 95 low- and middle-income countries (LMICs) can be explained by the diffusion of new health technologies.[3]

In this paper, we analyze how the ecosystem for global health research and development (R&D) should evolve over the next 20 years to accelerate the discovery and delivery of new health tools. Our focus is on product development for neglected diseases (NDs), emerging infectious diseases (EIDs), and maternal health (MH) technologies. We use the G-FINDER project's definitions of NDs, EIDs, and MH (Annex 1).

We review the evidence and provide recommendations on the high-impact shifts required in the R&D ecosystem to drive efficiencies to accelerate development and uptake of new health technologies by LMICs. The paper also examines R&D funding approaches and policies that could help deliver the highest impact innovations and save the most lives. It looks at options to close financing gaps and mechanisms to coordinate prioritization of R&D needs and resource mobilization and to ensure equity and ownership of LMICs in the end-to-end development of priority health tools.

This study builds on previous research conducted by the Center for Policy Impact in Global Health (CPIGH) at Duke University and Open Consultants. In our previous work, we have focused on the benefits and costs of investing in neglected disease R&D and manufacturing, as well as on measures to leverage efficiencies and expand global access to new health tools.[4,5,6] Our study complements other studies, such as the Wellcome Trust's 2023 report, "Towards a Reformed Research and Development Ecosystem for Infectious Disease," and Policy Cures Research's new report, "The Impact of Global Health R&D: The High Return of Investing in R&D for Neglected Diseases."[7,8]

Our paper is based on a **literature review** and **key informant interviews (KIIs)** with experts in both high-income countries (HICs) and LMICs. The aim was to identify (a) the key potential ecosystem shifts that would drive efficiencies in R&D, and (b) specific needs for product development and uptake. The study began with a "**validation workshop**"—a two-day workshop with over 30 senior policy actors who are engaged in global health R&D policymaking, held in London on August 8-9, 2023. In this workshop, which included strong representation from LMICs, we shared and received feedback on our proposed study approach. Workshop participants shared with us their views on the key shifts that are likely to occur in the R&D ecosystem over the next 20 years. The aim of this workshop was to ensure that we understood the views of a wide range of actors in the R&D space and took these into account in our work.

Following the workshop, we conducted KIIs with over 60 key informants between August 2023 and March 2024. A second virtual meeting was held in February 2024 to further discuss our findings. In March 2024, we assembled a group of trial and modeling experts to discuss the rising costs of clinical trials and their implications for our modeling. In addition, we organized regional consultations in Africa, Asia, and Latin America to better understand regional ecosystem needs. Over 60 additional stakeholders were consulted in this regional consultation process.

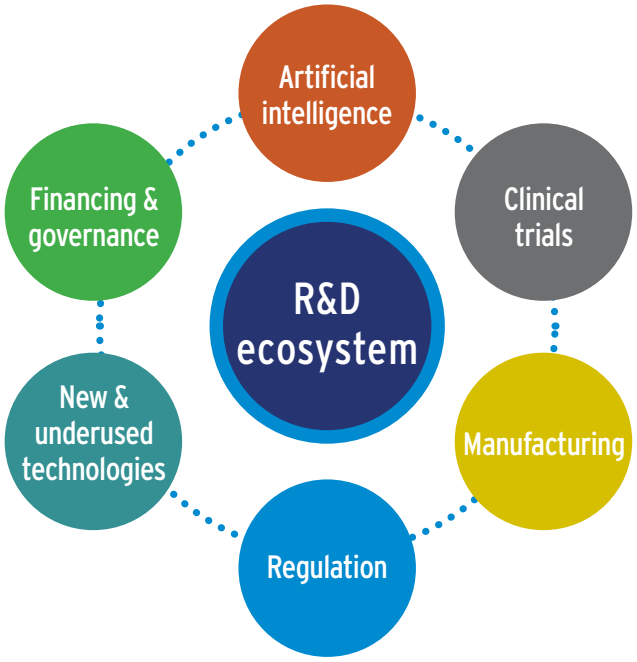
This working paper analyzes the R&D ecosystem across six key dimensions:

- Artificial intelligence (AI)
- Clinical trials
- Manufacturing
- Regulatory systems
- New and underused health innovations (mRNA-based vaccines/therapeutics; monoclonal antibodies)
- Financing and governance (Figure ES1).

We identified these six dimensions through a literature review and initial KIIs. We then validated the dimensions with stakeholders at the London workshop in August 2023.

In addition to laying out key shifts for improving the R&D ecosystem, including ways to lower costs, drive efficiencies, and improve product uptake, this working paper helped to inform a second working paper from our group. The second paper models the likely launches, costs, and public health and economic benefits of advancing the current global health R&D pipeline.[1] The results of this modeling also helped to identify and prioritize the highest impact ("game changing") health technologies, which are summarized in the second paper.

Figure ES1: Six key dimensions of the R&D ecosystem



Limitations of this study

There are at least four key limitations to our study.

1. First, we did not aim to assess in detail the opportunities and challenges of each of the six dimensions of the ecosystem. Such detailed analyses have previously been published, and we did not attempt to replicate them; instead, our aim was to collect, appraise, and analyze the evidence on potential efficiency gains and key ecosystem changes across multiple key areas, thereby focusing on evidence for major policy questions. Rather than providing a comprehensive assessment, we aimed to take a broader perspective to succinctly discuss key strategic issues and to lay out action points for the future.

2. Second, the evidence on potential efficiency gains is still nascent. This was expected, given that we aimed to identify new and emerging innovations and trends, and because we are assessing these innovations in the context of LMICs. For example, the evidence of efficiency gains in clinical trials mostly comes from HICs and often from trials on non-communicable diseases (NCDs), and these findings cannot be easily translated to LMICs and to NDs, EIDs, and MH. The evidence on the benefits of AI that we discuss in our report often came directly from biotech companies in HICs. However, we always tried to triangulate data from multiple sources and to validate our findings with independent experts.

3. Third, our paper is by design restricted to NDs, EIDs, and MH and does not include NCDs. Yet the burden of NCDs will continue to grow in LMICs over the next 20 years, a trend that is not captured by our paper. We do believe, though, that many of our findings are also applicable to NCDs – for example, our findings on the value of AI during drug discovery and of synthetic control arms in clinical research, the manufacturing of mRNA-based vaccines through modular facilities, and the need to expand access to mAbs in LMICs.

4. Fourth, this report assesses the R&D ecosystem but does not analyze the delivery systems that are essential to ensure access to new health tools. Such systems are beyond of the scope of this report, so we add a major disclaimer: a robust future R&D ecosystem alone is insufficient to improve the health of people living in LMICs. Adequately financed and effective health systems need to be in place to generate demand and deliver new health tools equitably. Other studies and initiatives, such as the Future of Global Health Initiatives (FGHI) process,[9] discuss the reform needs of global delivery systems.

Structure of this report

This report is organized into six further sections. In Section 2, we present the findings on efficiency gains driven by AI. Next, in Section 3, we analyze how innovations in clinical trial conduct could drive further efficiencies. In Section 4, we discuss the role of manufacturing, and Section 5 focuses on new and underused technologies. Section 6 discusses ways to streamline and accelerate regulatory approval. Section 7 focuses on governance and financing. It also provides a summary of outcomes from the regional consultations. Section 8 summarizes key efficiency gains from R&D ecosystem changes and lays out our key conclusions. Opportunities for efficiencies and ecosystem reform, as well as challenges, gaps, and missed opportunities are discussed across all sections.

SECTION 2

ARTIFICIAL INTELLIGENCE IN GLOBAL HEALTH R&D

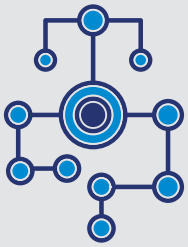
ARTIFICIAL INTELLIGENCE IN GLOBAL HEALTH R&D

KEY BENEFITS:

- **Faster discovery & preclinical research at lower cost**. AI offers substantial benefits during the discovery and preclinical phase. The standard time for screening, identifying, and validating target molecules is 3-5 years, with costs of up to US$10 million. There are examples of AI tools that have shortened the timeframe to less than 12 months and lowered the costs by a factor of up to 50. AI tools also enable a much more thorough screening of proteins (new target identification) compared with traditional screening approaches. This in turn could lead to improved quality candidates and therefore less attrition during the clinical phase and, eventually, better health technologies.
- **Valuable role in drug repurposing**. AI platforms have identified optimal drug combinations at significantly reduced time and cost, e.g., for COVID-19.
- **Prediction of clinical trial success**. One AI-based prediction tool was able to predict trial success with 79% accuracy, which has the potential to reduce the costs of the clinical phase.

KEY CHALLENGES TO BE ADDRESSED:

- **AI tools require substantial data to perform well**. While there is substantial data on the use of AI in R&D for NCDs and specific infectious diseases, there is much less data available on the most neglected diseases. In addition, most of the data feeding into AI tools comes from HICs.
- **Potential to deepen global inequalities**. Critics of AI in global health have warned that AI may deepen existing inequalities between LMICs and HICs. AI tools are owned by Northern entities, while LMICs have limited influence over the design and use of these tools.



SUGGESTED ECOSYSTEM CHANGES:

- **Further leverage the substantial efficiencies of AI in drug discovery and preclinical research**. There is great potential to reduce the timelines and costs of discovery and preclinical research on NDs, EIDs, and MH. R&D funders across sectors should leverage this potential and invest in AI-based companies to develop novel and de-risked drug candidates for clinical testing.
- **Expand the use of AI for epidemic and pandemic preparedness**. Use AI tools to predict protein structures for priority pathogens in a coordinated attempt to build a vaccine library.
- **Further assess the potential of AI in clinical research**. Fully leveraging the potential of AI during clinical research will also require the sharing of clinical trial data.
- **Enable LMICs to meaningfully participate in AI-driven R&D and build respective capacity and expertise**. Without such participation, existing inequalities in global health will be widened. Partnerships between AI companies, which are mostly in HICs, and LMIC researchers will be important.
- **Strengthen existing regulatory frameworks for AI in global health.**

2.1 Overview

The long timelines, high attrition rates, and high costs of R&D are impeding the development and delivery of new health technologies. A recent study, for example, estimated that the average R&D cost per drug is US$1.3 billion and the median drug development time ranges from 5.9 to 7.2 years for non-oncology drugs and 13.1 years for oncology drugs.[10] Another study of drug development projects involving 21,143 compounds estimated that the success rate (the proportion that reached the market) was only 5.2% in 2013, down from 11.2% in 2005.[11,12] Nine out of ten drug molecules usually fail to pass Phase 2 clinical trials and other regulatory approvals.[13]

AI tools can contribute to drug development across the whole R&D process, including:

Novel target identification	Molecular compound design and optimization
Understanding of target-disease associations	Development of new prognostic and predictive biomarkers
Drug candidate selection	Biometrics data analysis from wearable devices, imaging, precision medicine
Protein structure predictions	Clinical trial design, conduct, and analysis.

AI and machine learning are becoming increasingly important to global health R&D, allowing researchers to assess the safety, efficacy, and potential benefits of new drugs. AI has been used as a tool to reduce R&D time and costs. At the same time, AI poses several challenges and ethical considerations that demand careful attention. For example, AI systems collect and analyze vast amounts of personal data, raising concerns about privacy and data security.[14] The use of AI in the development of new health tools also risks increasing existing inequalities in global health.[15,16] In this section, we provide evidence on efficiency gains, gaps, barriers, and future opportunities in the use of AI and machine learning in global health R&D.

2.2. Benefits of AI during discovery and preclinical research

In section 2.2, we first discuss the potential of AI for improving the discovery phase, during which target identification and drug lead discovery occur, and in preclinical development, when the efficacy of the drug is interrogated in vitro and in vivo and drug toxicity properties are assessed. Then we discuss the role of AI in drug repurposing and the testing of drug-drug combinations.

AI is being increasingly used in discovery.

Optimization of a lead compound to deliver a safe and potent candidate for clinical testing requires parallel optimization of many parameters, including potency, pharmacokinetics, selectivity, and safety. AI tools can now outperform humans in integrating the outputs from predictive models to efficiently "home in" on an optimized candidate drug. In addition, AI tools have the potential to streamline complex drug discovery workflows and optimize decision making. Advances in AI-based compound synthesis prediction tools can also speed up drug discovery by enabling key compounds to be made more efficiently.

Between 2010 and 2021, there was rapid growth in the number of AI companies in the health sector, with an average annual growth rate of 36%. This growth was mostly driven by assets and programs at the discovery and preclinical stage. Jayatunga et al assessed the combined pipeline from 2010-2021 of 20 "AI-native" companies (i.e., AI is central to their drug discovery programs) and found 160 disclosed discovery programs and preclinical assets and 15 assets in clinical development. To put this in perspective, the discovery and pre-clinical pipeline of AI-native companies is about half the size of the pipeline of the top 20 pharmaceutical companies. The researchers were only able to find drug target information for about a quarter of these AI-enabled R&D programs. The targets were mostly well-established target classes, such as kinases and G-protein coupled receptors. Jayatunga et al acknowledge that there is uncertainty in "how many of the AI-enabled preclinical programmes reach the clinical trial stage, and how successful AI-derived assets will be in clinical trials."[17]

The COVID-19 pandemic further fueled the use of AI in health R&D. For example, the Google-owned company DeepMind was instrumental in helping virologists understand how SARS-CoV-2 was behaving. Using the AlphaFold AI program predictions, several of the Sars-CoV-2 proteins were mapped out, which were later experimentally confirmed to be accurate. DeepMind also partnered with DNDi to identify new treatments for neglected diseases like sleeping sickness, Chagas disease, and leishmaniasis. DNDi and its research partners found a molecule that can bind to a protein on *Trypanosoma cruzi*, the parasite that causes Chagas disease, killing the parasite; AlphaFold helped to rapidly predict the shape of the protein, which could help in drug design.[18,19]

Existing evidence indicates that AI offers significant efficiency gains.

AI tools have successfully supported new target discovery and toxicity prediction. AI-based algorithms have successfully been used to identify new targets for drug development, such as the specific proteins or genetic pathways involved in diseases. In addition, AI-based toxicity predictions could eventually replace in vitro and animal models during the pre-clinical stage. Models can be used as risk-management and prioritization tools by providing early indication of high-risk compounds flagged with significant safety concerns.

The efficacy and toxicity of new drug compounds can be predicted using these approaches, with greater accuracy and efficiency compared to traditional methods. For example, the costs for traditional reverse vaccinology studies can be as high as US$10 million and take up to 3-5 years. Reverse vaccinology involves sequencing the genome of a target pathogen and scanning for genes that may be useful for vaccines, such as those encoding for virulence factors or surface proteins. In addition, traditional approaches do not comprehensively screen all possible proteins. Existing evidence indicates that AI can substantially accelerate the drug discovery process at lower cost, while simultaneously being more comprehensive. Examples of companies that have used AI tools to cut the time and costs needed to identify preclinical candidates are given below:

Aiming to develop a new vaccine for antibiotic-resistant *N. gonorrhoeae*, the biotechnology company EVAXION used its AI antigen discovery model EDEN (Efficacy Discriminating Educated Network) to screen thousands of proteins of multiple *N. gonorrhoeae* strains. The AI prediction phase happened within 24 hours and led to a list of 26 gonococcal proteins that were predicted to be most efficacious. These 26 proteins were tested in mice; these tests showed that EDEN's protective scores correlated positively with the bacterial burden, providing evidence for the predictive potential of EDEN.[20] The protein antigens that gave best protection were used in EVAXION's final *N.gonorrhoeae* vaccine. EVAXION estimates that the entire costs for the drug discovery and preclinical phases totaled about €200,000 (~US$215,000), a fraction of the cost of traditional screening studies (see Panel 1).

Insilico Medicine's GENTRL platform designed a new drug candidate against fibrosis in 21 days and validated it in another 25 days.[21,22,23] The company also reported the development of a preclinical candidate for idiopathic pulmonary fibrosis in under 18 months, which also entered first-in-human studies in 9 months. A second preclinical candidate for kidney fibrosis was developed in 6 months.[17,24]

Exscientia reported that seven programs took less than 18 months from target identification to candidate identification (including for cardiovascular and oncology drug candidates). Exscientia developed five new assets in less than 14 months, compared to the five-year industry benchmark, with cost savings of more than 80% during the discovery phase and of 30% for the entire drug development process).[22,26]

PANEL 1 EVAXION's AI-Immunology™ Platform: Potential for faster, cheaper, and risk-reduced vaccine development

AI platforms are becoming increasingly important for target identification. One example is the AI-powered vaccine development by the biotech company Evaxion Biotech A/S (EVAXION). EVAXION is developing AI models to decode the human immune system and develop new vaccines for cancer, bacterial diseases, and viral infections. For the development of prophylactic vaccines against infectious diseases, EVAXION uses the AI models EDEN™* (B-cell targets) and RAVEN™ (T-cell targets), which comprise EVAXION's AI-Immunology™ platform.[27]

EDEN™ identifies vaccine targets that elicit an antibody response against infectious disease pathogens. As of November 2023, four vaccine candidates for *N. gonorrhoeae* and *S. aureus* were in the preclinical stage, with one of them being tested by Afrigen Biologics (Afrigen) in South Africa (see below). EVAXION also uses the AI-Immunology™ platform's AI models PIONEER™ (neoantigens) and ObsERV™ (ERV antigens) for personalized cancer vaccines, including for skin cancer and lung cancer.[28] A vaccine for metastatic melanoma is currently being tested in a small Phase 2 trial (others are in the preclinical phase or Phase 1).

There is evidence that EVAXION's AI models can rapidly and effectively identify highly and broadly protective vaccine targets, offering the opportunity for fast-tracking vaccine candidates into clinical testing and increasing the probability of clinical success. A study conducted by the University of Massachusetts and EVAXION showed that EDEN™ has identified two promising gonococcal antigens, which, when used in combination as a chimeric, have elicited functional bactericidal antibodies in vitro and have shown efficacy in a preclinical mice model.[20] The EDEN-discovered antigens showed high levels of protection in the study. These findings indicate that EDEN™ can effectively predict protein-specific antibody-mediated protection and highlight the utility of the EDEN™ model to rapidly identify novel vaccine candidates that have not been considered using more traditional approaches.

EVAXION also illustrates how AI companies can partner with LMICs. In September 2023, EVAXION announced a collaboration with Afrigen.[29] The collaboration aims to develop a prophylactic vaccine based on EVAXION's EDEN-discovered gonorrhea targets. Gonorrhea is a sexually transmitted disease that impairs global sexual and reproductive health (SRH). WHO reported 82 million new gonorrhea infections annually worldwide in 2020 with a rise in antibiotic-resistant cases; gonorrhea also increases susceptibility to HIV. The partnership will explore the expression and biological activity of the antigens in mRNA format, offering an opportunity to further accelerate clinical validation of the EDEN™ model.

**EDEN™ is an AI-driven model trained to identify novel protective antigens for use in vaccines against pathogenic bacteria. The core of EDEN™ is a proprietary machine learning ensemble of artificial neural networks used to interpret immunologically relevant information in relation to bacterial antigens that confer protection when administered as vaccines. EDEN™ has been trained on EVAXION's curated data set derived from publicly available data (publications and patents) describing protective and non-protective antigens tested in clinical and pre-clinical settings. EVAXION believes EDEN is applicable to virus vaccine development, hence it is being applied in the development of a virus vaccine against cytomegalovirus, EVX-V1.*

AI is also being used for drug repurposing and the identification of effective drug-drug interactions and combinations.

Many companies are using AI for drug repurposing. For example, Healx used machine learning techniques to predict 22.2% synergistic antimalarial combinations from 1,540 combinations.[30,31] In addition, Healx identified repurposed therapeutics for Fragile X syndrome, a genetic condition that results in learning disabilities. Using AI analytics as the basis of its in-silico Disease-Gene Expression Matching pipeline, it took 15 months from inception to readiness for the clinical trial phase. This project identified eight potential candidates, which were also validated in mice. Sulindac, a nonsteroidal anti-inflammatory drug, and metformin, a hepatic glucose production inhibitor, have been identified as promising repurposing candidates for Fragile X.[31]

Another important application of AI in drug discovery is the identification of drug–drug combinations and their optimal doses.[32] Within two weeks, Exscientia's AI platform identified remdesivir, ritonavir, and lopinavir as the optimal regimen to inhibit SARS-CoV-2 live virus out of 530,000 drug combinations. The regimen showed a 6.5-fold improvement in efficacy compared to remdesivir alone.[31] Shen et al developed an AI tool to determine the optimal dose of antiretroviral therapy for HIV treatment. The researchers administered a combination of tenofovir and efavirenz to ten patients, and, using an AI tool, they found that the dose of tenofovir can be reduced by 33% of the starting dose without causing viral relapse.[13,33] Pantuck et al developed an AI platform called "CURATE.AI" that used the personal data of a patient with prostate cancer to guide optimal combination chemotherapy dosing.[34]

2.3 Benefits of AI in clinical research

The use of AI in clinical trial stages is less advanced compared to the discovery and preclinical stages. Current applications of AI relate to clinical trial design, conduct, and analysis. Several researchers have suggested that using AI tools to inform clinical trial design can reduce the number of trial participants and trial length and speed up clinical development by increasing the probability of trial success and regulatory approval. However, there is limited quantitative data.

1. Prediction of trial success: AI can help to predict the probability of trial success and help design Phase 2 and Phase 3 trials that are more likely to transition to regulatory approval. For example, using its AI tool, the drug discovery company Insilico Medicine can predict the outcome of Phase II to Phase 3 clinical trial success with impressive accuracy. The prediction tool, trained on data from 55,600 unique Phase 2 clinical trials over 7 years, is able to predict trial success probability with 79% accuracy.[35] The clinical trial data comes from ClinicalTrials.gov, a database that includes studies from over 200 countries. Such tools have the potential to save substantial future costs.

2. Patient recruitment has been a particularly challenging aspect of clinical trials, with an estimated 80% of trials not meeting enrollment timelines and 30% of Phase 3 trials terminating early due to enrollment challenges.[36] AI can perform automated eligibility analysis, matching potential participants to trials, and simplifying trial searching capabilities. AI tools such as Criteria2Query and Dquest aim to make trial design and recruitment more efficient. Criteria2Query helps to standardize inclusion and exclusion criteria within databases and simplify data collection, while Dquest helps to improve patient recruitment for trials through dynamic processes (it "generates a series of dynamic questions for patients to answer and then filters their options based on the responses"). Dquest can exclude 60% to 80% of trials for which the patient was not eligible.[37]

3. Predicting patient outcomes in clinical trials can lead to shorter trial duration. Such tools can also predict dropouts and may help to reduce overall sample sizes, leading to cost savings, since fewer participants are needed for the trial. However, quantitative data on the use of AI for predicting trial outcomes is limited and lowering sample sizes involves risk. Thus, more research on the use of AI is needed in the clinical phase and respective safeguards need to be put in place to both protect patients and produce reliable results.

4. During the conduct of trials, AI can be used in many ways:
   (i) digital health technologies, including digital biomarkers developed based on AI algorithms, can help to interpret data and transform it into usable insights;
   (ii) analysis and workflow management of medical images using AI can streamline the review and supplement the analysis of medical images; and
   (iii) AI algorithms can support the automated annotation of important markers, which would normally be derived manually by experts.
   These are just some examples; however, there is little quantitative data on the potential efficiency gains.

5. Clinical trial data analysis and approval: AI has been used to:
   (i) determine effect heterogeneity to identify subgroups that showed differing treatment effects, as well as to identify key risk factors and fast-responders in sub-populations;
   (ii) impute missing data and missing study visits;
   (iii) facilitate more comprehensive statistical analysis; and
   (iv) support the automation of data extraction into statistical analysis tools to reduce the need for manual effort and associated human error.
   For example, the Highly Efficient Clinical Trials (HECT) simulator is an open-source, browser-based clinical trial simulator for planning adaptive and platform trials. It is a web application written in Rshiny, a package in the statistical software R and Rstudio. It caters to clinical trial investigators who do not have the statistical capacity for trial simulations available in their team.[38]

2.4 Use of AI for strengthening pandemic preparedness

Recent advances in AI technology make it possible to quickly and effectively model potential viral vaccine targets, which is important for pandemic preparedness. Efforts are ongoing to leverage AI for the development of vaccines for diseases with pandemic potential. CEPI has funded research to map potential antigenic targets for 10 priority virus families with epidemic or pandemic potential. [39,40] This CEPI-funded research will initially focus on paramyxoviruses and arenaviruses, which include Nipah virus and Lassa virus, respectively. CEPI intends to store AI-derived antigen designs in a "vaccine library" so they can be quickly used to develop vaccine candidates in the event of an outbreak of a novel pathogenic threat. In such an emergency, these antigen designs could be taken "off the shelf," and gene sequences could then be inserted into a rapid-response vaccine platform, such as mRNA, to start production of vaccines for clinical testing.


Image generated by Adobe Firefly 5/24: vaccine library

Establishing such a library would give the world a head-start by significantly compressing pandemic vaccine development, potentially down to just 100 days (this global goal is known as "the 100 days mission" and is supported by the G7 and G20).[41] The 100 days mission has become even more important in light of a new modeling study by authors from Gingko Bioworks, the Commission on Investing in Health, and the Disease Control Priorities Project showing that the risks of a major pandemic are higher than previously believed.[42] The modeling suggests "that an event having the mortality level of COVID-19 should not be considered a "once in a century" risk, but rather occurring with an annual probability of 2–3 percent (that is, a one in 33–50-year event)."

The creation of such a vaccine library requires inputs from multiple actors. In early 2023, the US National Institute of Allergy and Infectious Diseases, for example, announced US$100 million for similar work on vaccine libraries. However, private actors can also play an important role. For example, DeepMind started to curate protein structure predictions of specific priority pathogens in a much shorter timeframe compared to traditional approaches (which would have needed years).[43] However, DeepMind stopped such curation; experts interviewed for this study called on DeepMind to continue sequencing the proteins of every priority pathogen and to share this knowledge publicly.

There are also AI tools that can forecast viral mutations and derive vaccine targets based on these predictions. A tool called EVEscape developed by the Harvard Medical School can estimate the ability of a novel viral variant to escape immunity.[44] A recent study showed that had the EVEscape tool been used at the start of the COVID-19 pandemic, it would have predicted the most frequent mutations and identified the most concerning variants of SARS-CoV-2.[45] The tool also made accurate predictions about other viruses, such as HIV, influenza, Nipah, and Lassa.

2.5 Challenges for the use of AI in global health R&D

A recent critique on the use of AI in global health by Jonathan Shaffer and colleagues warned that AI (i) may deepen existing inequalities between LMICs and HICs, (ii) is controlled by large Northern companies, and (iii) is driving a "do more with less" paradigm that could undermine health service delivery for people living in the poorest countries.[16] In a similar vein, Leslie and colleagues asked in a commentary if AI stands for "augmenting inequality."[15]

Other studies have made similar arguments. For example, Vaisman et al highlighted several concerns with the use of AI for neglected disease R&D, including:

(i) unequal interrelationships between stakeholders (AI research is mostly being conducted in labs located in HICs with limited engagement with scientists and clinicians from endemic low-income settings);

(ii) inadequate informed consent from patients for biologic samples;

(iii) concerns about data security;

(iv) poor accessibility of technology to affected populations;

(v) ensuring that AI-derived diagnostic tools adhere to current and evolving care standards; and

(vi) deciding how to effectively use resources (implementation of AI diagnostics could unintentionally draw vital resources from other programs).[46]

The gains of AI for neglected diseases research will only be realized if LMICs are involved in the development and implementation of the technology. The speed with which AI is being developed poses a challenge —LMIC governments and communities must be included *now*. The key steps need to be determined in a strategic process and should be embedded in broader coordination processes, such as the pandemic treaty and the development of a coordination platform for medical countermeasures (MCMs). At the moment, LMICs and communities do not have a seat at the table to inform the models, so the statistical representations in these models may be less accurate compared to higher-income regions than for regions with better-represented data. If not properly managed, AI tools will do harm by inadvertently reinforcing biases, increasing existing inequalities, and providing misinformation. When AI algorithms are biased or unrepresentative, the resulting predictions may be inaccurate or unfair.[47] African researchers have therefore called for a research agenda on AI grounded in the African context to determine locally relevant strategies for its development and use.[48,49]

There are also questions around data quality, fragmentation of data, and data access. For example, while considerable data has been collected on NCDs in HICs, there is much less data on NDs and EIDs. This limits the use of AI for these disease groups, especially during the clinical phase.

The "black box" nature of ML models is an additional challenge, in which even experts cannot explain how the model arrives at a result and comprehend the biological mechanism behind it.[13] Global standards and oversight for the use of AI in general and for global health specifically are only slowly emerging (see, for example, the efforts by the UK government and the European Union[50,51]).

2.6 **Summary and suggested ecosystem changes**

While there is clearly a lot of hype about AI in global health, our review has shown that AI technologies *can* make significant contributions to global health R&D. Substantial efficiency gains can be achieved during the discovery and preclinical phases. Drug candidates can be brought to the clinical phase faster and at much lower cost (Table 1). In addition, AI can provide a much more comprehensive screening compared to traditional approaches, as shown by EVAXION's AI tool, which screened thousands of proteins of multiple *N. gonorrhoeae* strains within 24 hours. This more comprehensive screening may eventually lead to the development of better, more efficacious tools. AI may also have a positive effect on failure rates during the clinical phases, and the ability to predict clinical trial outcomes may offer substantial cost savings.

Table 1. Cost and time savings of AI in the discovery phase

	Traditional approaches*	AI-assisted approaches
Costs	US$10 million*	~ €200,000 (US$215,000)
Timelines	3-5 years	<1 year

**PAREXEL: Biopharmaceutical R&D Statistical Sourcebook 2018/2019.*

AI also has the potential to play a key role in pandemic preparedness. AI technologies can greatly increase the number of vaccine designs that can be used rapidly to identify the most promising candidates. There are also tools to predict the mutation of viruses.

At the same time, there are important issues to consider. First, AI itself is not the solution to any problem –highly qualified experts are still needed. For example, while AI can provide predictions, the results must still be validated and interpreted by experienced, skilled human researchers. Second, robust regulations and data protection measures are needed to safeguard individuals' privacy, and some experts thus suggest the creation of a global body for AI (similar to the International Atomic Energy Agency). Third, there is an urgent need to strengthen AI expertise and capacity in LMICs, otherwise global inequalities will widen.

Overall, we suggest the following ecosystem changes:

1. First, there is substantial potential to further leverage AI for discovery and preclinical research to accelerate the development of new tools for NDs, EIDs, and MH. Funders of global health R&D should leverage the potential of AI and invest in companies that show capability and interest in using their AI tools for neglected disease R&D. This should lead to a much better drug pipeline for these groups of diseases.

2. Second, LMICs need to be enabled to meaningfully participate in AI-driven R&D and build respective capacity and expertise. Without such participation, existing inequalities in global health will be widened. Partnerships between AI companies, most of which are in HICs, and LMIC researchers will be important. The capacity of major regional health agencies, such as Africa CDC, in AI-enhanced R&D needs to be built. These organizations are key when it comes to the development of strategies, data collection and analysis, and policy recommendations.

3. Third, funders should support the expanded use of AI for epidemic and pandemic preparedness. AI tools should be used to predict protein structures for priority pathogens in a coordinated attempt to build a vaccine library. Stronger engagement of AI companies, such as DeepMind, should actively be supported.

4. Fourth, the potential of AI in clinical research needs further assessment. There is evidence that AI has great potential in the clinical research phases but the current focus is more on drug discovery and preclinical research. For neglected disease R&D in particular, there is the need to build large datasets, which in turn requires stronger data access and data sharing.

SECTION

3

INNOVATIONS IN CONDUCTING CLINICAL TRIALS

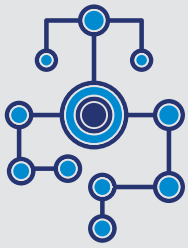
INNOVATIONS IN CONDUCTING CLINICAL TRIALS

KEY BENEFITS:

- **Decentralized clinical trials (DCTs) using digital health technologies (DHTs) can reduce trial costs, timelines, and the number of patients needed in a trial**. Such trials can also improve recruitment and retention of participants.
- **Platform trials can also drive efficiencies in a number of ways**. They can shorten trial duration, evaluate more treatments per trial, reduce the number of patients required per trial (by up to 70%), and increase the proportion of programs that accurately recognize an effective treatment.
- **Real-world data and evidence can lower trial costs**. The savings can be US$10 to US$20 million per trial, depending on how much synthetic control arms are used to replace traditional control arms.
- **Clinical trial networks can drive efficiencies by using existing sites instead of creating new ones, recruiting patients more quickly and reliably, and reducing the number of patients needed by sharing control groups with other trials**. Connecting trial sites, which allows a sponsor to find sites for rapid enrolment, could reduce Phase 2/3 trial costs by 23%. Costs could be reduced by 40-60% by sharing control groups and using control data from previous trials. The ability to rapidly test product candidates during outbreaks relies on the existence of effective and inclusive regional clinical trial networks that are kept active between outbreaks.

KEY CHALLENGES TO BE ADDRESSED:

- **The complexity of novel trial designs, such as platform trials, can be a barrier to adoption in LMICs.** Both trialists and regulatory authorities in LMICs may lack the expertise needed to implement and oversee complex trial designs.
- **Maintaining data quality and privacy can be a challenge in DCTs and DHTs.**



SUGGESTED ECOSYSTEM CHANGES:

- **Research funders and agencies should support sustained, long-term efforts to build clinical trial networks that have the capacity to adopt innovative approaches, building on existing capacities.**
- **Adoption of platform trials and other master protocols in low-resource settings will require funding agencies, IRBs, data safety boards, and regulators to become familiar with these designs.** As innovative trial designs become more widespread in LMICs, operational lessons need to be shared so that implementation barriers can be tackled and best practices adopted.

3.1 Overview

Clinical trials are essential in showing that a product is safe and effective. However, traditional trial designs are expensive, lengthy, and have low success rates. From 2009-2018, the median capitalized R&D cost for a new drug or biologic agent approved by the US Food and Drug Administration (FDA), including expenditures on failed trials, was US$985 million (in 2018 US dollars) across all phases of development.[10] The clinical development time for innovative new drugs—the period from initiation of first-in-human studies to regulatory marketing—was about 8.3 years on average for FDA-approved drugs between 2010 and 2020.[52] Fewer than 1 in 10,000 innovative therapies achieve FDA approval.[53]

Nevertheless, recent advances in clinical trial conduct are spurring more efficient trials. The COVID-19 pandemic validated many of these advances—e.g., trial networks were critical to the rapid development of vaccines, while platform trials (e.g., RECOVERY) helped usher in COVID-19 therapies.[54] In this section, we examine these advances to understand their potential for lowering trial costs and timelines, and improving the efficiency and success rate of trials. We exclude the impact of mRNA, AI, and machine learning on trials, as these are discussed elsewhere.

There are two important limitations to note about the data on trials. First, most data are from HICs. The burden of NDs, EIDs, and MH falls disproportionately on LMICs,[55] and new products for these conditions should be tested in these high-burden settings, ensuring inclusive and representative selection of trial participants. Yet most trials are conducted in HICs. A study by Coates et al of almost 90,000 trials conducted from 2006-2012 found that 83% were situated in 25 high-income Organization for Economic Co-operation and Development countries, while only 5% were in lower-middle or low-income countries.[55] One promising finding was that by 2012, 19% of Phase 3 trials were in LMICs (up from about 2% in 1999), suggesting that a "global migration of clinical research" is underway, mostly for late stage clinical trials.

Second, data on trial parameters (costs, timelines, success rates) comes mostly from trials of product candidates for NCDs and are often pooled from trials of medicines, vaccines, biologics, and other product archetypes. There have been only a few studies that have disaggregated parameters by disease type or product archetype. In one of these disaggregated studies, Moore and colleagues estimated the costs of "pivotal" trials—those that provide key evidence of the benefits of new therapeutic agents (usually phase 3)—and showed the variation in costs by disease type, from US$6 million-US$141 million (Table 2).[56] The most important driver of costs was the number of patients needed to show an effect (which ranged from 4 to 8,442), followed by the number of clinical site visits (range: 2-166). In another study, Gouglas et al estimated the costs of developing a vaccine against 11 priority EIDs with pandemic potential.[57] Considering the probability of success (i.e., including the costs of the failed candidates), they estimate that the average cost of successfully advancing at least one epidemic infectious disease vaccine from preclinical to the end of phase 2a is US$319 million –US$469 million (the cost from the start of phase 2 to the end of phase 2a is US$84 million–US$112 million). Research by the IQVIA Institute found that clinical trial duration varied by disease area, from 9.7 years (dermatology) to 12.5 years (rare oncology).[58] An important component of this duration is "white space" (the period between trial phases), which, for new drugs, accounts for an average of 43% of the development time (see Annex 3).

Table 2. Cost estimates of clinical trials for therapeutic agents that have received FDA approval by therapeutic area. Data are from 225 pivotal trials that supported the approval of 101 new drugs from 2015-2017

Therapeutic area	Drugs	Median cost (IQR) USD millions
Blood	2	6 (4-8)
Cardiovascular	6	141 (74-183)
Central nervous system	14	42 (16-85)
Dermatology	9	50 (31-77)
Endocrine/metabolism	12	72 (14-144)
Genitourinary	4	23 (12-37)
Gastrointestinal	7	31 (15-63)
Infectious	9	54 (26-102)
Musculoskeletal	2	68 (48-87)
Oncology	30	45 (29-72)
Ophthalmology	3	36 (34-44)
Respiratory	3	91 (73-110)
Overall	101	48 (20-102)

Source: Moore et al, 2020[56]

3.2. Benefits of innovations in trial conduct

Advances in clinical trial conduct can be categorized into:
a) **technological innovations** (e.g., digital clinical trials, open source trials software, disease forecasting);
b) **innovative trial designs** (e.g., master protocols, human challenge trials, real world evidence); and
c) **trial networks**.

TECHNOLOGICAL INNOVATIONS

Decentralized clinical trials (DCTs) using digital health technologies (DHTs)

DCTs are those in which some or all activities are conducted at non-traditional sites, such as a laboratory, a participant's home, or a local health center. Such trials usually incorporate DHTs, like wearable devices, telemedicine, and mobile applications. The FDA recently issued guidance on conducting DCTs.[59] The two main advantages of DCTs and DHTs are: (i) streamlining the identification, recruitment, and follow-up of participants, as well as data acquisition; and (ii) making trials more inclusive by reaching more diverse population groups, older people and people with disabilities who find it hard to travel, and patients who are distant from traditional clinical trial sites.[60] Reducing clinical visits is a major advantage, since such visits are costly: Moore et al found that "each additional trial visit added a median of US$2 million (IQR: US$1 million–US$3 million) to the overall estimated trial cost."[56] Durán et al assessed 91 clinical trial protocols across oncology, respiratory, and cardiovascular diseases and found that 74-85% of the studies were amenable to fully remote data collection using clinically validated devices,[61] reducing the number of clinical physical visits by up to 40%. These findings may not, however, be directly applicable beyond NCDs.

There have been several studies of the efficiencies associated with DCTs and DHTs (summarized in Annex 3), which have shown the benefits of DCTs and DHTs: reduced costs, a reduction in the number of participants needed, faster timelines, and lower participant drop-out rates. These have mostly been conducted in HICs, and the transferability of the findings to LMICs remains unclear.

Open source trials software

Advances in clinical trial design and methodologies, such as platform trials (discussed below), have necessitated the use of advanced software to compute possible outcomes of more complex trial designs. Proprietary software, such as FACTS and ADDPLAN, was developed to facilitate these computations,[62,63] but it is expensive and requires experts in the field of biostatistics and mathematics to operate. These barriers prevent clinical researchers with limited resources from adopting contemporary clinical trial designs. To help overcome these barriers, as mentioned earlier in this report, the knowledge integration trial services division of the Bill & Melinda Gates Foundation developed the Highly Efficient Clinical Trials simulator (HECT), an open-source web-based platform built using RShiny , which facilitates platform and adaptive trial simulation.[64] The HECT has been used by trialists together with early stage portfolio planning and "has been used to examine the likely costs and probabilities of success for a large number of candidate designs under various scenarios for possible target countries."[38] To our knowledge, there is no evidence in the published literature on the efficiency gains of using HECT.

Disease forecasting

Clinical trials for infectious diseases, including those conducted in response to epidemics, face unique challenges due to seasonal variation or sudden spikes in disease incidence. Furthermore, epidemics and infectious diseases occur across diverse geopolitical zones and disproportionately impact resource-poor settings. These challenges add complexity, time, and costs to infectious disease clinical trials. Forecasting hot spots through improved data gathering and real-time virus tracking can support agile and more efficient clinical trials.[65] For example, Airfinity, a London-based disease surveillance start-up specializing in real-time tracking, prediction, and simulation of population-level disease outcomes, has expertise in identifying and forecasting infectious disease hotspots. The company's COVID-19 tracking data were used by AstraZeneca to estimate the impact of its COVID-19 vaccine and its COVID-19 mAb, Evusheld.[66]

INNOVATIVE TRIAL DESIGNS

Master protocols, including platform trials

Randomized control trials (RCTs) are widely regarded as the gold standard for establishing effectiveness between health products or interventions and outcomes, but are costly and time consuming and their focus on narrow populations limits generalizability. To address these limitations and drive efficiencies, the past decade has seen the development and use of master protocols, defined by the US National Institutes of Health as "a trial design that tests multiple drugs and/or multiple subpopulations in parallel under a single protocol, without the need to develop new protocols for every trial."[67] The field of oncology has been at the forefront of using master protocols, but these have also been used for infectious disease trials. There are three key types of master protocols:

- *Basket trials* evaluate the use of a targeted therapy on multiple disease types that share the same underlying genomic abnormality.
- *Umbrella trials* investigate the effect of multiple targeted therapies on one disease entity that differs by genetic changes in each enrolled patient (i.e. "stratified by molecular alteration"[68]).
- *Platform trials* are multi-arm, multistage study designs that compare several intervention groups to one common control group. The landmark COVID-19 RECOVERY trial used a platform trial master protocol; it established that dexamethasone was effective and hydroxychloroquine was ineffective in treating COVID-19. A key benefit of platform trials is that new intervention arms may be added to an ongoing trial. Another example of a platform trial is UNITE4TB, a global clinical trials network, which aims to accelerate the development of new TB drugs by conducting clinical trials using a platform design.[69]

What kinds of efficiencies do master protocols drive? Saville and Berry conducted a simulation study to assess "the efficiencies of various platform trial designs relative to a traditional two-arm strategy."[70] They found that open adaptive trial platforms, which add new treatments to the treatment arm during the course of the trial to replace ineffective ones, could (i) evaluate more treatments per trial, (ii) reduce the number of patients required per trial, (iii) significantly reduce the duration of the trials, and (iv) increase the probability of program success (the percentage of programs that accurately recognize an effective treatment). The authors estimate that an open adaptive trial platform with 10 active treatments could see a "70% reduction in the number of patients and failures compared to the traditional strategy."

Human challenge trials

Human challenge trials (HCTs) involve the deliberate infection of healthy, consenting human study participants with an infectious agent in a controlled environment to better understand the disease biology, host immune response, and effects of drugs, vaccines, or diagnostics. HCTs are receiving increasing attention as they could potentially accelerate product development and reduce costs. There have been HCTs for a range of infections, including RSV, SARS-CoV-2, and schistosomiasis.

Real-world data and evidence

The FDA defines real-world data (RWD) as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources" and real-world evidence as "the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD."[71] RWD is increasingly being used in clinical trials in a variety of ways, including as synthetic control arms (SCA) – a type of control arm that consists of patient-level data from patients who are not in a clinical trial.[72] An analysis by BCG suggests that SCAs could generate around US$10 to US$20 million in savings per trial if 20 to 50% of a clinical trial control arm is replaced, and even greater if completely replaced (see Annex 3).[73]

3.3 Benefits of clinical trial networks

Trial networks are well established in the field of HIV prevention (see case study in Annex 3) as well as other infectious diseases such as tuberculosis (TB) and malaria in LMICs. The HIV Prevention Trials Network has shown several benefits: (i) it has been able to assess a range of different technologies and has expanded to include other diseases, such as TB; (ii) it was able to pivot rapidly to conducting COVID-19 vaccine trials and then Mpox vaccine trials; (iii) there are efficiency gains, such as time savings (using existing sites and capacities, including human resources, is quicker than establishing new ones); and (iv) the network has played a major role in building capacity to conduct trials in LMICs.

A multi-stakeholder working group convened by the Wellcome Trust examined how two types of clinical trial networks could play a critical role in driving efficiencies in the development of new antibiotics. The first type, which the group calls a Globally Connected Trial Sites System, connects a series of trial sites "so that sponsors can easily come to one if they have a drug they want to test, and can then run the trial as per usual, with each trial having its own individual protocol." This system could potentially reduce the costs of Phase II and Phase III trials by 23%. The second type, a Continuous Master Protocol model, is a "single global network operated by one entity with a single defined protocol"—trials can share control groups and potentially use control data from past trials. This approach could reduce costs by 40-60%.

Connected trial sites could potentially reduce the costs of Phase II and Phase III trials by 23%.

Continuous master protocols could reduce costs by 40-60%.

3.4 Challenges in adopting trial innovations

There are several challenges in adopting trial innovations, especially in LMICs.

1. DCTs and DHTs can pose challenges for data privacy and authentication, as well as navigating complex data and privacy laws that vary from country to country. The use of remote sensors and wearables raise questions about data reliability and quality.[75]

2. Barriers to adopting novel trial designs, such as platform trials, in LMICs include
   (i) difficulties in implementation due to the complexities of such designs;
   (ii) challenges in securing funders for the complex designs;
   (iii) acceptance and approval by ethics committees and regulatory bodies who may not have the capacity to vet the study protocols; and
   (iv) challenges in statistical analysis due to the scarcity of skilled labor with advanced modelling skills.[76]

3. Human challenge models face ethical debates and there is limited ethical guidance around their use. There have been questions about the informed consent process, and the risks and benefits of HCTs, particularly to the participants.[77] Furthermore, researchers have also called into question the appropriateness of HCTs in LMICs given the power dynamics, lack of ethical oversight and regulation, and the possibility of inducing participants by offering excessive payments.[78]

4. While the application of RWD to clinical trials may offer significant efficiency gains, it is not without its challenges and safety concerns, particularly related to the use of synthetic controls. RWD and real world evidence may have underlying biases affecting generalizability, as well as data privacy and quality issues.[79]

3.5 **Summary and suggested ecosystem changes**

There are multiple innovations in trial conduct that could potentially drive major efficiencies in R&D for NDs, EIDs, and MH (Table 3). Decentralized trials, master protocols (including platform trials), and trial networks hold particular promise. However, given that many LMICs lack trial capacity and infrastructure even for carrying out traditional two-arm trials, a sea change would be needed to scale up new trial approaches in these settings.

1. Research funders and agencies should support sustained, long term efforts to build clinical trial networks that have the capacity to adopt innovative approaches, building on existing capacities. Too often, capacity building efforts are short term, piece meal, and focused on a single trial site, meaning that the human resources and infrastructure can disappear when the trial ends. Building trial networks takes time and sustained funding, but pays large dividends; the HIV Prevention Trials Network, for example, was established 24 years ago. Trial networks have played a critical role in training trialists in LMICs, and would be well placed to help build capacity—including statistical expertise—in platform trials and other innovative approaches.

2. Adoption of platform trials and other master protocols in low-resource settings will require funding agencies, IRBs, data safety boards, and regulators to become familiar with these designs. As innovative trial designs become more widespread in LMICs, operational lessons need to be shared so that implementation barriers can be tackled and best practices adopted.

Table 3. Potential efficiency gains from adopting innovative trial approaches

Innovation	Cost savings
Synthetic control arm	US$10 million -20 million per trial
Rapid enrolment of trial participants through the connection of trial sites	23% (phase 2/3)
Sharing control groups and using control data from previous trials	40-60%

SECTION

4

ESTABLISHING MANUFACTURING CAPACITY IN LMICs

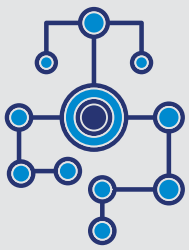
ESTABLISHING MANUFACTURING CAPACITY IN LMICs

KEY BENEFITS:

- **Innovative modular manufacturing approaches and optimized production processes for mRNA technologies can help to drive production costs down, speed up production, and globalize manufacturing.** Container-based modular facilities have a small footprint, so capital costs are much lower compared to traditional manufacturing sites. Optimized production processes for mRNA technologies also have much lower operational costs because of high yields, reduced reagent use, and efficient design. Optimized mRNA production processes using modular, small footprint facilities can save over 60% (more than US$70 million) of the annual cost of goods for the production of 100 million vaccine doses compared to conventional mRNA manufacturing. These savings could lower mRNA vaccine production costs to US$0.5 per dose.
- **An optimized mRNA production offers several other advantages.** These include the flexibility to quickly switch from making one vaccine to another, scalable production, and integration of product development with large-scale manufacturing.
- **Integration enables rapid development and production.** The integration of development and production is especially useful during pandemics, supporting a rapid response as defined by CEPI's 100 days mission target.

KEY CHALLENGES TO BE ADDRESSED:

- **The full potential of mRNA for LMICs remains untested.** While we find that modular mRNA sites offer substantial benefits compared with traditional manufacturing, their full potential for LMICs still needs to be tested over the coming years.
- **Most of the vaccines that are needed right now in LMICs are not mRNA-based vaccines.** From this perspective, the strong focus on mRNA manufacturing to the exclusion of other types of manufacturing is a concern.
- **Sustainable manufacturing in LMICs needs a market.** Health tools produced in LMICs need buyers, yet there are still many financial, political, and technical challenges to be addressed in this regard. Building production capacity also needs to go hand in hand with the strengthening of regulatory systems.



SUGGESTED ECOSYSTEM CHANGES:

- **Further strengthen efforts to build regional and sub-regional manufacturing capacity.** Building regional manufacturing capacity in a sustainable manner is important to develop tools for MH, EIDs, and NDs. The lack of distributed manufacturing capacity was a substantial barrier in the response to the COVID-19 pandemic. Investments in manufacturing accompanied by regulatory strengthening would have a major public health impact. Through investments in manufacturing, LMICs in the long run would be able to make their own vaccines rather than relying

on external support. While the construction of mRNA-based production sites should continue, diversified manufacturing is needed to enable production of non-mRNA vaccines in LMICs.

- **Donors need to support the creation of manufacturing capacity over the long term**. Building such capacity is part of planning for sustainable business models and routine immunization market demand. Gavi recently launched the African Vaccine Manufacturing Accelerator (AVMA), which will provide up to US$1 billion for creating sustainable vaccine production capacity on the continent. Other donors and funding mechanisms need to be willing to subsidize manufacturing from LMIC regions to allow for the creation of sustainable markets. They also need to be willing to provide guarantees that they will purchase from manufacturers in LMICs. They must set clear purchasing targets, following the example of Gavi and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR).
- **LMICs should commit to buying products manufactured by LMICs, such as through advanced purchase agreements, to help create sustainable markets.**
- **The many benefits of modular production should be leveraged**. Modular facilities can be established much faster and at lower costs compared to conventional approaches. Modular mRNA facilities offer specific benefits: they integrate drug discovery, clinical testing, and manufacturing and are able to develop, test, and produce drug candidates in a rapid, cost-effective manner. This is particularly useful during pandemic outbreaks.

4.1 Overview

Multiple high-level national and regional efforts are underway to increase manufacturing capacity in LMICs. The African Union (AU) and Africa Centres for Disease Control and Prevention (Africa CDC), for example, have established the Partnership for African Vaccine Manufacturing (PAVM) to make the African continent self-sufficient in vaccine research, development, manufacturing, regulation, and delivery.[80] The goal of the PAVM is to enable the African vaccine manufacturing industry to develop, produce, and supply at least 60% of the total vaccine doses required in Africa by 2040. PAVM has already launched several projects. In addition, the WHO and its partners have established an mRNA vaccine technology transfer hub in South Africa that will work with an extensive network of LMIC-based technology recipients to build mRNA vaccine production, quality control, and regulation capacity across LMICs.[81,82] LMICs in Latin America, Europe, and Southeast Asia have also started collaborations with other countries to increase vaccine manufacturing capacity in their respective regions.[83,84] While the initial emphasis of these efforts was on stronger vaccine production capacity, the ambition has become broader and now includes advancing production of vaccines, diagnostics, and therapeutics.[85]

In this section, we summarize the current evidence on the costs and timelines for manufacturing global health products (Section 4.2). We then analyze how efficiency gains—such as reduced production costs and accelerated production processes—could be achieved through optimized mRNA production and modular manufacturing processes (Section 4.3). Finally, we assess key challenges in strengthening LMIC production capacity (Section 4.4).

The goal of the PAVM is to enable the African vaccine manufacturing industry to develop, produce, and supply at least 60% of the total vaccine doses required in Africa by 2040.

4.2 Traditional manufacturing approaches: costs and timeframes

Studies show different price tags for building manufacturing capacity. In our own study, conducted by CPIGH at Duke University and Open Consultants, on late-stage clinical trials and manufacturing from the perspective of three middle-income countries (MICs), we estimated that US$250 million would be needed to strengthen production capacity in each of the three MICs (India, Kenya, and South Africa). We assumed that this amount would be sufficient to establish six manufacturing sites, three each for vaccines and therapeutics, which can collectively produce 90 million vaccine doses and 90 million drug doses per year.[4]

In 2022, members of our research team also supported a study on vaccine security in the Association of Southeast Asian Nations (ASEAN).[86] The study was commissioned by the World Bank and included a substantial collection of primary data on the costs of health R&D and manufacturing. One-time construction costs and annual operating costs for vaccine manufacturing were based on data shared by World Bank partners and ASEAN countries. The study estimated that the capital costs of a fully integrated vaccine production site amount to US$225-US$275 million, while the costs of fill and finish sites are substantially lower (US$72 million). Table 4 summarizes the evidence on the costs for establishing manufacturing capacity in LMICs.

Table 4. Cost estimates for conventional vaccine manufacturing

Source of cost estimate	Cost savings
UNIDO, 2017[87]	*Fully integrated facility*: 30m doses/yr; US$105-220m *Fill-finish only*: 30m doses/yr; US$46-98m
Boyd, 2020[88]	Annual operating costs range from US$58.7m in Copenhagen, Denmark, to US$14.0m in Bangalore, India
African Vaccine Manufacturing Initiative; WHO; UNIDO 2017[89]	Building a manufacturing facility (20 million doses/yr) can cost US$60m-US$130m, depending on technology and formulation. Capital expenditure accounts for over 60% of all costs (can be rationalized through economies of scale and scope)
Grootendorst et al, 2022[90]	"... commercial-scale facility costs are in the order of US$500 million to US$1 billion. Specifically, Plotkin et al (2017) estimate that the cost of a whole virus vaccine plant is between US$50 to US$500 million per antigen depending on the complexity of design, automation, segregation, utilities, and contamination controls, and as much as US$700 million for multiple vaccines. Sanofi's new egg-based whole virus plant at its Connaught campus is expected to cost C$925 million [Canadian dollars] to construct and certify (Sanofi Canada 2021). Lonza's vaccine and biologics contract facility in Switzerland cost US$715 million (Kansteiner 2021). Novartis' cell-based influenza vaccine plant (...) cost US$1 billion."
Plotkin et al, 2017[91]	Provides overview on major cost drivers and options to reduce costs
Open Consultants/ World Bank	30 million doses: • Construction cost for fully integrated manufacturing site (traditional): US$225m • Construction cost for fully integrated manufacturing site (mRNA): US$275m • Construction cost for fill and finish manufacturing site: US$72m

Abbreviations: m = million; yrs = years

4.3 Efficiencies from optimized mRNA production processes and modular manufacturing approaches

Modular manufacturing is not a new approach, but it has received renewed attention due to the emergence of mRNA vaccine manufacturing, which lends itself to smaller footprint facilities. However, a modular site with a smaller footprint does not mean that the annual production volume is necessarily lower. For example, one pharmaceutical company built a modular facility for seasonal influenza plus a contingency for pandemics. The capital costs for this particular facility were about US$20 million, with an annual dose output of 25-50 million doses. Another modular site for influenza vaccines was built in an existing building at a cost of just US$5 million. This facility was able to produce 25 million doses per year. In comparison, a different company created a site in North Carolina for about US$1 billion for 50 doses – twice the capacity, but 50 times the costs. Another example is the creation of a modular manufacturing site in Senegal. The facility, which is supposed to be operational by the end of 2024, will be based on 10 modules made in Sweden. It will be able to produce 200 million doses of COVID-19 vaccines in the first year, and up to 300 million doses from year two onwards if needed (the original plan was that it could even develop 1 billion doses a year).

There are already major partnerships that aim to build modular mRNA production capacity. In August 2021, BioNTech agreed to set up vaccine production capabilities in Africa together with the kENUP Foundation, President Paul Kagame of Rwanda, President Macky Sall of Senegal, and President Ursula von der Leyen of the European Commission. The decision was guided by the African Union (AU), Africa CDC, and the African Medical Agency (under formation). In June 2022, BioNTech started to build its first manufacturing facility in Kigali, Rwanda, to support the production of mRNA vaccines in Africa. In December 2023, the Kigali production site was inaugurated and it is expected to be operational with the manufacturing of mRNA-based vaccine batches required for process validation in 2025. The site can manufacture up to 50 million doses per year of a product and has an RNA process similar to that of the Pfizer-BioNTech COVID-19 vaccine. BioNTech itself has invested US$150 million in the construction of the production site.[92]

The company plans to also establish sites in Senegal and South Africa.[93] BioNTech has developed a container-based plug & play approach with modular design, standardized equipment, and software components. The container-based production sites are called “BioNTainers” and are supposed to be fully self-sufficient and capable of manufacturing a range of mRNA-based vaccines, which could include the COVID-19 vaccine, BioNTech’s investigational vaccine candidates for malaria and TB, and possibly cancer vaccines if developed and approved by regulatory authorities.[94] The Kigali plant will also feature power and water supply infrastructure, quality control labs, quality assurance set-up, warehousing, and cold and frozen storage. The facility’s initial production capacity is expected to be 50 million doses a year. Manufacturing in the BioNTainers can begin from 12 to 18 months post-installation. Local qualification runs will also be carried out before the start of production to ensure vaccine production is compliant with Good Manufacturing Practice (GMP) and to train local employees. More of these partnerships will be needed.

There are also companies that offer modular platforms. Quantoom is a key example—its modular facility offers substantial savings in terms of costs of goods sold (Panel 2).

PANEL 2 Quantoom’s modular mRNA manufacturing approach

Quantoom Biosciences is part of Univercells, a global life science company founded in 2013.[95] Quantoom aims to remove the barriers to making mRNA-based vaccines and therapeutics from sequence up to mass production.[96] mRNA-based manufacturing involves multiple barriers, such as complicated workflows (including the challenge to scale volumes from R&D to commercial production), highly specialized infrastructures, supply chain challenges, and complex operations that are prone to error and delay. The lack of tailored equipment and processes can result in delays and is also a major cost driver, which in turn affects the product price and is a key barrier to global access. To enable efficient end-to-end production of mRNA-based products, Quantoom introduced its Nfinity™ production platform, which consists of three technologies: Nplify™ for DNA production, Ntensify™ for RNA production, and Ncapsulate™ for lipid nanoparticle formulation.[97]

Here we discuss Ntensify™, an automatized mRNA production system that supports the entire drug development process from discovery to commercial production. With a small footprint, Ntensify™ is based on a construct-agnostic mRNA process that aims to drive high yields, minimize reagent use, and eliminate the need for resource-intensive scale-up.[98] These three elements should result in a much more efficient production. At the same time, Ntensify™ only requires a space as compact as a shipping container, and this small footprint contributes to cost savings and capital expenditure reduction while enhancing reproducibility. There are three Ntensify™ models. The mini is for drug discovery and preclinical research. It enables researchers to test multiple similar mRNA constructs in parallel. The midi is for clinical research and commercial production; it can make up to 15 million doses per year. The maxi, which will come to market in 2024, is for larger volumes, making up to 100 million doses per year, ideal for pandemic readiness.

Quantoom itself has estimated the savings resulting from Ntensify™. So, while these are self-reported estimates, Quantoom gave us a solid introduction to the underlying cost model. We also consulted external production experts to validate that Quantoom's approach can lead to efficiencies; these independent experts told us that Quantoom's self-reported cost estimates are realistic.

Time savings: Ntensify™ can reduce the timeline for mRNA-based vaccine production to just three months, aligning with CEPI's 100 days mission for expedited vaccine development. Ntensify™ also makes it possible to quickly ramp up volumes, a crucial feature during pandemics.[99]

Reduced cost of goods (CoGs): Conventional drug development entails annual CoGs of about US$2.3 million, while adopting Ntensify™ reduces this cost to only US$0.7 million (US$1.6 million savings). Immediate access to Ntensify™'s optimized process adds an extra US$2.3 million savings during drug discovery.[98] For *commercial vaccine production*, Quantoom estimates that Ntensify™ can reduce annual CoGs from US$307 million (conventional production) to US$129 million (savings of US$178 million).[100] Quantoom estimates that Ntensify™, for the annual production of 100 million doses of mRNA vaccines (50 µg/dose), saves 61% (or US$74 million) of the annual CoGs compared to conventional manufacturing (Ntensify: US$47 million; conventional: US$122 million).[101] At a scale of 100 million doses, 10% of the total annual CoGs of Ntensify is attributed to capital expenditures (equipment and facility), and 90% to operational expenditures (consumables and labor), of which 83% is allocated to reagents mixes.

Lower price per dose: Lowering production costs will have a positive impact on product prices. A company representative reported that the company has met a Bill & Melinda Gates Foundation-specified target of US$0.5 per vaccine dose (of this US$0.5, 50% is for DNA and mRNA production, and 50% for the formulation).[102]

Quantoom's technologies have been adopted by Bio-Manguinhos (Brazil), Institut Pasteur (Dakar), and Afrigen (South Africa), among others, demonstrating the relevance for LMICs.

4.4 Challenges for the strengthening of LMIC production capacity

There are multiple challenges for strengthening LMIC production capacity.

1. First, modular platforms and optimized product processes need to be tested further over the coming years. However, modular approaches are not new, so the risk of failure appears to be low.

2. Second, KIs highlighted that supply chain issues are a huge challenge.[103] The production of RNA requires the supply of more than 100 reagents or inputs, and 10-15 of these are very expensive and heavily controlled. Due to supply chain issues, producers face problems in accessing the needed reagents and ingredients. In addition, the patent holders for the various production inputs are mostly in HICs, which contributes to existing equity gaps. Addressing this issue requires stronger sharing of IP, licensing agreements, and technology transfer.

3. Third, the lack of regional manufacturing capacity was apparent during the COVID-19 pandemic. While there is a lot of discussion and some action on globalizing mRNA production, obstacles remain. For example, the mRNA hubs supported by WHO face the problem of no demand. A recent study by Africa CDC, CHAI and PATH emphasized that uncertain demand is a major challenge and that the creation of vaccine production capacity in other countries (China, India) has been supported by government-backed demand commitments.[104] According to a recent media report, Moderna decided to pause building an mRNA vaccine factory in Kenya due to a lack of demand.[105]

   Initially, the price of vaccines from countries with large existing production capacity, especially India, will be lower compared to newly established facilities. In cases where the global prices of vaccines are lower, global funders need to be willing to pay higher prices, or middle- and high-income countries in the subregions could collectively offer cross-subsidies to the poorest countries. Over the long run, such subsidies will help to establish a strong regional ecosystem for the production of health tools, with substantial medium-term health, economic, and societal benefits. In 2023, Gavi made important adjustments to its procurement policy to allow for procurement from vaccine producers in LMIC regions. Gavi also launched the African Vaccine Manufacturing Accelerator (AVMA), which can provide up to US$1 billion for creating sustainable vaccine production capacity on the continent. PEPFAR committed to procure 15 million HIV tests produced by African manufacturers in 2025 at an estimated cost of US$20 million. For antiretroviral drugs, PEPFAR aims to work alongside other partners to shift at least two million clients on first-line antiretroviral treatments to use African-made products by 2030.[106,107] Other global health financing mechanisms, such as the Global Fund, should also set concrete procurement targets and consider subsidizing manufacturing from LMIC regions to support the creation of sustainable markets.

The production of RNA requires the supply of more than 100 reagents or inputs, and 10-15 of these are very expensive and heavily controlled.

Around half of the market for in-vitro diagnostics is accounted for by just four companies.

4. Fourth, there are specific challenges around the manufacturing of diagnostics. Diagnostics experts highlighted the lack of production capacity for diagnostics in LMICs—FIND has recently been shining a light on this barrier.[108] KIs argued that the market for diagnostics is dominated by just a few major players. The Lancet Commission on Diagnostics showed that HICs also dominate the global supply of diagnostics: around half of the market for in-vitro diagnostics is accounted for by just four companies from the US and Europe, and three-quarters of the market for medical imaging is accounted for by just four companies from the US, Europe, and Japan.[109] These market failures contribute to high prices of, and inequitable access to, diagnostics.[110] LMICs cannot afford them: PATH estimates that 47% of the global population has little to no access to diagnostics. As such, the market needs to be diversified by creating more production capacity in LMICs. Key enablers include tech transfer, public-private partnerships, and technical support.

In addition to financial investments in R&D and manufacturing, targeted policy actions are required, for example through stronger regional regulatory harmonization and focused human resource development. As highlighted in a recent blog by the Center for Global Development, any effort to increase vaccine manufacturing capacity in LMICs needs to also consider the fact that many regulatory systems lack the required capacity (see Section 6 for details).[111] In addition, building sustainable production capacity also requires more technology transfer and technical support.

4.5 Summary and suggested ecosystem changes

Optimized mRNA production processes and modular manufacturing approaches offer multiple benefits over traditional manufacturing. We have summarized the cost and time savings in Table 5 and 6.

Table 5. CoGs: conventional mRNA production and efficiencies through optimized mRNA production

	Conventional mRNA manufacturing	Optimized mRNA production process
CoGs (drug development)	US$2.3 million	US$0.7 million
Annual CoGs (production of 100 million doses)	US$122 million	US$47 million
Vaccine development timeline	20 months during COVID-19	3 months (ambition)

Table 6. Conventional manufacturing and modular facilities (example: seasonal influenza vaccine)

	Conventional manufacturing	Modular mRNA facilities
Construction of production site	Up to US$1 billon	US$5-50 million
Construction timelines	Several years	~1 year

We recommend the following ecosystem changes:

1. Further strengthen efforts to build regional and sub-regional manufacturing capacity. Building regional manufacturing capacity in a sustainable manner is important to develop tools for MH, EIDs, and NDs. The lack of distributed manufacturing capacity was a substantial barrier in the response to the COVID-19 pandemic. Investments in manufacturing accompanied by regulatory strengthening would have a substantial public health impact. Through investments in manufacturing, LMICs in the long run would be able to make their own vaccines rather than relying on external support.

2. Donors need to support the creation of manufacturing capacity over the long term. Building such capacity needs to be part of planning for sustainable business models and routine immunization market demand. In 2023, Gavi made important adjustments to its procurement policy to allow for procurement from vaccines produced in LMIC regions. All donors need to be willing to subsidize manufacturing from LMIC regions to allow for the creation of sustainable markets, and donors should guarantee that they will buy products from manufacturers in LMICs. Setting clear purchasing targets and commitments, as Gavi and PEPFAR did, will be important to promote action and to track progress.

3. Leverage the multiple benefits of optimized mRNA production and modular facilities. Modular facilities can be established much faster and at lower costs compared to conventional manufacturing approaches. In addition, optimized mRNA production processes promise huge benefits because they integrate drug discovery, clinical testing, and manufacturing and can develop, test, and produce drug candidates in a speedy and cost-effective manner (Panel 2).

SECTION

5

NEW AND UNDERUSED HEALTH INNOVATIONS: mRNA-BASED TECHNOLOGIES AND MONOCLONAL ANTIBODIES

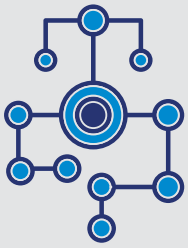
NEW AND UNDERUSED HEALTH INNOVATIONS: mRNA-BASED TECHNOLOGIES AND MONOCLONAL ANTIBODIES

KEY BENEFITS:

- **mRNA platforms are suited for speed and are highly versatile, which are major advantages, especially during pandemics**. Compared with conventional manufacturing of vaccines and therapeutics, the mRNA production process is simpler with fewer steps so production yields are less variable, production is much faster, and facilities can be smaller There are now multiple attempts to build regional self-sufficiency in mRNA manufacturing capacity.
- **Monoclonal antibodies (mAbs) have come of age in clinical medicine, and more than 100 monoclonal antibody products have been licensed over the past 30 years to treat, prevent, and cure NCDs**. However, only seven mAbs were licensed for infectious diseases. Availability and affordability are two of the biggest barriers impeding global access.

KEY CHALLENGES TO BE ADDRESSED:

- **The chances of developing mRNA vaccines against some pathogens are low, e.g., against bacteria and parasites with complicated structures that can evade the immune system**. Nevertheless, mRNA candidates for critical NDs, such as TB and malaria, are in the clinical phase of development (or at least in the preclinical stage, e.g., HIV).
- **While mAbs have substantial potential, there is too little R&D on mAbs that target NDs, EIDs, and MH**. The production of mAbs is complex and costly.



SUGGESTED ECOSYSTEM CHANGES:

For mRNA:

- **Investments should be scaled up in mRNA technologies for NDs, EIDs and MH.** mRNA platforms have significant comparative advantages over more traditional technologies.
- **It is critical for LMICs to be able to produce their own mRNA technologies**. The global health community needs to further strengthen its ongoing support to strengthen mRNA production capacity in LMICs.
- **A lipid needs to be available without the IP constraints.**

For mAbs:

- **There needs to be more investments in R&D on mAbs that target NDs, EIDs, and MH.**
- **New approaches are needed to bring down production costs**. One way to do this is to link discussions of manufacturing capacity for mRNA to mAb production in LMICs.
- **While the financial environment for mAbs is currently severely constrained, there is the opportunity to pilot their wide-scale introduction**. COVID-19 was a missed opportunity to do so. There is as yet no example of scaled up mAbs in LMICs, although India has licensed two mAbs-based products for post-exposure prophylaxis against rabies (one is a single human mAb, the other is a cocktail of two mice mAbs). We saw with antiretroviral therapies that it is possible to introduce expensive drugs in a relatively fast manner and see costs fall quickly. RSV mAbs could be a game changer—a low-cost mAb is believed to be under development—and could serve as a product for the global community to rally around.
- **In parallel, the case for using mAbs in LMICs needs to be further assessed**. From an equity perspective, there needs to be a strong push for developing, producing, and using mAbs in LMICs and for generating evidence on effectiveness and cost effectiveness in different settings.

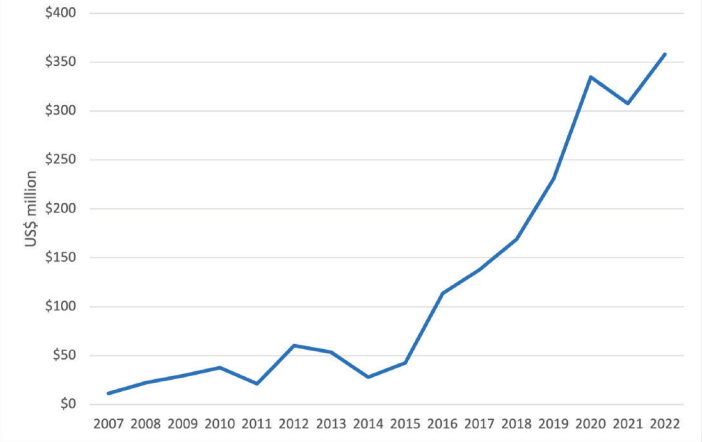
5.1 mRNA platform

OVERVIEW

Platform technologies can be defined as "an underlying technology or process that can be adapted for use in product development for more than one product or disease area."[112] Such platforms can be used to develop vaccines, biologics, drugs, and diagnostics, as well as the adjuvants and immunomodulators that are used to improve vaccine efficacy. COVID-19 validated two platform technologies for vaccines that had been based on decades of prior research. The first was the mRNA platform, used by Moderna and Pfizer-BioNTech to develop their COVID-19 vaccines, and the second was the viral vector platform, used by Oxford University/AstraZeneca and Johnson & Johnson in developing their COVID-19 vaccines. R&D funding for these technologies increased significantly from 2015, especially due to the COVID-19 pandemic. There has been a steady rise in annual funding for platform technologies for NDs, EIDs, and MH, reaching a record high of US$358 million in 2022.[113] There was a sharp jump from 2015 to 2016 (up US$71 million, 37%), after the WHO's addition of "Disease X" (an unknown pathogen) to the Blueprint list (Figure 2). During the COVID-19 pandemic, platform technologies benefited not just from large amounts of funding but also streamlined regulatory approval.[114]

Of the range of available platform technologies, KIs argued that mRNA is garnering the most attention given its potential applications for a range of diseases – including NDs, EIDs, and certain cancers.

Figure 2. R&D funding for platform technologies for neglected diseases over time



POTENTIAL OF mRNA PLATFORMS

The development of safe, effective COVID-19 vaccines in under a year was a powerful validation of the mRNA platform. It has "sparked optimism that a vaccine revolution is under way,"[114] potentially leading to vaccines for NDs, EIDs, and cancers. There are five major advantages of the mRNA platform.

Speed

First, mRNA is suited for speed.[114] The rapid production of vaccine candidates using mRNA technology can accelerate candidate identification and optimization, especially if preclinical models are available, as well as initiation of early phase clinical studies.[115] It took Moderna just 42 days to produce the first batches of its COVID-19 vaccine (mRNA-1273). This was revolutionary because most previous vaccines were developed using established platforms, e.g., whole inactivated virus (polio vaccine) or live attenuated virus (yellow fever vaccine). In the past, with traditional methods (cell-based, egg-based, or recombinant vaccine manufacturing), at best it would take 18 months to two years. And if large volumes of vaccines need to be made in a very short time period for a new pathogen, mRNA is at this stage the only available option.

Versatility

A second attractive feature of platform technologies is their versatility: developers can use existing mRNA platforms for multiple pathogens rather than creating new ones. This is much faster and cheaper than previous processes, i.e., the development of new platforms from scratch. There is no need to develop toxicity studies, which are expensive and take a minimum of seven months, because the platform is already validated. As mentioned by one KI, "you only change the immunogen, the FDA either says no toxicity study is needed or you do a modified one that is much quicker.....the dream is that we have a 'plug and play' platform, i.e., agnostic to the pathogen – you just plug in the new pathogen and it produces vaccine."

Faster production

Third, as we discussed in the manufacturing section, mRNA technology is promising because "the production process is simpler with fewer steps so production yields are less variable, production is much faster, and facilities can be smaller,"[115] compared with the traditional cell-based, egg-based, or recombinant vaccine manufacturing. Costs to establish a manufacturing plant are lower. "Product-independent manufacturing also makes multi-production facilities feasible to operate because a single facility can be leveraged for rapid sequential small-scale production of vaccines against several pathogens."[116] This is a key advantage for EIDs and NDs.

Proactivity

Fourth, platform technologies can be proactive rather than reactive to a pathogen—they have been successfully applied to a previously unknown pathogen.

Overcoming delivery challenges

Fifth, there is also hope that mRNA vaccines could help overcome delivery challenges for NDs, EIDS, and MH by being thermostable, single dose, or delivered nasally, though this will require intensified R&D.

The reasons why mRNA-based vaccine development for NDs has not been successful to date include:

1. Low scientific feasibility given that many PRND pathogens "are bacterial or parasitic with complicated structures, or lifecycles, rendering it difficult to identify the protective antigen(s) to be included in the vaccine."[117]
2. An uncertain regulatory pathway.
3. Lack of clarity about which groups and which geographies would benefit most from a vaccine. Some of these challenges are true for EIDs, except that the priority EIDs are all viruses.
4. For NDs and EIDs, there are scientific challenges with mRNA vaccines, e.g. the need for ultra-cold chain, lack of data in young children, waning immunity, shortages of raw materials, IP barriers, and the need to identify the antigen.
5. The biggest barrier for mRNA vaccine production is the lipids–they are the most complex part and are the part most constrained by IP.

Advances are now being made in mRNA platform approaches that could address some of the challenges. For example, the Duke Human Vaccine Institute (DHVI) has developed a "straightforward, scalable, reproducible production and purification platform that provides mRNA with the quality, purity, and safety profile required for clinical trial use."[118] DHVI is now developing mRNA vaccines against HIV and also against influenza (the influenza vaccine under development, funded by the NIH Collaborative Influenza Vaccine Innovation Centers [CIVICS] program, involves a cocktail of 10 strains).

Another innovation is the ferritin nanoparticle delivery system, which DHVI is using in developing HIV and COVID-19 mRNA vaccines. This system allows researchers to further decorate the mRNA platform with other immunogens – this could, for example, result in a combined vaccine for influenza, COVID-19 and RSV. A combination vaccine would be especially useful in LMIC settings, because only one shot would be needed for three diseases.

In this context, there are potential interlinkages between the technological advances that we discuss in our paper. First, one concern with the development of combined mRNA vaccines for respiratory diseases, using the ferritin nanoparticle delivery system, is that adverse reactions might be intense. In this context, AI could help to predict which combinations give the most severe reactions. Second, DHVI has ordered Quantoom's technology for making RNA (specifically, the midi). Third, for COVID-19 boosters, there could be a scenario akin to what happens with influenza vaccines: the WHO decides which strain is needed each year in the Northern hemisphere and the Southern hemisphere, and then companies make it. Similarly, the WHO could state which COVID-19 booster is needed, and mRNA manufacturing plants around the world would make the vaccine (provided they have the ingredients).

SUGGESTED ECOSYSTEM CHANGES

1. First, there should be increased investment in mRNA technologies for NDs, EIDs, and MH because mRNA platforms have significant comparative advantages over more traditional technologies. mRNA-based technologies for HIV, TB, and malaria are in the current R&D pipeline and could be powerful tools against the three diseases. LMICs also need to be enabled to produce their own mRNA technologies. This is a critical step.
2. Second, IP barriers need to be addressed. mRNA production requires many different inputs and the IP holders come almost exclusively from HICs; there is an urgent need for IP sharing and tech transfer programs. For example, a lipid needs to be available without the IP constraints, otherwise equity gaps will likely persist.
3. Third, at the same time, we acknowledge that there is low scientific feasibility for developing mRNA vaccines against certain bacteria and parasites with complicated structures that represent a substantial share of the disease burden in LMICs. Developing such vaccines is a key priority for these countries, so a diversified investment approach is needed. R&D funders need to invest in more traditional technologies, not just in mRNA.

5.1 Monoclonal antibodies

OVERVIEW

mAbs are a large and growing segment of the pharmaceutical market and they are also the largest class of biologic products in development.[119] More than 100 mAb products have been licensed over the past 30 years and they are transforming the way doctors treat, prevent, and even cure many diseases, especially NCDs, including certain cancers and autoimmune disorders. These mAb products are often more effective than previous therapies, easier to deliver, and better tolerated by patients.[120] In addition, in tackling infections, mAbs can have "dual use," i.e., they provide passive immunity and have a therapeutic effect in those already infected.[121]

There are mAbs in the clinical pipeline for selected EIDs and NDs. mAbs that target SARS-CoV-2 showed a reduction in viral load[122,123,124] and, in the US, COVID-19 mAbs were the first COVID-19-specific product to receive emergency use authorization (in November, 2020). However, laboratory studies found that the activity of anti-SARS-CoV-2 mAbs against specific variants and subvariants varied greatly. The NIH concluded that these products are not expected to be effective in treatment or prevention of COVID-19 in areas where the circulating variants and subvariants are resistant to mAbs.[125] Nevertheless, there is significant ongoing research on COVID-19 mAbs, including on broadly neutralizing antibodies for prophylactic and therapeutic use.[126]

Broadly neutralizing mAbs (i.e., against whole viral families) are also of great interest for other viruses, as well as for malaria—a broadly neutralizing

Since broadly neutralizing antiviral mAbs can be developed, manufactured, and stockpiled in advance, they could serve as a real-time intervention upon detection of a pathogen of concern while complementing vaccines.

malaria mAb would be of particular value in pregnancy.[127] A preventive malaria mAb (CIS43LS) is in the pipeline, with Phase 1 and 2 trials showing promising results.[128] There are also mAbs for Ebola virus, showing therapeutic benefits.[129,130] However, a recent study raised some concerns about the risk of reinfection or reactivation of the virus in patients previously treated with Ebola mAbs, pointing to the need for additional research.[131]

As highlighted by Gupta et al,[121] mAbs can potentially address critical needs in a pandemic – either to complement vaccines or because they have characteristics that are not being met by vaccines. They can:

Provide primary prophylaxis while waiting for vaccines to be developed.
Provide immediate protection during the time it takes for an individual to mount a response after vaccination; this could help in a ring vaccine response ("pre- and post-exposure mAb prophylaxis could help to quell an outbreak at its nascent stage"[121]).
Provide passive immunity to patients who do not mount an adequate immune response to vaccines or who are vaccine hesitant.
Reduce transmission by reducing viral load ("treatment as prevention").
Potentially be stockpiled. Gupta et al argue that since "broadly neutralizing antiviral mAbs can be developed, manufactured, and stockpiled in advance, they could serve as a real-time intervention upon detection of a pathogen of concern while complementing vaccines."[121]

CHALLENGES

We identified four challenges with mAbs.

1. Access. First, access to mAbs is severely limited in many countries – 80% of sales are in the U.S., Canada, and Europe, while 85% of the world's population live in LMICs. One factor, which the global community has largely neglected thus far, is the high costs (Panel 3). In low-income countries, very few mAbs are even registered, and those that are registered in middle-income countries are often not covered by the public health systems, impeding access due to high costs. Unless action is taken now, the access gap will further widen because mAbs constitute an increasingly large portion of the pharmaceutical pipeline. The biggest barriers to access are affordability and availability, including registration and inclusion on national medicine lists. Currently, the global ecosystem also lacks an international "buyer" for monoclonal products, which makes it difficult to shape markets and negotiate prices that are affordable to LMICs. So, even if a mAb became available for malaria, it is unclear who would buy it as no single organization is leading on this.

2. Insufficient R&D. Second, the development of mAbs for infectious diseases has been limited, partially due to their high production costs and limited duration of protection. Only seven currently licensed mAbs are for infectious diseases despite their potential for treating and preventing infectious diseases that disproportionately impact LMICs as well as emerging pathogens with pandemic potential. The insufficient R&D for infectious disease mAbs reflects a lack of commercial incentives to invest in R&D for mAbs in LMIC settings. For those mAbs that are available for infectious diseases, access and availability issues largely prevent their use in LMICs (Panel 3).

3. Lack of trials in LMICs. Third, only 12% of clinical trials for mAbs are conducted in LMICs. The scientific community remains concerned that large and complex trials for mAbs cannot be successfully conducted in low-resource settings. However, the Antibody Mediated Prevention study, which evaluated an innovative mAb for HIV prevention, was successfully conducted in seven countries in Sub-Saharan Africa, providing proof-of-concept for the feasibility of conducting complex trials.[132] Furthermore, it has proven more difficult to gain regulatory approval for biosimilars compared to small-molecule generics, mainly due to the requirement for comparative clinical trials and the limited experience of LMIC regulators with the review of mAbs dossiers. As highlighted in Section 6 of this report, more collaborative regulatory approaches are needed across countries.

4. Lack of target product profiles (TPPs) and preferred product characteristics (PPCs). Fourth, there are only a few TPPs or PPCs for mAbs for LMICs. TPPs and PPCs are released by WHO and lay out product attributes with a focus on LMICs. The lack of TPPs and PPCs for mAbs to guide product development by industry is a major roadblock. Developing such TPPs and PPCs would be an important step for accelerating and expanding access of new mAb tools.[133]

Overall there are multiple challenges – as one KI said, "even if I had a billion doses of a mAb for a specific disease in an LMIC, there is no buyer, there is no regulatory pathway, there is nothing....manufacturing, implementation, regulatory, procurement—who is going to do it? Companies aren't going to do it. There's no one-stop shop." However, there are also many opportunities to improve the landscape for mAbs, such as new manufacturing techniques, conducting trials in LMICs (rather than in HICs), and the creation of TPPs.

PANEL 3 mAbs for respiratory syncytial virus

Respiratory syncytial virus (RSV) can infect people of all ages, but young infants have the highest incidence of severe disease. RSV has been estimated to globally cause 33 million acute lower respiratory tract infections in young children annually, with 3.2 million severe cases requiring hospitalization, and 118,000 deaths. Although RSV is a global disease (e.g., it is the leading cause of hospitalization for children under one year old in the U.S.), 99% of global deaths and 88% of hospital admissions occur in LMICs. In 2023, a new monoclonal antibody for RSV (nirsevimab, made by AstraZeneca/Sanofi) was introduced. It was given an FDA Fast Track designation, a process designed to expedite drugs to treat serious conditions and fill unmet needs. Compared to a previous registered mAb for RSV (Synagis), nirsevimab is longer lasting (a single dose will shield infants for the whole RSV season), and it costs much less (US$400-500[134] in the U.S. and between US$300-900 in European countries) compared to Synagis.[135,136] Nirsevimab is effective at preventing RSV in young infants, providing around 75% protection against severe RSV disease and hospitalization.[137,138]

Nirsevimab illustrates an important point – it is an effective tool against a disease that causes a lot of harm globally, but especially in LMICs. For example, its use in HICs could reduce hospitalizations by 50%, preventing hundreds of thousands of children becoming severely sick and reducing pressure on healthcare systems.[139] However, for the time being, the monoclonal will not be available at scale in LMICs. Given the high costs and the reluctance of the producing companies to introduce tiered pricing for LMICs, LMICs cannot afford to purchase the monoclonal RSV product.

The TPP states that "the mAb price should be similar to other new vaccines for feasibility of use in LMIC settings" and that the price "should be acceptable to Gavi investment case for use in Gavi-eligible countries." However, the reality is that price is a barrier to global access. One key determinant of the high price is the fact that mAbs can be even more expensive to produce than vaccines. Antibody production is difficult, requiring multiple steps, particularly their downstream isolation and their purification, making it harder to produce larger batches. Still, for real progress in global health outcomes, these new breakthrough technologies need to benefit everyone. Several published articles have argued that there are ways to lower manufacturing costs.140, 141, 142 For example, in a paper on key considerations for global use of RSV mAbs, Sparrow and colleagues say:

> **"However, given the small dose of mAb required to protect young infants against RSV and given new manufacturing technologies, the cost of preventive RSV mAbs could be relatively low, potentially enabling them to be marketed in a price range similar to the price points of newer vaccines in use in LMICs. Based on projections, for a 50 mg dose of mAb, the cost of goods could be less than US$5 per dose."[141]**

Going forward, the potential to reduce production costs needs to be assessed. Recent improvements in antibody optimization, and advancements in manufacturing technologies and packaging and delivery, have the potential to lower mAb production costs. For example, one of the leading mAb manufacturers based in China has "a continuous bioprocess system integrated with single-use bioreactors that is predicted to reduce mAb manufacturing costs from $95–$200 per gram to less than $15 per gram, or $3 for an average 200 mg dose of most mAbs."[119] And while local mAb production in LMICs remains untested, the manufacturing of mAbs in LMICs must be put on the agenda, e.g., in the context of discussions about the creation of mRNA hubs. Studies of the cost-effectiveness of the use of mAbs in LMICs are needed, as well as post-introduction surveillance in early introducing countries to further assess the case for using mAbs in LMICs.

5.3 Summary and suggested ecosystem changes

IAVI and Wellcome put out a call to action to expand access to mAbs, highlighting the need to develop effective new solutions for increased global access to mAbs.[119] These two institutions highlight four immediate actions:

(i) increase advocacy and awareness around the need to make mAbs more widely accessible;

(ii) develop expanded policy and regulatory pathways to increase availability of mAbs;

(iii) invest in and apply new technologies to lower development costs; and

(iv) establish alternative business models to enable innovative market approaches that promote global access.

In addition to these broad steps, we suggest additional concrete steps to boost the development and use of mAbs in LMICs within the next 10-20 years:

1. There needs to be more investment in R&D on mAbs for NDs, EIDs, and MH. While there is substantial potential, current R&D efforts do not sufficiently target infectious diseases.
2. There needs to be investment in manufacturing capacity for mAbs in LMICs, including through mRNA. More attention has to be given to ways to bring production costs down.
3. There is no example of scaled up mAbs in LMICs, although India has licensed two mAbs-based products for post-exposure prophylaxis against rabies. Yet we saw with antiretroviral therapies that it is possible to introduce expensive drugs in a relatively fast manner and see costs fall quickly. While the financial environment is severely constrained, there is an opportunity to pilot the wide-scale introduction of monoclonals as a scale up project (COVID-19 was a missed opportunity to do so). The RSV monoclonal could be a game changer and could serve as a product for the global community to rally around. This will require funding and negotiations with industry, and it would also require a decision about who is going to invest in the product and procure it on behalf of countries. There is no appetite for new global mechanisms, so it would either be an existing global mechanism or potentially different regional mechanisms coordinated at global level.
4. In parallel, the case for using mAbs in LMICs needs to be further assessed. From an equity perspective, there needs to be a strong push for developing, producing, and using mAbs in LMICs. However, under the current financially constrained environment, there needs to be more evidence to guide development, production, and use in different settings, including cost-effectiveness studies and post-introduction surveillance.

For pandemic preparedness more specifically, we agree with Gupta et al that it would be possible to have "a stockpile of broad-spectrum predeveloped mAbs capable of targeting emerging pathogens that have a high barrier to resistance, are rapidly deployable, and can be administered in multiple settings to halt outbreaks through prophylaxis and treatment."[121] In other words, an arsenal of pandemic preparedness mAbs targeting priority pathogens could be created. Having such an arsenal ready would require seven things:

- Identifying the pathogenic targets
- Establishing TPPs
- Creating sustainable markets, e.g., advanced market commitments
- Defining and harmonizing regulatory pathways
- Building global trial networks
- Producing a ready-to-use supply and scalable manufacturing process
- Manufacturing sites able to produce non-pandemic Abs between outbreaks.

SECTION

6

REGULATION

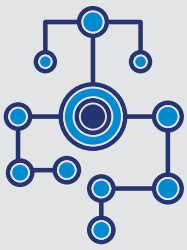
REGULATION

KEY BENEFITS OF RELIANCE AND ACCELERATED APPROVAL:

- **There is evidence that subregional regulatory initiatives have contributed to regulatory harmonization and reliance**. Mechanisms such as the use of reference agencies and joint reviews have significantly shortened registration timelines. Substantial progress towards regulatory harmonization has been made in Africa. However, there is potential to further deepen the collaboration between national regulatory authorities (NRAs). For example, many LMICs still lack legislation for the use of reference agencies and organizational policies and standard operating procedures that guide how to apply reliance. Strong leadership is needed to drive the institutional transformation required to optimize reliance.
- **The COVID-19 pandemic contributed to more efficient regulatory processes**. For example, in Europe, rapid scientific advice and review was reduced from 40-70 days to 20 days.

KEY CHALLENGES TO BE ADDRESSED:

- **There is still a substantial gap in market authorization of health products between LMICs and HICs**. One study estimated that there is lag of 4 to 7 years between first submission for regulatory approval, which is usually to a regulator in a HIC, and final approval in Sub-Saharan Africa (SSA). The study found that WHO's prequalification processes and NRAs often repeated assessments of quality, safety, and efficacy already performed by stringent regulatory authorities (SRAs) and that manufacturers did not prioritize market access in LMICs, slowing down access. While additional reviews may not have been needed, they are usually conducted out of good intent (e.g., to ensure availability of sufficient safety data for local contexts).
- **Globally, only 57 NRAs (30%) have the capacity to perform core regulatory functions. Of these, only five are in Africa**. Furthermore, of the 14 African countries where vaccine manufacturing projects have been announced, only two have regulatory systems operating at the level required for WHO vaccine prequalification. Without stronger regulatory systems, these countries will not be eligible for support from Gavi's African Vaccine Manufacturing Accelerator (WHO prequalification is a requirement for participation in this mechanism).



SUGGESTED ECOSYSTEM CHANGES:

- **Harmonization and reliance are key strategies to accelerate market registration and access to new drugs and vaccines**. They remain underused mechanisms.
- **In parallel, capacity gaps need to be gradually and strategically addressed**. LMICs should assess their current regulatory systems using existing WHO tools and allocate more funding to these systems. HICs should provide technical and financial support

to national and regional regulatory agencies, such as the African Medicines Agency, to ensure that these agencies can effectively perform core regulatory functions. Partnerships between regulatory authorities of HICs and those in LMICs, such as twinning or joint assessments, will also be critical to build capacity and achieve efficiency gains. Several of these types of partnerships were launched in recent years.

- **Any efforts to strengthen vaccine manufacturing capacity need to be accompanied by investments in regulatory systems**. To be eligible for WHO prequalification for vaccine manufacturing, maturity levels 3 or 4 are currently still a requirement.
- **While the WHO PQ system is currently still needed, there should be more flexibilities**. WHO PQ was introduced at a time when regulatory systems were very weak, but this has changed to a certain degree, and flexibilities are needed. Countries and global procurement agencies (e.g., UNICEF) should increasingly accept reviews from WHO-Listed Authorities (WLAs) and/or transitional WLAs (tWLAs) as an alternative to WHO PQ.

6.1 Overview

Effective regulatory systems assure the quality, safety, and efficacy of medical products. In contrast, poor regulatory systems are often a major barrier to providing safe, effective health tools. Globally, only 57 countries (about 30%) have regulatory systems at maturity level 3 or 4 as measured by the WHO Global Benchmarking Tool (GBT).[143] The WHO introduced this tool to assess and benchmark NRAs, promote coordination and good regulatory practices, improve the effectiveness of regulatory strengthening activities, and facilitate harmonization. GBT level 3 refers to stable, well-functioning and integrated regulatory systems, while level 4 refers to advanced systems (see Annex 4 for GBT definitions). Countries with GBT levels 3 or 4 can become a WHO-listed authority (WLA), which "designates regulatory authorities that may be considered as a reference point by WHO and other regulatory authorities for reaching their own decisions in approving medical products" (see Panel 4 for further details).[144,145] Most LMICs have maturity levels 1 or 2—weak systems that are only considered as functional when they rely on prior work by other regulators. As of October 2023, only five NRAs in Africa—Egypt, Ghana, Nigeria, South Africa, and Tanzania—had attained maturity level 3.[146]

PANEL 4 WHO-listed authorities (WLA)

This panel provides the WHO definitions of WLAs and transitional WLAs. The WLA replaces the SRA definition (the definition of an SRA, first published by the Global Fund in 2008, was based on membership in the International Conference [now Council] of Harmonization before October 2015). We still use "SRA" if studies that we cite used the term.

A **WHO-listed authority (WLA)** is defined as "a regulatory authority (RA) or a regional regulatory system (RRS) that complies with all the relevant indicators and requirements specified by WHO for regulatory capability as defined by an established benchmarking and performance evaluation process. A regulatory authority provides the framework that supports the WHO recommended regulatory functions. This is the authority and affiliated institutions that are responsible for regulatory oversight of medical products in a given country or region and in charge of assuring the quality, safety and efficacy of medical products as well as ensuring the relevance and accuracy of product information."

To be designated as a WLA, "a regulatory authority should undergo i) a formal assessment with the WHO-Global Benchmarking Tool (GBT) to demonstrate adequate maturity (ML3 as entry point) and ii) a performance evaluation (PE) process that complements the results of benchmarking, confirming consistency of advanced performance against international standards and best practices. Some transitional arrangements are in place for previously designated stringent regulatory authorities and regulatory authorities which had been previously assessed by WHO. RAs that have reached a high-level regulatory capability and performance (WLA) may be used as a reference and to be relied on by other authorities, to avoid duplicating activities, foster better use of human and economic resources, [and] increase oversight of the pharmaceutical products along the whole supply chain...."

A transitional WLA (tWLA) is an RA "previously included in the WHO Interim list of regulatory authorities (published by WHO from 2019 to 2022), which compiled all RAs already recognized by WHO that work at an acceptable level of regulatory performance before the introduction of the WLA concept. A transitional WLA is not a WLA, in that it still needs to undergo the performance evaluation process and demonstrate compliance with the requirements to be designated as a WLA. The transitional list will be valid until 31 March 2027. During this time, tWLAs are expected to apply for being subject to the performance evaluation (PE) to be able to transition either to the permanent WLA list or the list of RAs operating at ML3/4."

For further details, see WHO Listed Authorities. March 1, 2024. https://www.who.int/news-room/questions-and-answers/item/who-listed-authorities

In addition to NRAs, there is a complex system of global, regional, and subregional regulatory agencies and initiatives. At the global level, WHO supports the introduction of safe new health tools in LMICs through the Certificate of Pharmaceutical Product (CPP). One recent regional initiative is the African Medicines Agency (AMA), established as a legal entity in November, 2021. By January, 2024, 27 countries had ratified the AMA treaty. The agency was established to improve regulatory capacity, provide technical support to countries with limited regulatory expertise, strengthen governance in pharmacovigilance, and oversee clinical trials. AMA is still at a nascent stage, but is set to take on an important future role for the African continent.[147]

In this section, we summarize the evidence on existing regulatory challenges, such as the time lag in access to new health tools between HICs and LMICs (Section 6.2). We then analyze how regulatory processes could be accelerated (Section 6.3). Finally, we make suggestions on how the regulatory ecosystem could be strengthened (Section 6.4).

6.2 The gap between HICs and LMICs in market authorization of global health products

In 2022, the Centre for Innovation in Regulatory Science assessed new active substance approvals by six HIC regulatory agencies: the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the Japanese Pharmaceuticals and Medical Devices Agency, Health Canada, Swissmedic and the Australian Therapeutic Goods Administration. The study found that approval timelines are fast, with small differences between the agencies. In 2021, the median approval time ranged from 245 days (FDA) to 428 days (EMA).[148] The approval times reflect the fact that HICs largely adhere to a uniform set of scientific and technical standards, as a result of their membership in the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[149]

Three key studies have collected evidence on registration timelines in LMICs, pointing to substantial lags in product approval between HICs and LMICs. First, Ahonkhai and colleagues focused on vaccines and drugs eligible for WHO PQ.[150] Based on data for 2009-2012, they estimated that there was a lag of up to 4 to 7 years between the time medicines and vaccines were submitted for regulatory approval, which was usually in a HIC, and its registration in the last of the 20 SSA countries included in their analysis. Ahonkhai et al identified four main factors for these delays:

1. SRA-approved vaccines took a median of 16 months to complete the WHO PQ process. Many review activities were repeated as part of the process, despite previously being conducted by an SRA. Manufacturers also contributed to the delay due to their slow response to WHO questions. PQ time for drugs was much faster (4 months) because review activities were not repeated.
2. Generics from emerging markets required a median of 27 months to complete the PQ process. The standards for the registration of generics in emerging markets (e.g., China, India) were often less stringent than ICH standards required by WHO PQ. Thus, "additional time was often required for manufacturers from those countries to raise the standards of their submissions to meet the PQ requirements."
3. NRAs often repeated assessments already performed by SRAs or PQ. As a result, products first registered by an SRA or PQ process took an additional 1–2 years to receive NRA approval in SSA.
4. Submissions by manufacturers in SSA countries were usually spread over several years – one key reason was that producers did not prioritize registration due to limited commercial incentives.

Second, Miller et al assessed approval timelines of 34 new drugs approved by the FDA in 2012 and 2014 in selected HICs and upper- and lower-middle income countries.[151] Approvals were faster in HICs (median [IQR], 8 [0-11] months) than in upper-middle-income countries (median [IQR], 11 [5-29] months) and lower-middle-income countries (median [IQR], 17 [11-27] months) after FDA approval.

Third, Sithole et al analyzed approval times for mainly generics in six African countries (Mozambique, Namibia, South Africa, Tanzania, Zambia, and Zimbabwe) in 2019 and 2020.[152] These countries are members of the Southern African Development Community Medicines Regulatory Harmonization (SADC-MRH) initiative, and more specifically, of the ZAZIBONA Collaborative Procedure for Medicines Registration, through which the participating NRAs jointly assess medicinal product dossiers.[153] In the study by Sithole et al, approval times significantly varied across the six countries, with a range of 5-30 months.[154]

6.3 Potential for efficiencies: strategies to accelerate regulatory approval

Which regulatory reforms contribute to accelerating the introduction of new quality-assured and effective health tools in LMICs? We focus on three major categories:

(i) regulatory harmonization and reliance;

(ii) strengthening regional and national regulatory capacity; and

(iii) regulatory reforms induced by the COVID-19 pandemic.

REGULATORY HARMONIZATION AND RELIANCE

Regulatory harmonization refers to a process in which regulatory authorities align technical requirements for the development and marketing of pharmaceutical products.[155] The harmonization of technical requirements and standards for health product regulation enables work sharing between agencies, including joint reviews of marketing authorization applications, joint inspections of manufacturing sites, and the increased use of reliance in health product regulation. Harmonization has been pursued for many years through international and regional initiatives, and it can also be an important step on the way to regulatory convergence as provided by the ICH standards.

In the past decade, subregional regulatory initiatives, which are linked to regional economic communities (RECs), contributed to regulatory harmonization. In 2009, the African Medicines Regulatory Harmonization (AMRH) initiative under the leadership of the AUDA-NEPAD (African Union Development Agency-NEPAD) was launched to encourage harmonization of regulatory requirements, strengthen regulatory capacity, and accelerate access to medicines. AMRH is a platform to support health product regulation in RECs, and evidence indicates that it has contributed to faster product registration. Sithole and colleagues showed that ZAZIBONA members were able to shorten approval times because they relied on reference agencies and used verification and abridged review models for the assessment of applications for registration rather than full reviews.[152] An earlier study found that the ZAZIBONA initiative was able to reduce the median timeline from dossier submissions to national market authorization to less than one year.[156] Other studies found that the AMRH helped to shorten registration timelines from 2-7 years to less than one year in the East African Community (EAC).[157,158] PATH also conducted a modeling study to estimate the potential health impact of regulatory harmonization in selected EAC and SADC countries.[159] The model estimated that launching two medicines two years earlier through harmonization—heat-stable carbetocin for postpartum hemorrhage and amoxicillin dispersible tablets for childhood pneumonia—could save about 23,000 lives compared to a non-harmonized scenario.

These studies show that harmonization and reliance mechanisms, such as the use of reference agencies and joint reviews, can accelerate market authorization by limiting duplicative assessments. Reliance is an emerging trend to make regulatory processes more efficient; it is recommended by WHO[160,161], and is seen as a key concept by the private sector.[162] KIs from both the public and private sectors emphasized the positive experiences of regional harmonization initiatives, such as AMRH. At the same time, they highlighted the untapped potential to deepen harmonization. For example, they emphasized the lack of legislation for reliance in countries that also do not have capacity to fulfill the range of regulatory functions. They mentioned that the implementation of reliance is often done poorly. These KIs thus recommended stronger collaboration between WLAs/tWLAs and NRAs using the concept of reference agencies. In this context, there are also studies that question the continuing importance of the WHO CPP. Sithole et al found that five of the six countries analyzed require the WHO CPP. The authors recommended that countries should review the need for the CPP where there is capacity to conduct full reviews.[152] A study by Rodier et al showed that 16 out of 18 NRAs require CPP approval (the authors also question the need for the CPP in all of these countries).[163] Another challenge highlighted by our KIs is the poor coordination between regulatory agencies and ethics committees, leading to delays for product registration and also for clinical trial approval.

Overall, while there are still substantial gaps and barriers to rapid and effective regulation in LMICs, especially in SSA, the evidence indicates that African harmonization initiatives have contributed to regulatory efficiencies. Similar harmonization initiatives have emerged across other regions, such as the Pan American Network for Drug Regulatory Harmonisation and the South-East Asia Regulatory Network.[164] These provide important entry points to further deepen regulatory harmonization and reliance.

STRENGTHENING REGIONAL AND NATIONAL REGULATORY CAPACITY

While harmonization and reliance mechanisms appear to be successful strategies to bring efficiencies to regulatory processes, NRAs need further strengthening. LMICs need to fund their own NRAs and use the GBT process, which offers an important opportunity to measure and strengthen regulatory capacity. However, creating this capacity takes time and resources. For example, it took Nigeria four years to reach GBT maturity level 3 for medicines and vaccines (importation only, without production). Countries like Bangladesh and Rwanda, which underwent their first GBT assessments in 2016 and 2018, respectively, have still not achieved maturity level 3. Going forward, it will be important that WLAs and tWLAs from HICs provide more support to NRAs in LMICs. In Africa, countries with NRAs operating at ML3 should also collaborate with other countries. For example, Tanzania, which has an ML3 NRA, supports Rwanda's NRA.[165] Regional initiatives, such as the AMA, require more support from donors to ensure that the agency can effectively perform core regulatory functions. KIs emphasized that the AMA needs to play a key future role for the continent, including to allow for better access to complex drug therapies.

KIs argued that there are at least four major challenges that need to be addressed. First, there is a lack of expertise and human resources in the regulatory system. Second, NRAs may engage in too many unnecessary activities, e.g., the testing of a huge number of batches. Third, there is a challenge to enforcement – the interests of the wider government may conflict with the work of the NRA, undermining efforts that are needed to ensure safety and quality. It is a GBT requirement that NRAs can function independently. Fourth, another issue that is not fully under the control of the NRA relates to pharmacovigilance – the required post-introduction data need to come from the health system (hospitals, primary health care centers, etc.) and underreporting can affect a country's regulatory performance as measured by the GBT. This data collection is not entirely outside the control of NRAs—they can work with other health system actors to improve reporting and they can mandate market authorization holders to collect and report evidence. Nevertheless, the collection of sufficient quality data also relies on the ability of the wider health system.

LMICs need to invest more in their NRAs and use their Global Benchmarking Tool (GBT) to measure and strengthen their regulatory capacity.

The literature also highlights the need to strengthen regional and national regulatory capacity. As pointed out by Greenhoe and Guzman, there is a specific need to build regulatory capacity in those countries that aim to establish vaccine manufacturing capacity: "Of the 14 African countries where manufacturing projects have been announced, only two—Egypt and South Africa—have NRAs operating at ML3 for producing vaccines."[111] In vaccine manufacturing countries, strong NRAs will be needed to assure product quality and efficacy.[166] NRAs at ML3 or 4 are needed to qualify for WHO prequalification, and many countries legally require WHO PQ before the introduction of new vaccines. UNICEF, as the procurement agent for Gavi, also requires WHO PQ, as does the Global Fund. The WHO PQ process was introduced to support the Expanded Program on Immunization, i.e., at a time when regulatory systems were very weak across most LMICs. To a certain extent, this has changed. Today, there are more SRAs and, since the introduction of the GBT, about 10 countries have achieved ML3. While the WHO PQ system is currently still needed, there should be more flexibilities. Countries and global procurement agencies (e.g., UNICEF) should increasingly accept reviews from SRAs as an alternative to WHO PQ, which itself can be complicated and lengthy. Any initiative that aims to increase vaccine manufacturing capacity in LMICs should include a strategy for the strengthening of regulatory capacity through technical and financial assistance. Vaccine production plans need to go hand in hand with NRA strengthening. For example, Rwanda aims to produce mRNA vaccines in the near future, but it is still at ML2 and does not qualify for WHO PQ. However, Rwanda is currently also bolstering its NRA and may become a good example of developing both capacities together.

DIAGNOSTICS

LMICs, and particularly LICs, are less likely to have functional regulatory systems for medical devices, the category under which pathology and laboratory medicine diagnostics and diagnostic imaging devices fall. This impedes the ability of LMICs to conduct pre-market evaluation, ensure quality and safety, and perform post-marketing controls.

In addition, diagnostics have their own unique approvals process, which can be complex. For example, the European Union Medical Device Regulation led to a backlog of medical devices that required approval.[167] Some regulatory bodies lack capacity (WHO PQ), while others do not cover diagnostics (EMA). There is also no organization working to convene and synergize efforts around diagnostics regulation globally. At the regional level, the African Medical Device Forum brings together experts in collaboration with Africa CDC to address the issue. Like vaccines and therapeutics, diagnostics also need common, cloud-based platforms for sharing master files and data.

LESSONS FROM COVID-19

The COVID-19 pandemic led to the introduction of a range of regulatory agilities that aimed to accelerate development and authorization of COVID-19 control tools. For example, measures adopted by the EMA for the development, authorization, and monitoring of COVID-19 treatments and vaccines included:

- **Rapid scientific advice and review**: review time was reduced from 40-70 days to 20 days.
- **Rolling reviews**: an ad hoc process for continuous assessment of data for highly promising products.
- **Accelerated marketing authorization and temporary exemptions** to expedite access to COVID-19 products.
- **PRIority MEdicines scheme (PRIME)**, which was used to enhance R&D for COVID-19 treatments and vaccines.
- **Remote source data verification** for monitoring of trials.

The COVID-19 pandemic also increased regional harmonization. For example, the African Union (AU) launched the African Union-Smart Safety Surveillance (AU-3S).[168] African NRAs used the AU-3S to quickly implement or enhance ongoing safety surveillance protocols and activities for COVID-19 vaccines. Chong et al reviewed progress in regulatory convergence in the Asia-Pacific region during COVID-19 across four areas of best practice.[169] As described further below (see Section 7.3.2), their study concluded that convergence efforts accelerated medical product availability. Geraci et al provide an industry perspective: "Standard regulatory frameworks during normal times can be enhanced by leveraging digitalization, further simplifying and harmonizing requirements, and using reliance mechanisms which can help to increase efficiency in regulatory decision-making regarding medicinal products."

KIs interviewed for this study argued that many of the regulatory innovations triggered by COVID-19 are no longer in use and that it would be valuable to assess which ones should be retained. The African Vaccine Regulatory Forum (AVAREF), for example, was used for accelerated authorization of vaccines by Africa countries following the WHO Emergency Use Listing Procedure. This platform is still in place and run by WHO AFRO. It is very likely that digitalization is one of the advances that should become routine worldwide.

6.4 Summary and suggested ecosystem changes

Strong regulatory systems are key to accelerating the introduction of new health tools in LMICs, and they are also a critical determinant to successfully expanding regional manufacturing capabilities. In this section, we have shown that approval times in LMICs can be significantly reduced through regional harmonization and reliance mechanisms. If these strategies were to be applied more rigorously, market authorization of—and thus access to—new health tools could happen on a similar timeline as in HICs. We suggest three broad ecosystem changes:

1. Harmonization and reliance. Existing evidence indicates that regulatory harmonization and reliance are key means to achieve regulatory efficiencies. Some African RECs have made great progress in this regard and other initiatives should learn from their examples. Rather than duplicating existing reviews, reliance mechanisms, such as the use of reference agencies, should be expanded and become standard operating procedure – for both NRAs and WHO PQ. CPP continues to be highly important for many countries, as, for example, shown by Rodier et al (in their study, 16 out of 18 NRAs require CPP approval).

2. Strengthening regulatory capacity in LMICs. While regional harmonization and reliance are important, regulatory capacity in LMICs needs to be strengthened. Global health donors should provide support to regulatory hubs, such as AMA, which can serve as WLAs/tWLAs and promote cooperation and mutual recognition of regulatory decisions. WLAs/tWLAs should partner with LMIC counterparts to conduct joint inspections, twinned regulatory reviews, and other capacity-building activities.

3. Strengthening NRAs is also important for countries that are currently building manufacturing capacity. As highlighted by Greenhoe and Guzman, WHO PQ is the only regulatory pathway for Gavi support through AVMA.[111] However, vaccine manufacturers can only apply to WHO PQ if the country of the manufacturer has a regulatory authority that has reached at least ML3. Going forward, it will be critical, say the authors, to establish "alternative, viable regulatory pathways." These alternatives may include WHO-listed authorities or capacities within regional or sub-regional mechanisms, such as AMA. Currently, some of these mechanisms lack sufficient regulatory capacity, so it will be important to strengthen them and to recognize them as future regulatory pathways. Gavi should be open to alternative regulatory pathways, such as formal collaborations between African NRAs and WLAs/tWLAs. Such pairing arrangements could address the short-term capacity issues and contribute to the capacity building of selected African NRAs. An example of such a strategy is a European Commission-funded project that supports Rwanda's FDA.[170]

SECTION

7

FINANCING AND GOVERNANCE

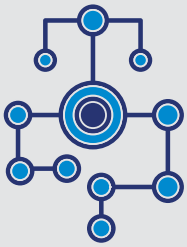
FINANCING AND GOVERNANCE

KEY BENEFITS:

- **Financing innovations have played an important role in supporting R&D**. Financial instruments, such as priority review vouchers (PRVs) and volume guarantees, have played an important market shaping role for neglected disease R&D and access to new health tools.
- **Regional governance mechanisms are becoming increasingly important**. While the COVID-19 pandemic showed that the world's response was too centralized, it also led to the emergence and strengthening of regional R&D governance initiatives.

KEY CHALLENGES TO BE ADDRESSED:

- **There is too little funding for R&D for NDs, EIDs, and MH**. R&D funding for NDs peaked at US$4.6 billion in 2018 but has been on a downward trend since then (to US$3.9 billion in 2022). Funding for EIDs R&D has substantially increased, but the increase was mostly due to the COVID-19 pandemic. While funding for SRH R&D grew from 2018 to 2021 (totaling US$593 million[7] in 2021), only a small share of this funding was for MH tools and the share declined over time. Funding from industry only accounts for a small share of funding for R&D for NDs, EIDs, and MH, and while there has been a recent increase in domestic LMIC funding for such R&D, the absolute amount remains very small.
- **The 100 days mission is under-funded**. Despite the substantial benefits of health innovations, there remain substantial funding gaps for NDs, EIDs, and MH. This gap became apparent in CEPI's 2022 replenishment. Even after the worst pandemic in a century, donors did not provide the US$3.5 billion requested by CEPI for its "100 days mission".



SUGGESTED ECOSYSTEM CHANGES:

Financing

- **A priority review voucher (PRV) should be created in Europe, hosted by the European Medicines Agency**. An EU voucher would provide an additional incentive of US$100million-US$200 million, which investors say would be a meaningful stimulus.
- **Volume guarantees should remain a key mechanism to promote access to new health tools**. There needs to be new thinking on how to best expand the use of these guarantees while managing associated risks (overreliance on such guarantees can create a moral hazard).

- **Rather than only targeting individual research projects, such as clinical trials, R&D funders also need to invest in the underlying research system**. A system-wide approach would include investments in clinical trial infrastructure, capacities for drug discovery and preclinical research, and local manufacturing.
- **LMIC governments need to increase their own funding for health R&D. This will be important to advance product development for NDs, EIDs, and MH.**

Governance/priority setting:

- **The overarching R&D ecosystem would be improved by stronger regional priority setting and the creation of regional and sub-regional hubs for clinical trials, regulatory systems, and product manufacturing**. The coordination gap is especially large for therapeutics.

In this section, we discuss trends in R&D funding (section 7.1), the evidence on resource mobilization mechanisms for R&D (section 7.2), and ways to improve the governance of global health R&D (section 7.3).

7.1 Trends in R&D financing for NDs, EIDs, and MH and the respective pipelines

In this section, we analyze funding trends for product development for NDs, EIDs, and MH and review the candidate products that are in the pipeline, using data from Policy Cures Research.

NDs: R&D FUNDING AND PIPELINE

Funding

Annual funding for PRND R&D increased from US$3.7 billion in 2013 to US$4.6 billion in 2018, then fell to US$4.4 billion in 2021 (Figure 3).[171] In 2022, funding dropped by another 10% compared to the previous year, down to US$3.9 billion, the lowest level since 2016. However, this large fall is accounted in part by global inflation eroding the real value of R&D funding.[172]

Funding for HIV R&D accounted for 34.4% of this funding, totaling US$1.6 billion in 2022. TB and malaria accounted for 17.9% and 15.4%, respectively, which means that HIV, TB, and malaria received more than two-thirds (67.6%) of R&D funding for NDs in 2022.

Between 2007 and 2022, two-thirds (66.5%) of R&D funding for NDs came from public sources; the US National Institutes of Health was the largest public funder (46.2% of all funding). While the data, which are collected through an annual survey, may underestimate funding from LMIC sources, there is very little investment in R&D on NDs by LMICs. Philanthropy accounted for 20.6% of all funding between 2007 and 2022, with most of the philanthropic funding coming from the Bill & Melinda Gates Foundation (18.0% of all funding). Industry only accounted for 12.9% of all funding (Figure 3).

In summary, funding for R&D on NDs:

(i) has declined since 2018 and further dropped in 2022,

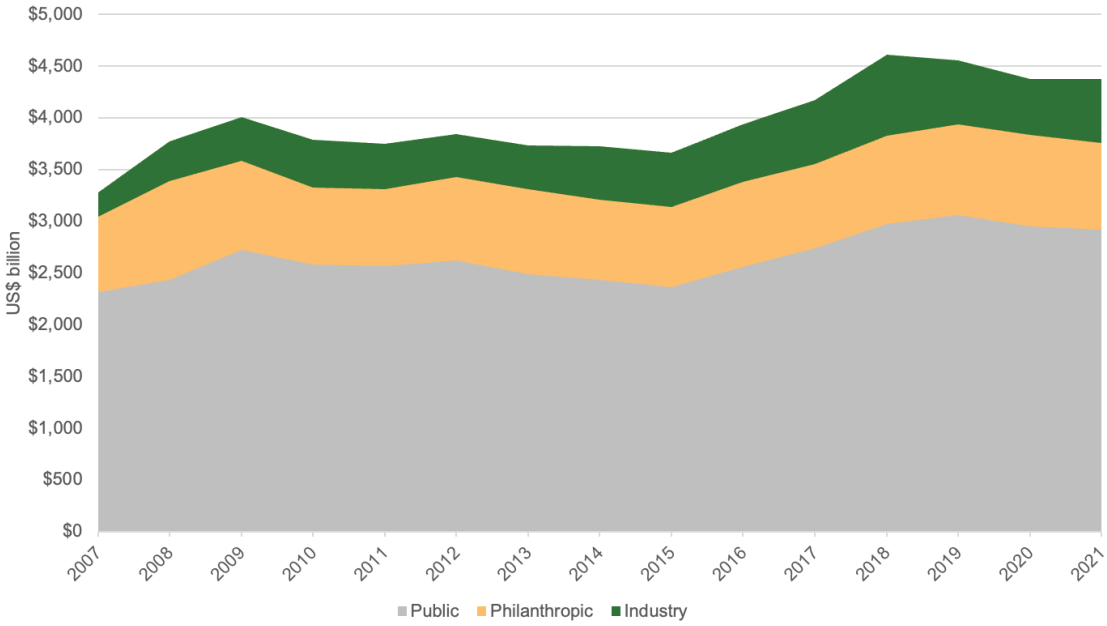
(ii) remains heavily focused on HIV, TB, and malaria,

(iii) relies on a few public and philanthropic donors,

(iv) receives limited funding from industry, and

(v) involves very low levels of investment from LMICs.

Figure 3. Funding for R&D on NDs by funder type



Pipeline

New cutting-edge solutions are on the horizon. According to Policy Cures Research, the innovation pipeline to tackle neglected diseases has grown by 27% since 2019.[8] Two malaria vaccines were launched in 2021 and in 2023.Three TB vaccines candidates have now entered late-stage trials: (i) M72, a fusion protein of two *M. tuberculosis* antigens administered with a potent adjuvant; (ii) VPM 1002, a next-generation, genetically modified BCG vaccine, and (iii) MTBVAC, an *M. tuberculosis* strain attenuated via two genetic mutations. Still, many key products are missing and the pipeline is totally empty for others. For example, the pipeline lacks preclinical and clinical vaccine candidates for cryptosporidiosis, multiple helminth infection, sleeping sickness, and strongyloidiasis as well as drug candidates for hookworm, lymphatic filariasis, multiple Salmonella infections, non-typhoidal *S. enterica*, scabies, strongyloidiasis, and tapeworm.

EIDs: R&D FUNDING AD PIPELINE

In 2019, R&D funders provided US$1.5 billion for R&D on EIDs. Due to the COVID-19 pandemic, funding for R&D on EIDs increased substantially to US$7.6 billion and US$7.7 billion in 2020 and 2021, respectively. In 2022, funding dropped to US$5.8 billion. **These trends highlight four challenges**.

1. First, funding for COVID-19 R&D drove the increase in EID R&D funding. Of the US$21.1 billion for EID R&D, 81% (US$17.0 billion) was for coronaviral diseases, and R&D for many other EIDs remains under-funded.[173]
2. Second, funding for vaccines is about twice as high as funding for diagnostics and therapeutics (US$2.7 billion for vaccines vs. US$1.4 billion for diagnostics and therapeutics in 2022).
3. Third, EID funding is highly reactive. The world has not yet adopted a preparedness approach and the drop in funding in 2022 may be considered as a good proxy that we are already in a phase of neglect.
4. Fourth, funding is overly reliant on the US government, with 66.5% of all EID R&D funding in 2022 coming from US agencies. This lack of diversify puts sustainable funding at risk.

Only COVID-19 and Ebola (the Zaire and ebolavirus species) have a full set of approved drugs, vaccines, and diagnostics, and these are not available to patients in all countries who need them. Diagnostics are only approved for Crimean-Congo haemorrhagic fever, Rift Valley Fever, Lassa and Zika, none of which have been approved in endemic countries. Other priority pathogens have no approved MCMs at all.[174,175] When it comes to candidates that have reached the clinical trial phase, the reactive nature of R&D means that pathogens that have caused recent outbreaks (and are thus perceived as a greater threat) have a more mature pipeline (the pipelines for COVID-19, Ebola, and Zika are mature). However, with the exception of COVID-19, all vaccines and therapeutic candidates are in phase 1. Even the preclinical pipeline is empty for many of the Blueprint diseases, which highlights the need to invest in preclinical research using AI.

MATERNAL HEALTH: R&D FUNDING AND PIPELINE

In 2021, total funding for SRH R&D was US$593.7 million.[176] In the same year, R&D funding for sexually transmitted infections, excluding HIV, hepatitis B, and potentially sexually transmissible infections (e.g., hepatitis C and Zika virus), totaled $146.3 million. In addition, US$142.5 million was spent on R&D for human papillomavirus (HPV) and HPV-related cancers, US$93.0 million on platform technologies, US$49.9 million on multipurpose prevention technologies, and US$23.6 million on other R&D areas (including core funding).

Only a small share of R&D funding was allocated to maternal health. R&D funding for preeclampsia and eclampsia (PE&E) totaled US$20.7 million in 2021, though it saw a 25% reduction in funding from 2020 to 2021. Between 2018 and 2021, US$101 million was spent on PE&E, with basic research consistently accounting for about 60% of spending. Funding for postpartum hemorrhage (PPH) has fallen since 2018, with a 56% reduction between 2020 and 2021. The total spending on R&D for PPH between 2018 and 2021 was US$16.0 million, with US$0.9 million spent in 2021. While SRH funding overall has been on the rise, increasing by about 50% since 2018, funding for maternal health R&D fell by 15% since 2018. This disparity in R&D investment reflects a focus on HIC markets, where the burden of maternal health challenges is lower than in LMICs.

The 2022 Access to Medicine Index, which tracks the engagement of the 20 largest pharmaceutical companies, found that "five diseases and conditions are not addressed at all by any R&D project. Conditions related to maternal health are especially underrepresented, with just four projects split between maternal hemorrhage and maternal sepsis."[177,178] PPH is the leading cause of maternal deaths. Currently, treatment for this condition requires intravenous or intramuscular administration of oxytocin by a skilled healthcare worker. A new formulation is needed that is both heat stable and can be easily and quickly administered as an alternative. Companies covered by the Access to Medicine Index have no R&D projects to address this need. Another key gap in R&D for maternal health is for diagnostics for preeclampsia. None of the companies covered by the index have projects addressing this gap.[179] A Policy Cures Research report on R&D for SRH confirms that there are substantial gaps for pre-eclampsia, PPH, and sexually transmitted infections particularly hepatitis B, herpes simplex virus type 2, chlamydia, gonorrhea, syphilis, human T-cell lymphotropic virus type 1 (HTLV-1) and HIV/AIDS. There are other major R&D gaps for women's health that we do not discuss here, including for HPV-related cervical cancer.

R&D FUNDING GAPS

In previous studies, we tried to estimate funding gaps for R&D on NDs. Using the 2019 PRND R&D pipeline, in 2020 we published a study that suggested that that there was an annual product development funding gap of up to US$2.6 billion.[6] We also estimated that the total annual resource needs for late-stage trials of product candidates for NDs were US$1.72 billion, while only about US$700 million was being spent on Phase 3 trials. As such, we argued that there was an annual funding gap of at least US$1.0 billion specifically for late-stage clinical trials.[180] Our new modeling paper led by Ogbuoji provides an updated R&D funding gap analysis for NDs. It also assesses the R&D funding gap for EIDs and MH.[1]

Many reports have identified the need for new for funding for PPR and more specifically for R&D for EIDs in the wake of the COVID-19 pandemic. CEPI called for US$3.5 billion for its "100 days mission," which is part of CEPI's five-year (2022–2026) pandemic plan. While the 100 days mission has been endorsed by the G7, G20, and other governments, the global community failed to provide the requested funding to essentially break the cycle of panic and neglect—the replenishment fell short of the target (only US$1.5 billion was raised at the pledging event).[181,182] From an R&D perspective, CEPI plays a key role for PPR. However, breaking the cycle requires support for other rapid response technologies, including diagnostics. FIND estimates that it needs US$80-100 million for its 100 days mission diagnostics framework. The Pandemic Fund, which will likely not invest in R&D, has also only secured about US$2 billion so far and thus it is falling far short of the ambitious target of US$10.5 billion in international financing per year indicated as the required level by the G20 High-Level Independent Panel.[184,185]

7.2 Evidence on resource mobilization mechanisms for R&D on NDs, EIDs, and MH

The large, rapid rise in funding to develop COVID-19 tools showed how quickly HICs can mobilize significant amounts of funding for new health tools when their own populations are affected by global health threats. The pandemic also showed the potential of the global pharmaceutical industry in the development of new tools. Within just 326 days, the first safe and effective vaccines were being rolled out to begin to reduce cases of severe disease and COVID-19 death rates. However, we have not seen a similar level of engagement when it comes to R&D for diseases of poverty. Indeed, as indicated by the Access to Medicine Index, there is limited progress in the NDs pipeline of companies.[178] Most ND candidates get stuck in early R&D stages (preclinical; Phase 1) and do not progress into more advanced clinical stages, which account for the lion's share of the costs (Annex 3). In this section, we discuss mechanisms to mobilize additional funding for ND research.

INCENTIVIZING INDUSTRY ENGAGEMENT: PRIORITY REVIEW VOUCHERS (PRVs) AS AN R&D INCENTIVE

In 2007, the US Congress and the FDA introduced the "Tropical Disease Priority Review Voucher Programme to encourage product development (therapeutics and vaccines) for neglected diseases."[186] Voucher eligibility was expanded to rare pediatric diseases and for MCMs in public health emergencies in 2012 and 2016, respectively. PRVs are a pull incentive to reward developers of a new health product for an eligible neglected or rare disease with a tradeable voucher that grants priority review of a second product candidate. The US voucher entitles the developer to regulatory review in six months rather than the standard ten months. In addition, two drugs receive priority review: the drug winning a voucher for an eligible neglected or rare pediatric disease, and the drug using a voucher for another indication (e.g., a blockbuster drug for the US market). The potential for additional revenue from marketing a blockbuster drug four months sooner is an incentive for companies to develop drugs for neglected diseases. In addition, the developer can sell the voucher—a small company may win a voucher for developing a drug for a neglected disease and sell the voucher to a large company for use on a commercial disease. As such, PRVs can help to incentivize the development of new health tools for neglected diseases, while they may also accelerate the approval of potential blockbuster therapies in the US.

More than 60 priority review vouchers have been awarded since 2007. Vouchers were sold for about US$100 million each.

What do we know about the effectiveness of PRVs, as of March 2024? Research on the US voucher program points to four benefits. First, more than 60 vouchers have been awarded since 2007, roughly four per year, which indicates that the prospect of accelerated marketing of a commercially viable product draws industry interest.[186] Second, vouchers were sold for about US$100 million each, showing that the financial incentive is also substantial.[187,188] Third, the US voucher has yielded multiple concrete benefits. It contributed to the development of a drug for river blindness, provided commercial incentives for continuation of a new TB drug, and helped enable patient access to a Chagas drug through the sale of a voucher. Fourth, the accelerated regulatory pathway itself may contribute to faster access to the drug and as such may have a positive public health impact.[189] In addition, there is no evidence from the US voucher program that the accelerated regulatory pathway negatively impacted on the quality of product.

Nevertheless, the true incentive effect of the US voucher remains debated. First, a report by the US Government Accountability Office (GAO) from 2020 questioned whether the voucher has rewarded research that would have been conducted anyway even without the voucher. It concluded that existing studies found little effect of the PRV on drug development, but it also reported that "all seven drug sponsors GAO spoke with stated that PRVs were a factor in drug development decisions—six sponsors said they were one of a number of factors, while one sponsor said they were pivotal in its development of a drug."[190,191] Second, the amount that vouchers are selling for (about US$100 million) is less than the overall drug development costs.[192] Some investors thus indicated that US$100 million is no longer sufficient as an incentive – if that is correct, the voucher might be most useful to pull through drugs that have already started development.

We agree with David Ridley at Duke University, one of the researchers who proposed the creation of the PRV in 2006, that the PRV should be introduced in Europe, hosted by the European Medicines Agency (EMA).[187,193] An EU voucher would provide an incentive of US$100 to US$200 million, so the combined value of the US and EU vouchers would be in the range of US$200 to US$300 million, which investors say would be a meaningful stimulus. In addition, Ridley and colleagues argue that an EU voucher could cut regulatory times by six months.

An EU voucher program should involve the obligation for developers to provide detailed access plans. In addition, the voucher program should have stringent eligibility criteria to ensure that the focus is on NDs and to reward research that would not have been conducted without the stimulus. Finally, the program should be embedded in a larger strategy for stimulating research rather than being a standalone solution. An EU voucher should be integrated with the PRIority MEdicines scheme (PRIME) and the EUM4all programme, a coordinated mechanism between EMA, the WHO, and national regulators, providing a scientific opinion on high priority human medicines for use outside the EU.

VOLUME GUARANTEES TO INCENTIVIZE MANUFACTURING AND LOWERING PRICES

In the past, volume guarantees played an important role in creating sufficient incentive to manufacture health products. There are many successful examples of volume guarantees in global health. For vaccines, one example is a volume guarantee in 2012 for the production of the pentavalent vaccine by an Indian producer, which led to substantial cost savings for Gavi.[194] For HIV, a volume guarantee to two manufacturers allowed the transition to a newer combination of HIV therapies in 2016/17 (from tenofovir, lamivudine, and efavirenz [TLE] to tenofovir, lamivudine, and dolutegravir [TLD]). Millions of people had access to this new drug combination due to the price reduction generated by volume guarantees.[195,196,197] For malaria, a four-year volume guarantee for innovative bed nets that combine pyrethroid and chlorfenapyr insecticides led to a reduction in price by two-fifths.[198] More recently, there were also volume guarantees for COVID-19 vaccines and therapeutics.[199]

Volume guarantees should remain a key mechanism to promote access to new health tools. There needs to be thinking on how to best expand the use of these guarantees while managing associated risks. For example, there is a risk of overreliance on such guarantees and creating a moral hazard.[198]

DOMESTIC FINANCING FOR R&D BY MIDDLE-INCOME COUNTRIES

Domestic funding for R&D on NDs, EIDs, and MH from LMIC governments remains highly limited according to the data from G-FINDER.[173] Many countries will not have the capacity to increase these investments over the short-term. For example, low-income countries accounted for only 0.24% of global health expenditures, despite having 8% of the world's population, according to the WHO's 2023 Global Health Expenditure Report.[200] Middle-income countries face additional challenges, such as slowing economic growth, high inflation, and increased debt servicing obligations, as recently highlighted by the latest report of the Lancet Commission on Tuberculosis.[201]

Still, increased domestic investment in R&D platforms, regulatory systems, and manufacturing by middle-income countries is critical to advancing the R&D ecosystem. Existing evidence indicates that these investments pay off. For example, an upcoming study on the vaccine security and self-reliance initiative of the Association of Southeast Asian Nations (ASEAN) finds that coordinated investments at the regional level could avert up to 61.5 million disability-adjusted life years (DALYs) and 1.9 million deaths in ASEAN by 2040, with economic returns outweighing investments by a factor of 35.[86] This modeling was based on five NDs and an additional outbreak scenario, simulating an outbreak of a magnitude similar to the COVID-19 pandemic in the 10 ASEAN countries. ASEAN can also serve as an interesting example because the 10 member countries have different income levels. Countries with higher income levels can take a leading role in upgrading the existing ecosystem, considering their investments as a contribution to a regional public good.

Coordinated investments at the regional level could avert up to 61.5 million disability-adjusted life years (DALYs) and 1.9 million deaths in ASEAN by 2040, with economic returns outweighing investments by a factor of 35.

AFFORDABILITY REQUIREMENTS/IP WAIVERS

In a recent analysis paper in the BMJ, Suleman and colleagues acknowledge the contributions of push and pull mechanisms and pooled funding approaches, but argue that these mechanisms are in themselves insufficient to ensure fair pricing.[202] They argue that governments and other R&D funders should insist on binding affordability requirements as a condition of all R&D to ensure fair pricing of medicines.

HOW R&D FUNDING SHOULD FLOW – THE NEED TO INVEST IN FUNDAMENTAL R&D SYSTEMS

LMIC representatives interviewed for this study emphasized the need to move away from funding individual research projects, such as clinical trials, to invest in the underlying research system. A system-wide approach would include investments in clinical trial infrastructure, capacities for drug discovery and preclinical research, and local manufacturing. LMIC interviewees emphasized that fragmented project-by-project funding has heavy transaction costs and is both unpredictable and unsustainable.

In addition, ownership of LMICs in research projects is often limited. LMIC representatives highlighted the need to sustainably strengthen the underlying R&D system through the provision of long-term funding, which will enable countries to conduct their own R&D in the future. Indeed, a recent analysis of grant investments by 10 of the world's largest international funders of health research shows significant differences in resource allocation across countries. Adam and colleagues note that: "In 2020, out of grants totaling US$ 37 billion, low-income countries (LICs) received only 0.2% (US$ 85 million). Lower-middle-income countries (LMICs) and upper-middle-income countries (UMICs) received each 0.5% (US$ 188 million US$ 193 million, respectively).[203]

7.3 Governance

7.3.1 Global coordination efforts

For PPR, the evaluation of the Access to COVID-19 Tools Accelerator (ACT-A) found that the ACT-A agencies working on R&D did not sufficiently coordinate their R&D efforts across and to some extent within the pillars. The evaluation recommended enhanced coordination through three permanent MCM structures for each product type, with defined leads for diagnostics, therapeutics, and vaccines. In addition, it recommended that a joint platform should be established to coordinate the work across the three product areas. The discussion has been taken forward – led by WHO, there is now discussion on an interim coordination mechanism to enhance collaboration for timely and equitable access to MCMs against pandemic threats.

While the ongoing discussion on the interim MCM platform is critical, it does not cover the coordination for other global health R&D needs. As highlighted elsewhere,[180] LMICs must be included in R&D prioritization processes, including prioritization across product types and diseases/conditions. Our KIs indicated that TPPs and PPCs are useful, but these are often outdated. In addition, evidence indicates that the actual candidates in the pipeline do not align sufficiently with the TPPs. This mismatch also highlights the need for better health R&D data sharing, particularly on R&D investments and capacity, to enable better coordination and informed decisions. The Global Observatory on Health R&D may be able to support this effort by serving as a platform to track and analyze relevant health R&D data and document progress in key indicators over time.

7.3.2 Regional R&D ecosystems

We conducted three regional consultation processes in Africa, Asia, and Latin America to better understand the key needs of the three regional R&D ecosystems. The aim of these consultations was to throw a spotlight on major themes across the regions. More details on the regional R&D ecosystem can be found in Annex 5.

THE NEED FOR PRIORITIZATION AND COORDINATION AT REGIONAL LEVEL

Coordination and prioritization at regional level need to play an increasingly important role, feeding into global coordination. For example, Africa CDC has recently published its first list of priority pathogens, including a risk ranking and analysis of areas such as risk trajectory, epidemic potential, disease severity, and preparedness.[204] At the same time, African stakeholders who we interviewed reported that there is a need for stronger structured processes to determine regional health R&D priorities. These stakeholders also recommended that regional R&D coordination and priority setting should build on national R&D priorities.

For Asia, KIs emphasized that countries are characterized by significant political, economic, cultural, and health-related differences, which makes R&D coordination very complex. Still, the KIs argued that stronger regional R&D coordination would be useful and called for regular analysis of the R&D pipeline. Such analysis, they said, should include technology assessments, feasibility studies, eliciting expert opinions, understanding changes in patient demand, and other indicators. They also argued that AI tools should be used to predict product pipeline developments and to eventually ensure the development of needed technologies over the next two decades. Latin American stakeholders pointed to several significant coordination challenges, including political tensions between countries. KIs believed that Latin American countries even failed to collaborate during the COVID-19 pandemic due to diverging political views. Latin American KIs also considered existing R&D capacity as limited and were concerned about a lack of R&D culture among policymakers.

THE NEED FOR REGULATORY HARMONIZATION AND CAPACITY BUILDING

In Section 5, we described the urgent need to further strengthen African regulatory systems and to support regional regulatory harmonization initiatives on the continent. In Latin America, KIs described important steps towards strengthened and harmonized regulatory systems, highlighting the useful role of the Pan American Health Organization (PAHO) in this process. However, stakeholders also mentioned that PAHO needs to show even stronger leadership and support to foster harmonization and stronger NRAs. For example, only about a quarter of the 35 PAHO member states have established comprehensive legal bases and organizational frameworks for regulation (see Annex 5 for details). Countries are considered as "overprotective," which often results in duplicative processes, according to our KIs. Countries also tend to "hyperregulate" rather than trying to optimize existing processes. Some KIs mentioned that governments at times threaten the autonomy and independence of NRAs. One major recommendation for Latin America was stronger collaborations with international regulatory initiatives, such as ICH, to further improve regional and national systems.

For Asia, KIs argued that the region has seen progress in terms of regulatory harmonization, which is also indicated in a study by Chong et al.[169] The study found that from 2008-2020, there was a 14% increase in the number of APEC (Asia-Pacific Economic Cooperation[205]) members' regulatory authorities sharing GMP certificates and a 28% increase in the number of regulatory authorities accepting multisite licenses. However, the capacities of NRAs vary widely across Asian countries. In addition, the KIs reported that regulatory agencies have difficulties keeping pace with rapidly evolving global clinical guidelines and statistical designs. KIs recommended that Asian NRAs should learn from European and American countries to improve regulators' understanding, professional ability, and knowledge of specific products and technology fields. In addition, governments should adopt a more innovation-friendly approach rather than focus only on constraints and restrictions. Chong et al recommend that APEC should pilot a regional reliance program, including a mechanism that coordinates multiple regulators to jointly reach regulatory decisions.[169]

Only about a quarter of the 35 PAHO member states have established comprehensive legal bases and organizational frameworks for regulation.

THE NEED TO STRENGTHEN REGIONAL MANUFACTURING CAPACITY

As highlighted in Section 4 above, there are multiple coordinated efforts on the way to strengthen manufacturing capacity and expertise in Africa. The African Union has taken a strong leadership role and, with Africa CDC and AMA, there are also strong technical regional leads. While many hurdles still need to be overcome, building up manufacturing capacity for all product types is of critical importance to the region. For Asia, KIs pointed to the significant differences between Asian countries in terms of manufacturing capacity. While China and India have comparatively strong capacity, manufacturing capabilities of many other Asian countries is much more limited or even non-existent. For example, certain ASEAN countries (Indonesia, Thailand, and Vietnam) have strengthened their vaccine manufacturing capacity, including for COVID-19 vaccines, through fill and finish arrangements, a significant asset for building regional vaccine security. However, despite these growing manufacturing capacities, the existing ASEAN vaccine production is far from meeting the demand of ASEAN for their routine immunization programs and emergency response.[86] Consulted KIs pointed to the need for much more international cooperation and tech transfer agreements.

Experts from Latin America argued during the consultations that the region remains strongly reliant on Western producers, which became apparent during the COVID-19 pandemic. The supply of essential materials poses a significant challenge, with supply shortages and sustainability of reagents being considered as major concerns, among others. KIs encouraged greater local production of supplies, reagents, and key health technologies. They argued for government subsidies, partnerships with private companies, and investments in local manufacturing to ensure sufficient capacity to produce key health technologies. Such a shift will also require training local scientists and other personnel to strengthen the region's self-sufficiency. Finally, KIs in Latin America recommended greater regional collaboration to share resources and knowledge, and collectively negotiate better access to health technologies.

THE NEED FOR EQUITABLE AND SUSTAINABLE FINANCING

African KIs emphasized the need to move away from funding individual research projects towards investment in the underlying research system. They also argued that more domestic funding for health R&D is needed. African governments, they said, should inject a much larger proportion of domestic funds into R&D value chains and ecosystems, including into capacity building. Improving the R&D ecosystem in Africa will require human capacity development, including in innovation and manufacturing relevant to the continent, so that all the necessary human resources are in place along the whole value chain.

Latin American stakeholders argued that there is a notable lack of funding for R&D, and that health R&D investments by Latin American countries significantly lag behind other regions. Thus, they also highlighted the need for more domestic R&D funding.

For Asia, KIs argued that the obstacles faced in healthcare innovation are multifaceted. Industry representatives highlighted that costs of new medicines might be too high for those who need them. At the same time, the costs for R&D are also high and increasing. Complex regulatory environments and high costs for certification exacerbate these issues, according to industry KIs. The mismatch between technology standards across borders and difficulties in obtaining rare samples further complicate the economic viability of health products. Stakeholders recommended increasing domestic government funding to ensure that new products are affordable. From an industry perspective, the solutions include developing a more flexible research environment, encouraging innovation, and establishing partnerships supporting start-ups and established technologies.

THE NEED FOR SUSTAINABLE CLINICAL TRIAL HUBS

Long-term, sustainable clinical trial networks and hubs have played a critical role in trials of many candidate products for NDs and EIDs, including for HIV, COVID-19, and Mpox. For example, the HIV Prevention Trials Network (HPTN) conducts trials of biomedical HIV prevention approaches across 69 study sites in 14 countries, including countries in Latin America (Argentina, Brazil, Peru), SSA (Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, Zambia, Zimbabwe) and Asia (Thailand, Vietnam). These kinds of networks have many advantages over establishing single, unconnected trial sites. Networks or hubs can test many

Networks or hubs can test many different types of health technologies and pivot quickly between diseases when needed (the HPTN pivoted to conduct COVID-19 vaccine trials and then again to conduct Mpox trials).

different types of health technologies. They can pivot quickly between diseases when needed (the HPTN pivoted to conduct COVID-19 vaccine trials and then again to conduct Mpox trials). They drive multiple efficiencies by, for example, coordinating trials across the network, pooling data ,and sharing knowledge, such as on recruitment strategies for trials. For all these reasons, there would be great value in all regions developing strong, coordinated hubs for clinical trials.

With respect to better coordination, Africa CDC and AUDA-NEPAD convened experts in May 2023 to discuss concrete solutions for strengthening the impact and efficiency of the African clinical trials ecosystem, with the goal of accelerating access to new lifesaving technologies in line with public health priorities. The experts agreed that a coordination mechanism was needed to enable increased efficiency and impact and recommended that this mechanism be housed at Africa CDC and managed in partnership with AUDA-NEPAD, WHO AFRO, and AVAREF.[206] This is a critical step given that most clinical trials are being conducted in HICs (studies show that between 2007 and 2018, 38% of infectious disease trials took place in North America and only 10% in Africa[7]).

Conducting clinical trials in Latin America presents both challenges and opportunities. A significant challenge is the lack of needed infrastructure, such as trained medical staff and the certified centers necessary for conducting clinical trials. The regulatory processes also pose significant challenges, with countries like Mexico, despite having substantial infrastructure, facing many barriers due to these processes. There is a tendency among many countries to duplicate efforts, leading to inefficiencies, instead of optimizing existing processes. Despite these challenges, there is a significant opportunity for optimization of the regulatory framework and capacities of the region, which would facilitate an environment conducive to clinical research. There are bright spots, with Argentina serving as a hub for clinical trials and Brazil standing out for the volume of its clinical trials. These regional hubs represent key opportunities for growth and development in the field of clinical research. Asian stakeholders pointed to the difficulties in conducting clinical trials across different ethnic groups. They also requested more government support, such as reducing or exempting clinical trial fees to lower R&D costs.

SUMMARY OF REGIONAL CONSULTATIONS

In summary, stakeholders see the need to strengthen regional R&D systems, including regional priority setting and the creation of regional and sub-regional hubs for clinical trials, regulatory systems, and product manufacturing (Table 7). These regional platforms could play an important role for each region and need to be meaningfully integrated into global structures to ensure that regional priorities are reflected.

Table 7. Strengthening regional systems to drive R&D and improve access to new tools

Action points	Outcomes
Adopt a portfolio approach at regional level	• Decentralized decision-making, feeding into global priority setting (e.g., MCM platform) • Regional level priority-setting
Build regional capacity	• Pool of clinical trial sites • Sub-regional production linked to free-trade zones • Harmonized regulation to accelerate registration of new tools
Ensure access and equity through global public goods	• New tools with strong global public goods element (supply, pricing, licensing) • Industry buy-in through incentivizes • LMIC government commitment to invest in R&D, NRAs, and local production
Strengthen delivery systems	• Stronger regional procurement • Regional technical support

SECTION

8

CONCLUSIONS: TOWARDS A REFORMED R&D ECOSYSTEM

In this study, we examined key shifts and innovations across six major domains of the R&D ecosystem for NDs, EIDs, and MH. We found that there is great potential for accelerating R&D, lowering R&D and production costs, and shortening market approval timelines. Below, we highlight ten key practices to make the product development ecosystem more efficient, effective, and equitable:

1. **Scale-up adoption of AI for product development for NDs, EIDs and MH.**

AI has great potential in the discovery and preclinical phases. There are examples of AI tools that have shortened discovery timeframes to less than one year and lowered the costs by a factor of up to 50. There is also an urgent need to expand the use of AI for epidemic and pandemic preparedness: AI should be used to predict protein structures for priority pathogens in a coordinated attempt to build a vaccine library. While the evidence on the benefits of AI in clinical trials is less strong, it indicates that AI can also play an important role during the clinical stages. In clinical evaluations, AI tools can predict the probability of trial success and help design Phase 2 and Phase 3 trials that are more likely to transition to regulatory approval. AI tools can also help with patient recruitment, the prediction of patient outcomes, and clinical trial data analysis and approval. However, if AI is rolled out inequitably, it could augment inequalities between LMICs and HICs. African researchers have therefore called for a research agenda on AI grounded in the African context to determine locally relevant strategies for its development and use.

2. **Leverage the efficiencies from innovative clinical trial designs.**

DCTs using DHTs can reduce trial costs, timelines, and the number of patients needed in a trial. Platform trials can shorten trial duration, evaluate more treatments per trial, reduce the number of patients required per trial (by up to 70%), and increase the proportion of programs that accurately recognize an effective treatment. Synthetic control arms can lower trial costs. The savings can be US$10 million to US$20 million per trial, depending on how much synthetic control arms are used to replace traditional control arms.

3. **Unlock the efficiency potential of clinical trial networks.**

Clinical trial networks can drive efficiencies by using existing sites instead of creating new ones, recruiting patients more quickly and reliably, and reducing the number of patients needed by sharing control groups with other trials. Connecting trial sites, which allows a sponsor to find sites for rapid enrolment, could reduce Phase 2/3 trial costs by 23%. Costs could be reduced by 40-60% by sharing control groups and using control data from previous trials. Furthermore, the ability to rapidly test product candidates during outbreaks relies on the existence of effective and inclusive regional clinical trial networks that are kept active between outbreaks.

4. **Scale-up quality-assured, low-cost manufacturing across regions.**

Optimized mRNA production processes can save over 60% (about US$70 million) of the annual cost of goods for the production of 100 million vaccine doses compared to conventional mRNA manufacturing. While mRNA technologies offer significant potential, diversified vaccine manufacturing is needed to also enable production of existing licensed products (routine non-mRNA vaccines) across regions, including Africa. Modular production facilities have also been used in the past to lower production costs of non-mRNA-based vaccines. Production capacity for drugs and diagnostics also needs to be strengthened. To build more sustainable, resilient, and equitable future markets, firm purchasing commitments from funders are a key requirement.

5. **Strengthen regional regulatory harmonization and reliance models.**

Regulatory harmonization through stronger national regulatory agencies and the use of reliance mechanisms can accelerate market authorization by limiting duplicative assessments.

6. **Leverage the potential of mRNA platforms for NDs, EIDs and MH.**

mRNA platforms have significant comparative advantages over more traditional technologies, including their versatility and the ability to rapidly develop new tools.

7. **Scale-up investments in R&D on mAbs that target NDs, EIDs, and MH.**

Developing mAbs for EIDs, for example, would offer many benefits. In addition, the global inequity in access to existing mAbs needs to be addressed. RSV mAbs could be a game changer—a low-cost RSV mAb is believed to be under development—and could serve as a product for the global community to rally around. COVID-19 was a missed opportunity to do so.

8. **Introduce a PRV in Europe to help incentivize industry investment.**

An EU voucher would provide an additional incentive of US$100 million to US$ 200 million, which investors say would be a meaningful stimulus.

9. **Rather than only targeting individual research projects, such as clinical trials, R&D funders also need to invest in the underlying research system.**

A system-wide approach would include investments in clinical trial infrastructure, capacities for drug discovery and preclinical research, and local manufacturing. LMIC governments need to increase their own funding for health R&D. This will be important to advance product development for NDs, EIDs, and MH.

10. **Strengthen regional R&D ecosystems.**

The overarching R&D ecosystem would be improved by stronger regional priority setting and the creation of regional and sub-regional hubs for clinical trials, regulatory systems, and product manufacturing. Regional coordination on priority products is critical to ensure that R&D investments are driven by LMIC priorities. Global prioritization also needs to be strengthened—the coordination gap is especially large for therapeutics.

Figure 4 summarizes the efficiency gains resulting from the innovations and improvements in the R&D ecosystem identified in our study. In addition, we believe that investments in R&D for LMICs should be driven by the priorities that they set themselves. The shifts identified above must link to these priorities if we are to move in the direction of equity. These shifts in R&D must be accompanied by increased ownership by LMICs and increased investments from LMIC governments, as well as from the private sector and industry players.

Our report's findings have been an important input into the upcoming third report of the Lancet Commission on Investing in Health ("CIH 3.0"), Global Health 2050, which will be launched at the World Health Summit in Berlin in October 2024 (several of us are CIH Commissioners).[207] The CIH 3.0 report examines the feasibility of all countries halving their probability of premature death (defined as death before the age of 70 years) by 2050, with an interim target of reducing this probability by 30% by 2035. Global Health 2050 points to the critical importance of developing new health technologies for NDs, EIDs, and MH in reaching these 2035 and 2050 milestones.

Figure 4. Key efficiency gains from shifts in the R&D ecosystem

Discovery & preclinical phase	Clinical trials	Manufacturing	Regulation	Financing and governance
• AI can substantially reduce costs and timelines • AI enables more comprehensive screening, with potential for identification of novel compounds, improved quality candidates, (less attrition in clinical stages), and eventually better technologies	• DCTs/DHTs reduce costs and timelines (e.g., reduction of physical visits by 40%) • Synthetic control arms lower costs (savings of US$10-US$20 million per trial) • Trial networks can reduce trial costs by 23% • AI predicts probability of moving to Phase 3 with 79% accuracy	• Optimized mRNA production offers substantial cost savings (60% of annual CoGs for 100 million vaccines doses) • Modular manufacturing has been used in the past to lower vaccine production costs	• Regional harmonization and reliance mechanisms have successfully shortened approval times • Bilateral partnerships between NRAs (LMIC-LMIC & HIC-LMIC) are also critical	• Introduction of a PRV in Europe could provide an additional incentive of US$100-US$200 million per drug candidate to industry

Definitions of neglected diseases, emerging infectious diseases, and maternal health

Neglected diseases*

- Bacterial pneumonia & meningitis
- Buruli ulcer
- Cryptococcal meningitis
- Dengue
- Diarrheal diseases
- Helminth infections
- Hepatitis B
- Hepatitis C
- Histoplasmosis
- HIV/AIDS
- Kinetoplastid diseases
- Leprosy
- Leptospirosis
- Malaria
- Mycetoma
- Rheumatic fever
- Salmonella infections
- Scabies
- Snakebite envenoming
- Trachoma
- Tuberculosis
- Yaws

Note: The G-FINDER definition refers to diseases and products, i.e., not all product areas are included for all diseases in the G-FINDER scope (for more details, see the "G-FINDER Neglected Disease R&D Scope"*).

Emerging infectious diseases**

- COVID-19
- Crimean-Congo hemorrhagic fever, Rift Valley fever, and other bunyaviral diseases
- Chikungunya
- Ebola, Marburg, and other filoviral diseases
- Lassa fever and other arenaviral hemorrhagic fevers
- MERS, SARS & multiple coronaviruses
- Mpox
- Nipah and other henipaviral diseases
- Zika
- Disease X

Maternal health***

- Preterm labor/birth
- Preeclampsia/eclampsia
- Intrauterine growth restriction
- Postpartum hemorrhage
- Intrapartum fetal distress
- Maternal enteric microbiome/environmental enteric dysfunction
- Maternal iron deficiency anemia

*https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2023/05/05211731/G-FINDER_ND_RD_scope.pdf

** https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2024/04/08192259/G-FINDER_EID_RD_scope.pdf

***https://www.policycuresresearch.org/maternal-health-pipeline/

Portfolio to Impact (P2I) modeling tool

Table A2. Assumptions for the product pipeline development model

	Cost per phase (US$ million)				Length of phase (years)				Probability of success (%)			
Archetype	**Pre-clinical**	**Phase 1**	**Phase 2**	**Phase 3**	**Pre-clinical**	**Phase 1**	**Phase 2**	**Phase 3**	**Pre-clinical**	**Phase 1**	**Phase 2**	**Phase 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-innovative	$7.50	$4.83	$6.10	$34.46	2.70	1.81	3.35	3.10	60.0%	51.9%	28.4%	57.8%
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 repurpose-simple	$-	$-	$5.81	$17.61	0.00	0.00	2.14	2.14	100.0%	100.0%	45.7%	68.1%
Drug repurpose-complex	$5.00	$2.21	$5.81	$17.61	2.33	1.63	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 development	$3.00	$2.00	$3.50	$-	1.00	1.25	1.33	0.00	50.0%	100.0%	100.0%	100.0%
Diagnostic, simple platform development	$-	$100.00	$3.50	$-	0.00	2.50	2.00	0.00	100.0%	75.0%	100.0%	100.0%

Source: Terry RF, Yamey G, Miyazaki-Krause R, et al. Funding global health product R&D: the Portfolio-To-Impact Model (P2I), a new tool for modelling the impact of different research portfolios. Gates Open Res 2018;2:24

ANNEX 3

Clinical trials

Table A3.1. Examples of studies of the efficiencies associated with decentralized clinical trials and digital health technologies

Type of efficiency	Study details	Magnitude of benefit	Innovations studied
Cost reduction	DAPA-MI trial (Sweden, UK): evaluated use of dapagliflozin in patients with myocardial infarction incorporating digital approaches; compared costs with those of DAPA-HF (a similar study that did not use digital approaches)[1]	• 60% reduction in no. of patient study visits • 43% reduction in total cost per patient from US$ 22,698 in traditional approach to US$12,826 using DCT/DHT • US$25 million in savings	• Digital clinical platform for patients and sites • AI cardiovascular event detection platform • Digital patient registries
	Eastern Research Group study: modeled the effect of different DCT/DHT innovations, using data on >27,000 trials for over 1400 indications[2]	**Innovations most likely to reduce costs were:** • use of lower cost facilities or at-home testing: up to 17% reduction in phase III trial costs • mobile technologies for data capture: up to 12% reduction • electronic health records (EHRs) to recruit patients and capture data: up to 9% reduction • simplified clinical trial protocols (up to 8% reduction)	• Use of lower cost, non-traditional sites (e.g., local clinics and pharmacies) • At-home testing • Mobile tech • EHRs • Simplified trial protocols
Fewer participants needed, reduced costs, shorter timeline	CRESCENDO trial: is using digital technologies to evaluate a new drug (AZD4831) for chronic obstructive pulmonary disease (COPD)[1]	• Required no. of participants was reduced from an estimated 604 (for a traditional trial) to 288 • 32% reduction in costs (the number of in-person visits is halved) • 15% reduction in trial duration	• Digital primary and secondary endpoints • Smart spirometer (home-based) • Digital clinical platform • AI
Shorter timelines, improved patient recruitment, lower drop-out rates	IQVIA analysis of DCTs: analysis of 12 DCTs for 3 therapeutic areas—neurology, infectious diseases, dermatology; 17% Phase 1, 25% Phase 2, 58% Phase 3[3]	• 49% reduction in the time taken from finalizing the protocol to enrolling the 1st patient [1st patient in, FPI] (in oncology, the average time from protocol submission to enrolling the 1st patient is 33 weeks[4]) • 78% reduction in time taken from enrolling the 1st patient [FPI] to enrolling the last patient [last patient in, LPI] • In a phase III DCT for infectious diseases, involving over 23,000 patients, there was an 86% reduction in final protocol to FPI and a 94% reduction in FPI to LPI timelines—with huge financial and time implications • 39% reduction in "screen failure rate" (the proportion of patients screened as eligible to be in a trial who do not enroll) • 15% lower dropout rates—probably related to lower time and travel burden for the participants	• Hybrid trials that combined "site visits with technology-enabled data collection and home-based services"[3]
	IQVIA analysis of phase 2 or 3 remote, virtual, or decentralized (RVD) trials: the highest number of trials in the analysis were from infectious diseases, vaccines, immunology and neurology	• Despite higher average complexity, the cohort of RVD trials "completed just over 20% faster than non-RVD trials"[5]	

Case study

The HPTN, established in 1999, is a powerful example of a sustained international trials collaboration that partners with academia, industry, and philanthropy to conduct trials of biomedical HIV prevention approaches across 69 study sites in 14 countries. In addition to the U.S., the 13 other countries are in Latin America (Argentina, Brazil, Peru), sub-Saharan Africa (Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, Zambia, Zimbabwe) and Asia (Thailand, Vietnam). The network is remarkable in five key ways:

Multiple technology types

The HPTN conducts trials of different types of HIV prevention technologies: HIV vaccines in partnership with the HIV Vaccines Trial Network (HVTN); pre-exposure prophylaxis (antiretrovirals, broadly neutralizing antibodies); and multipurpose prevention technologies, which are designed to simultaneously prevent HIV and pregnancy, STIs, or opioid dependence.

Pivoting rapidly to other emerging infections

As long-running established platforms, the HPTN and HVTN could pivot quickly to conduct COVID-19 vaccine trials. They joined the COVID-19 Prevention Network (CoVPN), along with the Infectious Diseases Clinical Research Consortium (IDCRC) and the AIDS Clinical Trials Group (ACTG). "By bringing together multiple networks," say CoVPN authors in a recent paper, "CoVPN was able to draw on existing clinical and laboratory infrastructure, community partnerships, and research expertise to quickly pivot clinical trial sites to conduct COVID-19 vaccine trials as soon as the investigational products were ready for phase 3 testing."[6] The HPTN/HVTN pivoted rapidly again to run Mpox vaccine trials.

Efficiency gains

The rapid launch of the CoVPN showed that trial networks can drive several efficiencies. There were time savings, since existing trial sites, infrastructure, laboratories, human resources (including analytics expertise), and community outreach mechanisms could be used—saving time that would have been spent establishing new sites and hiring and training staff. Using the HPVN for COVID-19 vaccine trials meant that a network of clinician investigators was already in place. Lawrence Corey, HPVN Principal Investigator, says that these clinicians "could discriminate between mild and serious disease, follow people sequentially, do pulse oximetry, and draw bloods for correlates of protection."[7] Time was also saved by using rapid, simplified budgeting and payment to trial sites. Another efficiency was generated by pooling data. The CoVPN used data generated by multiple existing platforms (HPTN, HVTN, IDCRC, ACTG) across the US, Latin America, and sub-Saharan Africa, involving 136,382 trial participants. Data from these multiple trials and platforms were shared and analyzed. The CoVPN authors argue that this cross-platform approach "led to harmonization of data collection across trials and the ability to analyze data from all studies, a novel approach that will continue to yield answers to pressing questions and help guide public health policy."[6] Trials networks also share knowledge, such as on recruitment strategies for trials.

Potential to be used to study additional PRNDs

The HVTN, the ACTG, and the International Maternal Pediatric Adolescent AIDS Clinical Trials Network have been leveraged to facilitate the development of a tuberculosis vaccine.

Capacity building

The CoVPN runs international scholarship programs. One of these is a scientific leadership development program that is providing support to promising junior clinical investigators who may be in a position in 5-10 years to be a clinical trials site leader.

1 IQVIA Institute. Global Trends in R&D, 2023. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-trends-in-r-and-d-2023/iqvia-institute-global-trends-in-rd-2023-forweb.pdf

2 Lauer MS, Gordon D, Wei G, Pearson G. Efficient design of clinical trials and epidemiological research: is it possible? Nat Rev Cardiol. 2017 Aug;14(8):493–501.

3 IQVIA Institute. DCTs Deliver Big ROI. 2022. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/dcts-deliver-big-roi.pdf

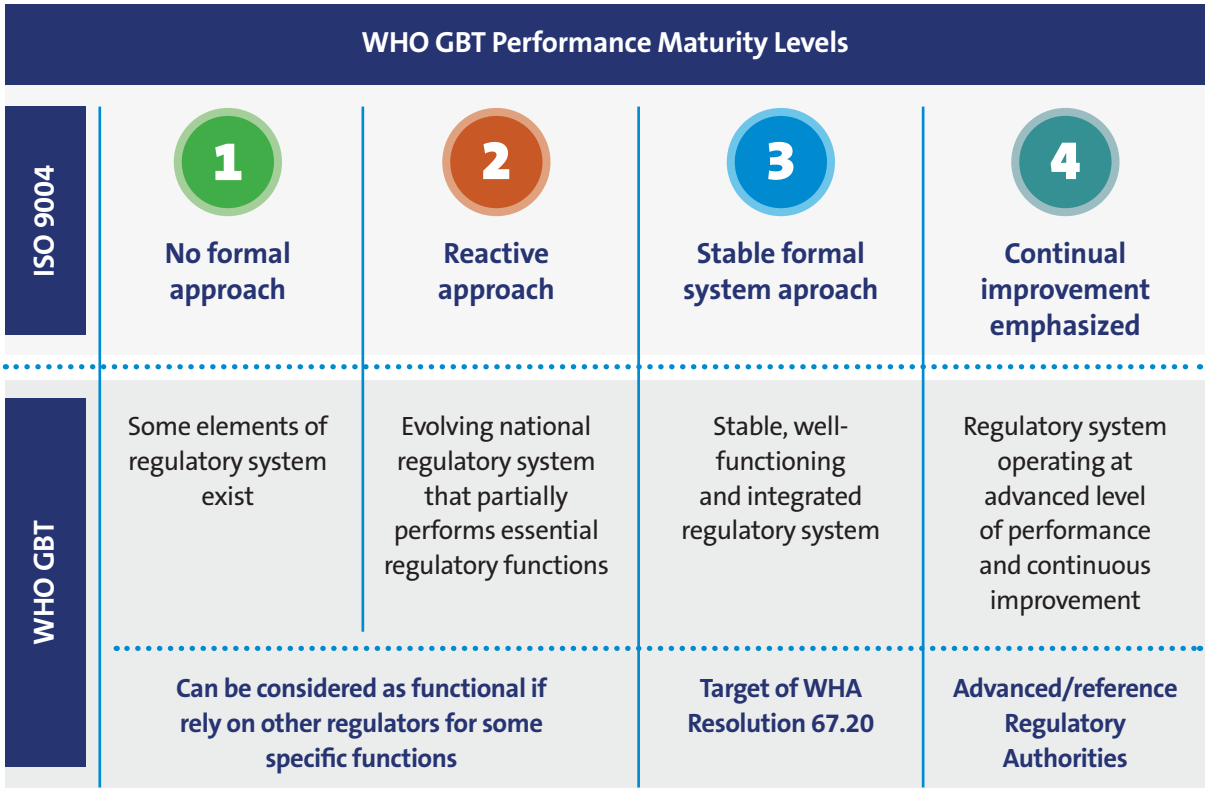
4 Byatt L, Deutsch K, Dayao ZR. Improving start-up times in oncology clinical trials: An ASCO quality improvement project. JCO. 2018 Oct 20;36(30_suppl):297–297.

5 IQVIA Institute. Global Trends in R&D, 2023. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-trends-in-r-and-d-2023/iqvia-institute-global-trends-in-rd-2023-forweb.pdf

6 Mena Lora AJ, et al. Rapid Development of an Integrated Network Infrastructure to Conduct Phase 3 COVID-19 Vaccine Trials. JAMA Network Open 2023;6(1):e2251974, at https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2800703

7 From HVTN to CoVPN: the importance of vaccine trial networks [Internet]. BioInsights. [cited 2023 Nov 18]. Available from: https://www.insights.bio/vaccine-insights/journal/article/2926/From-HVTN-to-CoVPN-the-importance-of-vaccine-trial-networks

WHO Global Benchmarking Tool (GBT) Performance Maturity Levels



Source: Figure from Broojerdi AK, Sillo HB, Dehaghi ROA, et al. The World Health Organization Global Benchmarking Tool an Instrument to Strengthen Medical Products Regulation and Promote Universal Health Coverage. Front Med (Lausanne) 2020;7:457.

ANNEX 5

5.1. Latin America: key regional shifts needed in the regional R&D ecosystem

The regional assessment involved consultations with stakeholders from 10 countries (Argentina, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, Mexico, Panama, Peru, Uruguay). It also included consultations with representatives from two major regional organizations: the Pan American Health Organization (PAHO) and the Latin American Federation of the Pharmaceutical Industry (FIFARMA). Consultations were conducted with policymakers and technical experts from government, public sector institutions (e.g., ministries of health, national institutes of health), national regulatory authorities (NRAs), industry, academia, multilateral institutions, and civil society.

THE CLINICAL TRIAL ECOSYSTEM IN LATIN AMERICA

Conducting clinical trials in Latin America presents both challenges and opportunities. A significant challenge is the lack of critical infrastructure for conducting trials, such as trained medical staff and certified centers. However, even when there is substantial infrastructure, such as in Mexico, inefficient regulatory processes create barriers to conducting trials (see below). Despite these challenges, there are some bright spots, with Argentina serving as a hub for clinical trials and Brazil standing out for the volume of its trials. These regional hubs represent key opportunities for growth and development in the field of clinical research.

REGULATORY SYSTEMS IN LATIN AMERICA

There is wide variation in how well NRAs function. Around one fifth of the 35 PAHO countries have limited legal and organizational regulatory structure. About one quarter have established comprehensive legal bases and organizational frameworks for regulation (including Argentina, Brazil, Canada, Chile, Colombia, Cuba, Mexico, and the US). PAHO is in the process of transitioning to the Global Benchmarking Tool (GBT) to assess NRAs. However, no NRA in Latin America has been fully assessed with this tool yet—only self-assessments have been conducted. The introduction of the GBT is expected to be very beneficial in benchmarking, harmonizing, and strengthening regulatory systems.

Over the last decade, there have been a number of regional efforts to improve regulation, including efforts to adopt a more uniform approach to regulation across different jurisdictions and greater use of reliance. For example, thanks to the North American Free Trade Agreement, there is now reliance between the NRAs of the US, Canada, and Mexico. In terms of harmonization and international convergence, organizations like the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) have incorporated NRAs from middle-income countries. This has facilitated the strengthening of regulatory systems. Currently, Brazil and Mexico are Latin American members of the ICH, with Colombia and Argentina participating as observers.

However, despite these improvements, there are still gaps in the regulation of medicines. These include:

(i) the use of self-assessments, which are not as comprehensive or objective as a full assessment using the GBT;

(ii) resource limitations and a lack of political will and sustainable plans;

(iii) dependence on the administration in power, which often leads to a reset with each new government;

(iv) nationalism or protectionism in some nations, often under the guise of respecting national sovereignty;

(v) the use of physical documentation for administrative processes, instead of using electronic methods; and

(vi) poor preparation for assessing and registering new types of medicines, such as monoclonal antibodies and mRNA-based technologies.

In addition to adopting the GBT, key informants (KIs) made several recommendations to improve regulatory systems:

- **Expedite the review of tools**. The COVID-19 pandemic necessitated expedited review of tools such as vaccines, which were found to be effective post-pandemic; this shows the value of expedited review processes.
- **Maintain data quality and ethics**.
- **Adopt faster trials processes**. KIs stressed the need for faster evaluation models with shorter clinical trial phases that can be evaluated simultaneously.
- **Create multidisciplinary groups**. The pandemic underscored the need for multidisciplinary groups, including social scientists such as anthropologists, to understand cultural differences and improve community communication.
- **Adapt to urgent situations**. COVID-19 pushed regulatory authorities to adapt to urgent situations and speed up their processes.
- **Establish better communication channel**s. KIs emphasized the importance of continuous communication between regulators and those being regulated.

MANUFACTURING OF HEALTH PRODUCTS IN LATIN AMERICA

Latin America faces significant hurdles in manufacturing health tools, including a lack of incentives and support, making it challenging to foster innovation and production. The COVID-19 pandemic highlighted the region's dependency on the Global North for health products and its vulnerability in times of global health crises. Other challenges include shortages of supplies, sustainability of reagents, and maintenance of equipment.

Strengthening local and regional production of supplies, reagents, and key health technologies could be achieved through government subsidies, partnerships with private companies, and investment in local manufacturing facilities and in training and capacity building.

R&D GOVERNANCE IN LATIN AMERICA

The governance of the R&D ecosystem faces significant barriers, gaps, and challenges. At the heart of these issues is poor health systems, which are often characterized by deficits in infrastructure, logistics, and funding for R&D, and high levels of corruption leading to the misuse of resources. Another challenge is the gap between research and policy—there is a pressing need to develop communication channels or strategies to translate research results into public health policies. The knowledge of and capacity for research among health and regulatory authorities is often lacking. There is also a noticeable lack of R&D culture among health authorities and decision-makers, which can stifle innovation and slow down the development of new health technologies.

Our study highlighted the importance of adopting intersectoral, interdisciplinary approaches to improve the R&D governance ecosystem, such as improving coordination between institutions and fostering greater regional collaboration to facilitate the sharing of resources, knowledge, and best practices.

R&D FINANCING IN LATIN AMERICA

One of the primary obstacles to product development in the region is the lack of sufficient funding for R&D, including for pre-clinical research and clinical trials. Often, research is conducted more for the benefit of the researcher rather than out of necessity, and the research agenda is heavily influenced by the availability of funding.

In terms of R&D investment, Latin America significantly lags behind other regions. While countries like the United States, Japan, Korea, and the European Union allocate 2-3% of their gross domestic product (GDP) to R&D, Latin America only dedicated 0.65% of its GDP to R&D in 2020, the most recent year for which data are available.[1] The lack of R&D financing leads to a lack of specialized training and capacity building opportunities within the R&D field and a lack of institutional capacity.

Nevertheless, there are new players emerging within academic circles and the private sector who are beginning to make their mark on the R&D landscape. A new report on "Health Innovation and Technology in Latin America and the Caribbean," by the Inter-American Development Bank, maps out these emerging actors,[2] which include finance organizations and philanthropies.

1. https://data.worldbank.org/indicator/GB.XPD.RSDV.GD.ZS?locations=XJ.
2. IDB. Health Innovation and Technology in Latin America and the Caribbean. April 2024. https://publications.iadb.org/en/health-innovation-technology-latin-america-caribbean

5.2. Africa: key regional shifts needed in the regional R&D ecosystem

The regional assessment involved interviews with key stakeholders in the R&D ecosystem in Africa to identify priorities for ecosystem changes. These key informants included heads and key personnel in science, regulatory, funding, and manufacturing organizations, as well as conveners of innovators in Africa. They included representatives of the South African Health Products Regulatory Authority, AfricaBio (an independent non-profit stakeholders' association that represents Africa's biotechnology sector), the Drugs for Neglected Diseases Initiative, Institut Pasteur de Dakar, the Science for Africa Foundation, Amref Health Innovations, the African Union COVID-19 Commission, Africa CDC, and Ghana's Food and Drugs Authority.

THE CLINICAL TRIAL ECOSYSTEM IN AFRICA

Clinical trials that test medicines, vaccines, and diagnostics for high-burden neglected diseases, emerging infectious diseases, and maternal health conditions in countries in Africa need to be conducted in those countries themselves. These trials, say Toto and colleagues "can benefit from local healthcare knowledge and are better able to address context-specific questions that would then lead to more effective interventions."[1] Yet, less than 10% of all clinical trials are conducted in Africa.[2] Trials in Africa are hindered by a range of barriers. For example, a qualitative study investigating barriers to conducting trials in Ethiopia found "limited funding allocation, weak regulatory and administrative systems, few learning opportunities, limited human and material capacity and poor incentives for conducting research."[3]

In May 2023, the Africa Centres for Disease Control and Prevention (Africa CDC) and the African Union Development Agency (AUDA-NEPAD) held a convening to examine the state of the clinical trial ecosystem in SSA and identify ways to strengthen its impact and efficiency.[4] Participants agreed that the current trials ecosystem is "not equipped to effectively manage a global health product pipeline that is expected to grow in both complexity and size." Recommendations arising from the convening included:

- **Urgently improving coordination of trials**, including through the sharing and reporting of information, data, processes, and tools.
- **Establishing a new coordination mechanism** housed at Africa CDC and managed in partnership with AUDA-NEPAD, the African Vaccine Regulatory Forum (AVAREF), and the WHO Regional Office for Africa. Its mandate would be "evaluation of the pipeline of clinical trials in line with African public health and research priorities, aligning on financing needs and mechanisms, building cohesive capacity strengthening partnerships, and driving evaluation of the impact of these changes on the clinical trial ecosystem."[4]
- **Strengthening the clinical trials workforce**.

THE REGULATORY SYSTEM IN AFRICA

Regulatory bodies in Africa have been working on three priorities: (i) the African Medicines Regulatory Harmonization (ARMH) initiative, which was "launched to accelerate access to quality, safe, effective medical products by optimizing the regulatory environment on the continent"[5] ; (ii) strengthening regulators, and (iii) setting up the African Medicines Agency (AMA). The ARMH process resulted in a pilot of a continent-wide review mechanism, with an information technology platform hosted by the South African Health Products Regulatory Authority (SAPHRA); capacity building is a large component of the process.

The strengthening of regulators is focused on the process of getting accreditation for advanced levels of maturity e.g., transitioning from maturity level (ML) 2 to ML 3, and putting in place interventions in partnership with global health actors to achieve the necessary progression. Progress has also been seen in setting up the AMA, with at least 26 countries now subscribed; the Africa Union is in the process of appointing a governing Board and a Director General. These interventions are taking place at three levels of governance: the continent level, with the Africa Union and associated entities; the regional level, such as through the Economic Community of West African States (ECOWAS) and the Southern African Development Community (SADC); and the national level to accommodate national priorities and needs.

Barriers to strengthening regulatory bodies include lack of human capacity, weak systems and processes, and inadequate financial resources. Since government funding is limited for most regulators, and no additional strategic investments have been made, nearly all countries depend on donor funding to finance interventions to strengthen their regulatory bodies. Regulators attempt to maintain their independence and reduce potential conflicts of interest by not taking funds from industry, since regulators review industry's submissions. Currently, there is no explicit disease prioritization pathway to help understand national priorities and priority products in South Africa, and the same problem likely

applies in most African countries. Finally, African regulators are confronted with the major challenge of navigating the WHO pre-qualification process to unlock local manufacturing, which is considered too slow and expensive for local manufacturers. It is hoped that current interventions, with the support of the WHO, can assist in resolving the bottlenecks at continental, regional and national levels.

MANUFACTURING OF HEALTH PRODUCTS IN AFRICA

Key informants (KIs) argued that the main priority is to achieve "end-to-end" manufacturing, implying the whole value chain of manufacturing from laboratory to shelf. One of the major gaps that the KIs identified is production of active pharmaceutical ingredients (APIs)—Africa needs the capacity to produce these. The mRNA platform may be a game-changer in that it would not require APIs; however, the cold chain infrastructure required for mRNA is also a potential barrier.

Around a dozen countries in Africa are considered to have the capacity to build or strengthen their manufacturing capability, considering both public and private sector resources. Stakeholders propose that manufacturing platforms and product pipelines should not be duplicated. Instead, unique and focused manufacturing can happen in different regions of Africa, and these products can then be made available to the rest of the continent, provided barriers to distribution and procurement can be overcome.

Africa will need to have access to intellectual property (IP) to manufacture health products. Open science and innovation will be crucial. The patent pool and other IP owners could become partners to support the development of the R&D ecosystem in Africa. Part of the scholarship on the continent could be to track and trace IPs that are no longer under protection, and learn how to repurpose products and innovations that may have previously failed in light of new technologies.

The ecosystem in Africa will require a much stronger cold chain if tools such as mRNA and monoclonal antibodies are going to be used. The temperatures in Africa can be very high, and tools that require storage levels at -70 degrees Celsius can make operations very difficult.

R&D GOVERNANCE IN AFRICA

Stakeholders in Africa reported a lack of cohesive and structured processes to determine priorities for health R&D product development. At best, stakeholders have been able to reach some consensus on priority diseases, but these priorities are also adopted as a reaction to crises and tend to vary depending on the interests of conveners and participants of such proceedings. As a result, there is no reputable platform currently known to facilitate such proceedings for SSA, particularly when one considers the need for a forward-looking perspective to planning.

KIs said that there is a range of infectious diseases, including emerging infections, and non-communicable diseases that are high priority for R&D. Products need to be developed in preparation for future pandemics. KIs argued that efforts in SSA in the wake of the COVID-19 pandemic to build biomanufacturing capability in preparation for future pandemics have been a positive outcome of the pandemic era. However, much work is still needed in mapping pathogens that constitute an outbreak threat.

Stakeholders made it clear that conversations about health product prioritization in Africa will be have to be held both at national and regional levels before these are collated at the continent level. It also seems the actions or operations will also unfold much more smoothly if implemented at a regional level and national level. Therefore, focused discussions with ECOWAS, SADC and the West African Health Organization (WAHO) in Western Africa may bear fruit, perhaps together with groups in Northern and Central Africa.

At a continent level, a large role is played by the African Union; most representatives at this level are country presidents. However, much of the leadership in health is led by ministers of health, including leadership of biomanufacturing and product development. KIs pointed out the anomaly of having such ministers leading these conversations when their focus is generally only health services—they are rarely involved in manufacturing, science innovation, or the research enterprise. Stakeholders pointed out that in the countries in Africa that are leading in health product development, Egypt, Rwanda, and South Africa, their presidents—Kagame, El Sisi, and Ramaphosa—are the ones personally coordinating efforts around health innovation.

R&D FINANCING IN AFRICA

KIs said that R&D is currently mostly funded by international agencies and funders, with very little injection of funds from African governments. Countries that already have significant funding from their governments are the ones ahead in terms of manufacturing capabilities. Therefore, a clear shift is needed: African governments should inject a much larger proportion of public funds into R&D value chains and ecosystems. Funding is needed for capacity building, including human capacity development.

1. Toto N, Douglas E, Gmeiner M, et al. Conducting clinical trials in sub-Saharan Africa: challenges and lessons learned from the Malawi Cryptosporidium study. Trials 2020;21:680

2. Singh N. Benefits of conducting clinical trials in developing countries like India. Pharmaceutical Regulatory Affairs. 2018;7(2):1–2.

3. Franzen SRP, Chandler C, Enquselassie F, et al. Understanding the investigators: a qualitative study investigating the barriers and enablers to the implementation of local investigator-initiated clinical trials in Ethiopia. BMJ Open 2013;3: e003616.

4. Africa CDC, AU-NEPAD. Optimizing efficiency and impact in the African clinical trials ecosystem. Meeting report. May 2023. https://africacdc.org/download/meeting-report-optimizing-efficiency-and-impact-in-the-african-clinical-trials-ecosystem/

5. Ndomondo-Sigonda M, Azatyan S, Doerr P, et al. Best practices in the African Medicines Regulatory Harmonization initiative: Perspectives of regulators and medicines manufacturers. PLOS Glob Public Health 2023;3:e0001651.

5.3. Asia Pacific region: key regional shifts needed in the regional R&D ecosystem

INTRODUCTION

The regional assessment involved consultations with 30 interviewees from a wide range of sectors. About half were from leading pharmaceutical and biotech companies, including major domestic and multinational firms in China and across the Asia Pacific region (APR). Interviewees were also from governmental agencies, such as China's National Medical Products Administration (the country's national regulatory agency), and from national level specialized organizations, such as the Chinese Center for Disease Control and Prevention (which reports to the cabinet-level National Health Commission).

Other stakeholders represented international, regional, and Chinese domestic not-for-profit organizations, industrial associations, and public institutions—including APACMed (the Asia Pacific Medical Technology Association, based in Singapore); the Chinese Preventive Medicine Association; the Global Health Drug Discovery Institute; and the China Chamber of Commerce for Import and Export of Medicines and Health Products. Finally, we interviewed infectious disease experts from hospitals in the Philippines and scholars from think tanks and universities in the region, including key informants in India and South Korea.

THE CLINICAL TRIAL ECOSYSTEM IN THE ASIA PACIFIC REGION

In recent decades, there has been a sharp rise in the number of trials conducted in the APR. For example, a study by Ali et al found a 7-fold increase in the annual number of registered clinical trials in Asia between 2008 and 2017.[1] This rise was driven in particular by sharp increases in Japan, China, Republic of Korea, and India.

The APR has substantial clinical trial capacity for infectious diseases, but it is concentrated in a few countries.[2] For example, Postigo analyzed all vaccine clinical trials as of March 2022, and found that just under one quarter (24.1%) were conducted in the APR.[3] China was in the lead—responsible for a fifth of all vaccine trials in the APR and about 1 in 20 vaccine trials worldwide. The other countries where trials were concentrated were Australia, Japan, Republic of Korea, and Thailand. The increase in vaccine trials in more recent years might be related to the COVID-19 pandemic.

Given the benefits of trial networks, there have been several initiatives to establish such networks for infectious diseases at national and regional level. Examples include:

- **The Indian Clinical Trial and Education Network (INTENT)**, launched by the Indian Council of Medical Research. INTENT is a "pan-India network of clinical trial sites, with the overarching goal of providing evidence-based, robust, and culturally sensitive solutions to priority health problems of the country through conduct of large multicenter clinical trials."[4]
- **The Asian Infectious Diseases Clinical Trials Network (ADVANCEID)**, a network of over 30 hospitals across Asia that collaborate on clinical trials for infectious diseases.
- **The Southeast Asia Influenza Clinical Research Network**, which includes Indonesia, Thailand, and Vietnam.

- **The Asian Health and Welfare Initiative (AHWIN)**, created by the Japanese government in 2019, which has "promoted establishing a clinical research network to improve the infrastructure and development capacity of clinical research in Asia."[5] The network, called ARISE—the ARO (academic research organizations) Alliance for Association of Southeast Asian Nations (ASEAN) & East Asia—promotes regional clinical trials in Indonesia, the Philippines, Vietnam, and Thailand.

THE REGULATORY SYSTEM IN ASIA

While the regulatory landscape is diverse and heterogeneous in the APR, there is a general trend towards regulatory harmonization and convergence.[6] Japan, a founding regulatory member of the ICH, has played a leading role in this trend. China, Republic of Korea, Singapore, and the region of Taiwan are also ICH members; India and Malaysia are observers. The main regional harmonization initiative is ASEAN, founded in 1967, which now has 10 member states—its goals include "facilitating reorganization and harmonization within the member countries."[6] The association's Consultative Committee for Standards Quality and its Product Working Group on Pharmaceuticals take the lead in developing harmonization schemes across ASEAN member states.

National regulatory authorities (NRAs) in China, India, Indonesia, Thailand, and Vietnam are operating at maturity level (ML) 3.[7] The Republic of Korea and Singapore are operating at ML4 (Singapore was the first WHO member state to achieve ML4).

MANUFACTURING OF HEALTH PRODUCTS IN ASIA

Establishing vaccine security and self-sufficiency is of particular importance to Southeast Asia. Countries in the region are dependent on imports not only for COVID-19 vaccines, but also to a large extent for national immunization programs. Moreover, Southeast Asia has long been recognized as a hotspot for emerging infectious diseases.[8] Increasing vaccine development, manufacturing, and regulation capacity in the region as well as efforts to boost health system strengthening is therefore essential to ensuring that countries can sustain their immunization programs and respond effectively and efficiently to future outbreaks and pandemics.[9] To achieve this goal, ASEAN established the ASEAN Vaccine Security and Self-Reliance (AVSSR) initiative.

R&D GOVERNANCE IN ASIA

Investment case modeling conducted by Open Consultants for the World Bank in 2023 showed that a coordinated investment approach in ASEAN countries would have many benefits.[9] Through investments in trial sites and manufacturing capacity for both traditional vaccine technologies and new mRNA vaccine technologies, ASEAN countries would be enabled to leverage their own research, product development, and manufacturing capacity rather than relying on external support. Investments in trial sites and manufacturing will be useful for a much broader range of infectious and non-communicable diseases, as well as for the development and production of other medical countermeasures such as therapeutics and diagnostics. Investments in local manufacturing will also produce new jobs thereby generating additional economic growth. Improved regulatory capacity will have an impact on the quality of locally produced medicines. In addition, vaccinations have multiple other socioeconomic benefits and they also have benefits throughout health systems.

However, NGOs and governments face a number of obstacles, including insufficient policy support, asymmetric information, limited awareness, and limited global health practice experience, particularly in China. Poor alignment between research institutions and businesses, alongside weak monitoring and early warning capabilities, also hinder the effective response to health emergencies. Despite strong political will for international cooperation, substantial action is lacking, and international assistance struggles to ensure health equity.

R&D FINANCING IN ASIA

From an economic perspective, the obstacles faced in healthcare innovation and delivery in the APR are multifaceted. Financial challenges such as unaffordability, high R&D investment with low returns, and significant funding gaps impede progress. A lengthy R&D cycle, complex regulatory environments, and high costs for certifications like WHO prequalification exacerbate these issues. Additionally, market-related challenges like unclear demand, access barriers, and the high incidence of diseases in poor areas create a challenging landscape for new developments to gain traction. The mismatch between technology standards across borders and difficulties in obtaining rare samples further complicate the economic viability of health products.

Medically, the industry grapples with inadequate and ineffective vaccines, disparities in expert levels, and limited drug certification fields. High skill requirements for medical trainers, cultural constraints limiting technology applications, and fluctuating disease stages demanding varied treatments present substantial hurdles. Moreover, the lack of consensus on medical product regulations and neglect of certain diseases highlight systemic issues in global healthcare. The medical community also contends with the need for more targeted investment, particularly in overlooked conditions like non-tuberculous mycobacterial diseases. The pharmaceutical sector faces its own challenges, including disparities in international standards and limited communication with global counterparts, which hinders China's ability to export domestically developed drugs. Technological deficiencies in curing diseases like HIV/AIDS and the infancy of vaccine development reflect the sector's innovation struggles. Additionally, Chinese regulatory agencies face the complex task of aligning with rapidly evolving global clinical guidelines and continuously optimizing products post-market release.

A range of solutions has been proposed to address the obstacles identified across economic, medical, pharmaceutical, NGO, and government sectors. Economically, the focus is on improving affordability and funding accessibility. This includes increasing health financing inputs, better policy formulation to enhance foreign aid, and creating information exchange platforms integrating academia, business, and government. There is a call for synchronization of foreign personnel training and fostering specialization and interdisciplinary collaboration. Capacity building is one of the most important tasks to fulfil, including specialized training for professionals in companies and for staff in drug regulatory administration. Given the diversity of countries in the region, a tailored approached must be adopted in a country-specific context, especially for low-resource countries. The World Health Organization has formulated its policies to promote local production with the focus on capacity building, which can be leveraged. Therefore, one or two regional training centers are needed.

From a pharmaceutical perspective, the solutions include developing a more flexible research environment, encouraging innovation, and establishing partnerships supporting start-ups and established technologies. The survey advocates for a government-led effort in manufacturing and distribution, ensuring equitable access to products and technologies.

NGOs and governments play a crucial role in implementing the proposed solutions. They are advised to increase funding, focus on disease management, and facilitate communication among stakeholders. Solutions such as boosting international aid and adopting the public-private partnership model are suggested to aid in R&D and ensure the equitable distribution of technologies. By taking these steps, NGOs and governments can significantly contribute to the improvement of healthcare accessibility and affordability. In academia, recommendations are made to engage in dialogue with various stakeholders, such as regional entities, governments and professional institutions, promote the application of technologies through field interventions, and leverage public health projects to apply products and technologies more widely. Technology transfer needs to be promoted and patent pools can be created to meet the growing demand for the large-scale supply of badly needed products in the region. Moreover, market-shaping strategies are also needed to galvanize companies into R&D and production.

1 Ali S, Egunsola O, Bbar ZUD, Hasan SS. Clinical trials in Asia: A World Health Organization database study. Perspect Clin Res 2019;10: 121-124.

2 Yamey G, McDade KK, Mao W, Osakwe E. Financing research and development for new vaccines in Asia-Pacific developing countries. ESCAP Working Paper, 2022. https://artnet.unescap.org/publications/working-papers/financing-research-and-development-new-vaccines-asia-pacific-developing

3 Postigo A. Reseach and development in vaccines in the Asia-Pacific: state of play and the potential. ESCAP Working Paper, 2022

4 Sabu ST, Venkatraman S, Cherian JJ, et al. A review of clinical trials registered in India from 2008 to 2022 to describe the first-in-human trials. Perspect Clin Res 2024;15: 18-23.

5 Sonoda M, Urbiztondo MRU, Siburian MD, et al. Boosting multiregional clinical trials (MRCT) in Asia through the establishment of the Japan-led network for clinical research, the ARO alliance for ASEAN & East Asia (ARISE). Glob Health Med 2022;4: 247–249.

6 Han F, Weiss K. Regulatory trends in drug development in Asia Pacific. Ther Innov Regul Sci 2019;53:497-51.

7 https://www.who.int/publications/m/item/list-of-nras-operating-at-ml3-and-ml4

8 Morand S, Jittapalapong S, Suputtamongkol Y, et al. Infectious diseases and their outbreaks in Asia-Pacific: biodiversity and its regulation loss matter. PloS ONE 2014;9:e90032.

9 Mutasa R, Gandham R, Newmarch G, et al. ASEAN regional vaccine manufacturing and development. The World Bank Group. April 18, 2023. Chapter 5 includes the investment case prepared by Open Consultants. https://shorturl.at/tGJN6

REFERENCES

1. Ogbuoji O. et al. Health and economic benefits of improving efficiencies in product development for neglected diseases, emerging infectious diseases, and maternal health, May 21, 2024. https://centerforpolicyimpact.org/wp-content/uploads/sites/18/2024/05/reforming-research-and-development-ecosystem.pdf
2. World Health Organization. Global immunization efforts have saved at least 154 million lives over the past 50 years. April 24, 2024. https://www.who.int/news/item/24-04-2024-global-immunization-efforts-have-saved-at-least-154-million-lives-over-the-past-50-years
3. Jamison DT, Murphy SM, Sandbu ME. Why has under-5 mortality decreased at such different rates in different countries? J Health Econ 48:16-25.
4. Schäferhoff M, Zimmerman A, Diab MM, et al. Investing in late-stage clinical trials and manufacturing of product candidates for five major infectious diseases: a modelling study of the benefits and costs of investment in three middle-income countries. Lancet Glob Health 2022;10:E1045-E1052.
5. Zimmerman A, Diab MM, Schäferhoff M, et al. Investing in a global pooled-funding mechanism for late-stage clinical trials of poverty-related and neglected diseases: an economic evaluation. BMJ Global Health 2023;8: e011842.
6. Bandara S, Chapman N, Chowdhary V et al. Analysis of the health product pipeline for poverty-related and neglected diseases using the Portfolio-to-Impact (P2I) modeling tool. F1000Res 2020; 9:416.
7. Wellcome Trust. Towards a reformed research and development ecosystem for infectious disease. May 30, 2023. https://wellcome.org/reports/towards-reformed-research-and-development-ecosystem-infectious-disease
8. Policy Cures Research. The impact of global health R&D: the high return of investing in R&D for neglected diseases. Forthcoming.
9. Future of Global Health Initiatives. https://futureofghis.org/about/
10. Wouters OJ, McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. JAMA 2020;323:844–853.
11. Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics 2019; 20:273–86.
12. Another study found that the proportion of all drug development programs that lead to approval is 13.8%: Kolluri S, Lin J, Liu R, et al. Machine learning and artificial intelligence in pharmaceutical research and development: a review. AAPS J 2022;24:19.
13. Gupta R, Srivastava D, Sahu M, et al. Artificial intelligence to deep learning: machine intelligence approach for drug discovery. Mol Divers 2021;25:1315–60.
14. Vaisman A, Linder N, Lundin J, et al. Artificial intelligence, diagnostic imaging and neglected tropical diseases: ethical implications. Bull World Health Organ 2020;98:288–9.
15. Leslie D, Mazumder A, Peppin A, et al. Does 'AI' stand for augmenting inequality in the era of COVID-19 healthcare? BMJ 2021;372:n304.
16. Shaffer J, Alenichev A, Faure MC. The Gates Foundation's new AI initiative: attempting to leapfrog global health inequalities? BMJ Glob Health 2023;8:e013874.
17. Jayatunga MKP, Xie W, Ruder L, et al. AI in small-molecule drug discovery: a coming wave? Nat Rev Drug Discov 2022;21:175–6.
18. Nast C. DeepMind wants to use its AI to cure neglected diseases. Wired UK. June 23, 2021. https://www.wired.co.uk/article/deepmind-alphafold-protein-diseases
19. DNDi. Harnessing AI and new technologies to meet neglected patients' needs. https://dndi.org/about/annual-reports/annual-report-2021/harnessing-ai-and-new-technologies-to-meet-neglected-patients-needs/
20. Gulati S, Mattsson AH, Schussek S, et al 2023. Preclinical efficacy of a cell division protein candidate gonococcal vaccine identified by artificial intelligence. mBio 2023;14:e0250023.
21. GENTRL stands for Generative Tensorial Reinforcement Learning.
22. Deloitte. Intelligent drug discovery. Powered by AI. November 6, 2019. https://www2.deloitte.com/content/dam/Deloitte/ch/Documents/life-sciences-health-care/deloitte-ch-en-intelligent-drug-discovery.pdf
23. Zhavoronkov A, Ivanenkov YA, Aliper A, et al. Deep learning enables rapid identification of potent DDR1 kinase inhibitors. Nat Biotechnol 2019;37:1038–1040.
24. Insilico. New Milestone in Kidney Fibrosis. 2021. https://insilico.com/blog/pcc_kidney
25. Savage N. Tapping into the drug discovery potential of AI. Nature. News feature. May 27, 2021. https://www.nature.com/articles/d43747-021-00045-7
26. Exscientia. 2021 Annual report and Financial Statements. https://s28.q4cdn.com/460399462/files/doc_financials/2021/ar/2021-UK-Annual-Report.pdf
27. RAVEN™ is an AI model for uncovering unique cross-protective T-cell antigens, which can boost vaccine efficacy and response time. See: Persson G, Restori KH, Emdrup JH, et al. DNA immunization with in silico predicted T-cell epitopes protects against lethal SARS-CoV-2 infection in K18-hACE2 mice. Front Immunol 2023;14:1166546.
28. Evaxion Biotech. Pipeline. https://www.evaxion-biotech.com/pipeline
29. Evaxion Biotech. Evaxion partners with pharmaceutical company Afrigen Biologics. September 20, 2023. https://investors.evaxion-biotech.com/news-releases/news-release-details/evaxion-partners-pharmaceutical-company-afrigen-biologics
30. Mason DJ, Eastman RT, Lewis RP, et al. Using machine learning to predict synergistic antimalarial compound combinations with novel structures. Front Pharmacol 2018;9:1096.
31. Rashid MBMA. Artificial intelligence effecting a paradigm shift in drug development. SLAS Technol 2021;26:3–15.
32. Ianco-González A, Cabezón A, Seco-González A, et al. The role of AI in drug discovery: challenges, opportunities, and strategies. Pharmaceuticals (Basel) 2023;18;16:891.
33. See also: Shen Y, Liu T, Chen J, et al. Harnessing artificial intelligence to optimize long term maintenance dosing for antiretroviral naive adults with HIV 1 infection. Adv Therap 2020;3:1900114.
34. Pantuck AJ, Lee D, Kee T, et al. Modulating BET bromodomain inhibitor ZEN 3694 and enzalutamide combination dosing in a metastatic prostate cancer patient using CURATE.AI, an artificial intelligence platform. Adv Therap 2018;1:1800104.
35. Aliper A, Kudrin R, Polykovskiy, et al. Prediction of clinical trials outcomes based on target choice and clinical trial design with multi-modal artificial intelligence. Clin Pharmacol Ther 2023;114:972-980.

36. Kolluri S, Lin J, Liu R, et al. Machine learning and artificial intelligence in pharmaceutical research and development: a review. AAPS J 2022; 24:19.
37. Cramer G. Forward thinking for the integration of AI into clinical trials. ACRP. June 20, 2023. https://www.acrpnet.org/2023/06/forward-thinking-for-the-integration-of-ai-into-clinical-trials/
38. Thorlund K, Golchi S, Haggstrom J, et al. Highly Efficient Clinical Trials Simulator (HECT): Software application for planning and simulating platform adaptive trials. Gates Open Res; 2019;3:780.
39. CEPI. Machine vs nature: new machine learning platform to accelerate vaccine development against new viral threats. June 5, 2023. https://cepi.net/news_cepi/machine-vs-nature-new-machine-learning-platform-to-accelerate-vaccine-development-against-new-viral-threats/
40. CEPI. Using AI to speed up vaccine development against Disease X. July 18, 2023. https://cepi.net/news_cepi/using-ai-to-speed-up-vaccine-development-against-disease-x/
41. CEPI. Delivering pandemic vaccines in 100 days. What will it take? 2022. https://static.cepi.net/downloads/2024-02/CEPI-100-Days-Report-Digital-Version_29-11-22.pdf
42. Madhav NK, Oppenheim B, Stephenson N, et al. Estimated future mortality from pathogens of epidemic and pandemic potential. November 4, 2023. https://www.cgdev.org/sites/default/files/estimated-future-mortality-pathogens-epidemic-and-pandemic-potential.pdf
43. UK Government. 100 days mission: first implementation report. December 7, 2021. https://www.gov.uk/government/publications/100-days-mission-first-implementation-report/100-days-mission-first-implementation-report-html
44. Caruso C. An AI tool that can help forecast viral variants. October 11, 2023. https://hms.harvard.edu/news/ai-tool-can-help-forecast-viral-outbreaks.
45. Thadani NN, Gurev S, Notin P, et al. Learning from prepandemic data to forecast viral escape. Nature 2023;622: 818–825.
46. Vaisman A, Linder N, Lundin J, et al. Artificial intelligence, diagnostic imaging and neglected tropical diseases: ethical implications. Bull World Health Organ 2020;98:288–9.
47. Blanco-González A, Cabezón A, Seco-González A, et al. The role of AI in drug discovery: challenges, opportunities, and strategies. Pharmaceuticals (Basel) 2023;16:891.
48. Adams, R., Alayande, A., Brey, Z. et al. A new research agenda for African generative AI. Nat Hum Behav 2023;7: 1839–1841.
49. Hooda Y, Saha S. Code sharing and artificial intelligence can help decolonise public health modelling. BMJ 2024; 384:q27.
50. UK Government. AI regulation: a pro-innovation approach (white paper). August 3, 2023. https://www.gov.uk/government/publications/ai-regulation-a-pro-innovation-approach/white-paper
51. European Parliament. Artificial intelligence in healthcare. Applications, risks, and ethical and societal impacts. June 2022. https://www.europarl.europa.eu/RegData/etudes/STUD/2022/729512/EPRS_STU(2022)729512_EN.pdf
52. Brown DG, Wobst HJ, Kapoor A, et al. Clinical development times for innovative drugs. Nat Rev Drug Discov 2022;21:793–4.
53. Ramsey BW, Nepom GT, Lonial S. Academic, foundation, and industry collaboration in finding new therapies. N Engl J Med 2017;376:1762–9.
54. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021; 384:693-704.
55. Coates MM, Ezzati M, Aguilar GR, et al. Burden of disease among the world's poorest billion people: An expert-informed secondary analysis of Global Burden of Disease estimates. PLoS One 2021;16:e0253073.
56. Moore TJ, Heyward J, Anderson G, et al. Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015–2017: a cross-sectional study. BMJ Open 2020;10:e038863.
57. Gouglas D, Le TT, Henderson K, et al. Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimization study. Lancet Glob Health 2018;6:e1386-e1396
58. Iqvia Institute. November 16, 2023. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-trends-in-r-and-d-2023/iqvia-institute-global-trends-in-rd-2023-forweb.pdf
59. U.S. Food and Drug Administration. FDA takes additional steps to advance decentralized clinical trials. May 2, 2023. https://www.fda.gov/news-events/press-announcements/fda-takes-additional-steps-advance-decentralized-clinical-trials
60. Inan OT, Tenaerts P, Prindiville SA, et al. Digitizing clinical trials. NPJ Digit Med 2020;3:101
61. Durán CO, Bonam M, Björk E, et al. Implementation of digital health technology in clinical trials: the 6R framework. Nat Med 2023;29:2693-2697.
62. Berry Consultants. FACTS. Fixed and Adaptive Clinical Trials Simulator. https://www.berryconsultants.com/wp-content/uploads/2014/09/FACTS-Overview.pdf
63. Berry Consultants. ADDPLAN. https://www.berryconsultants.com/software/addplan/
64. HECT – Highly Efficient Clinical Trial simulator. https://mtek.shinyapps.io/hect/
65. Sigfrid L, Maskell K, Bannister PG, et al. Addressing challenges for clinical research responses to emerging epidemics and pandemics: a scoping review. BMC Med 2020;18:190.
66. Financial Times. Airfinity gives decision makers big picture on health. November 14, 2023. https://www.ft.com/content/f7b3f9ff-b57a-4fcd-8dd7-83301b1908b9
67. National Center for Advancing Translational Sciences. Master protocol. https://toolkit.ncats.nih.gov/glossary/master-protocol/
68. Subbiah V. The next generation of evidence-based medicine. Nat Med 2023;29:49–58.
69. UNITE4TB. UNITE4TB concept. https://www.unite4tb.org/about/unite4tb-concept
70. Saville BR, Berry SM. Efficiencies of platform clinical trials: A vision of the future. Clin Trials 2016;13:358–66.
71. U.S. Food and Drug Administration. Real-world evidence. February 5, 2023. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
72. Medidata. Synthetic control arm® in clinical trials. 2021. https://www.medidata.com/wp-content/uploads/2021/09/SCA-Whitepaper.pdf
73. BCG Global. Transforming clinical trials with real-world evidence. February 17, 2021. https://www.bcg.com/publications/2021/synthetic-control-arms-changing-clinical-trials
74. Wellcome Trust. Clinical trial networks for antibiotic development. 2016. https://www.wellcome.org/sites/default/files/clinical-trial-networks-for-antibiotic-development-wellcome-oct16.pdf
75. Oracle. Top 5 challenges in decentralized clinical trials. https://www.oracle.com/a/ocom/docs/industries/life-sciences/ls-top-5-challenges-decentralized-clinical-trials-wp.pdf

76. Bhandari N, Upadhyay RP, Chowdhury R, et al. Challenges of adopting new trial designs in LMICs. Lancet Glob Health 2021;9:e575–6.
77. Sekhar A, Kang G. Human challenge trials in vaccine development. Semin Immunol 2020;50:101429.
78. Kaewkungwal J, Adams P, Sattabongkot J, et al. Conducting human challenge studies in LMICs: A survey of researchers and ethics committee members in Thailand. PLoS One 2019;14:e0223619
79. McKinsey & Company. Real-world data quality: What are the opportunities and challenges? https://www.mckinsey.com/industries/life-sciences/our-insights/real-world-data-quality-what-are-the-opportunities-and-challenge
80. Africa CDC. African Union and Africa CDC launches Partnerships for African Vacccine Manufacturing (PAVM), framework to achieve it and signs 2 MoUs. April 16, 2021. https://africacdc.org/news-item/african-union-and-africa-cdc-launches-partnerships-for-african-vaccine-manufacturing-pavm-framework-to-achieve-it-and-signs-2-mous/
81. World Health Organization. The mRNA vaccine technology transfer hub. https://www.who.int/initiatives/the-mrna-vaccine-technology-transfer-hub
82. World Health Organization. Recipients of mRNA technology from the WHO mRNA technology transfer hub. https://www.who.int/initiatives/the-mrna-vaccine-technology-transfer-hub/recipients-of-mrna-technology-from-the-who-mrna-technology-transfer-hub
83. Zeng W, Bajnauth D, Jarawan E, et al. Strengthening pandemic preparedness: Build the vaccine manufacturing capacity in low- and middle-income countries. Public Health Pract (Oxf) 2022;4:100326.
84. ASEAN. ASEAN leaders' declaration on ASEAN vaccine security and self-reliance (AVSSR). November 2, 2019. https://asean.org/asean-leaders-declaration-on-asean-vaccine-security-and-self-reliance-avssr/
85. Africa Centres for Disease Control and Prevention. USP and Africa CDC launch MOU to advance regional manufacturing and strengthen regulatory and laboratory systems in Africa. June 30, 2023. https://africacdc.org/news-item/usp-and-africa-cdc-launch-mou-to-advance-regional-manufacturing-and-strengthen-regulatory-and-laboratory-systems-in-africa/
86. Mutasa R, Gandham R, Newmarch G, et al. ASEAN regional vaccine manufacturing and development. The World Bank Group. April 18, 2023. https://shorturl.at/tGJN6
87. UNIDO, WHO. Establishing manufacturing capabilities for human vaccines (white paper). 2017. https://www.unido.org/sites/default/files/files/2017-12/Establishing-Manufacturing-Capabilities-for-Human-Vaccines-ebook.pdf
88. Boyd, John H. Biomanufacturing cost in cities around the globe. Genet Eng Biotechn N 2020;40:58-60.
89. African Vaccine Manufacturing Initiative, WHO, UNIDO. Vaccine Manufacturing and procurement in Africa. An analytical assessment of vaccine manufacturing capacity and procurement mechanisms for establishing sustainable vaccine manufacturing capacity in Africa. 2017. https://www.avmi-africa.org/wp-content/uploads/2017/09/VMPA-Study-e-book.pdf
90. Grootendorst P, Moradpour J, Schunk M, et al. Home remedies: how should Canada acquire vaccines for the next pandemic? May 2022. https://www.cdhowe.org/sites/default/files/2022-05/Commentary_622.pdf. Grootendorst et al cite the following articles: Sanofi Canada. Vaccines. https://www.sanofi.ca/en/products-and-resources/vaccines; Sanofi Canada. Sanofi to build new manufacturing facility in Toronto to strengthen domestic pandemic preparedness and increase global supply of high-dose influenza vaccine. March 31, 2021. https://www.sanofi.com/en/media-room/press-releases/2021/2021-03-31-14-05-00-2202566; Pharmaceutical Technology. Novartis vaccine manufacturing facility, North Carolina. March 21, 2013. https://www.pharmaceutical-technology.com/projects/novartis-vaccine/?cf-view; Kansteiner F. Lonza plots $935M in capacity upgrades in Europe and U.S., plans to add 550 jobs over next 3 years. Fierce Pharma. May 6 2021. https://www.fiercepharma.com/manufacturing/lonza-plots-nearly-1b-mammalian-capacity-upgrade-switzerland-and-new-hampshire-adding
91. Plotkin S, Robinson J, Cunningham G, Iqbal R, Larsen S. The complexity and cost of vaccine manufacturing–an overview. Vaccine 2017;35:4064–71.
92. BioNTech SE. BioNTech achieves milestone: mRNA-based vaccine manufacturing. December 18, 2023. https://investors.biontech.de/news-releases/news-release-details/biontech-achieves-milestone-mrna-based-vaccine-manufacturing-0.
93. Pharmaceutical Technology. BioNTech mRNA vaccine manufacturing facility, Rwanda. April 24, 2024. https://www.pharmaceutical-technology.com/projects/biontech-mrna-facility-rwanda/?cf-view
94. Africanews. BioNTech mobile mRNA vaccine labs reach Rwanda. March 14, 2023. https://www.africanews.com/2023/03/14/biontech-mobile-mrna-vaccine-labs-reach-rwanda/
95. Univercells. Who we are. https://www.univercells.com/who-we-are
96. Quantoom Biosciences. https://quantoom.com/
97. Quantoom Biosciences. mRNA production reinvented. April, 2023. https://quantoom.com/wp-content/uploads/2023/04/Quantoom-Biosciences_Non-Confidential_2023-04.pdf
98. Quantoom Biosciences. A new paradigm in mRNA bioprocessing. How Ntensify reshapes affordability and reduces time-to-market. White paper. https://content.quantoom.com/white-paper-tco
99. Coalition for Epidemic Preparedness Innovations. CEPI 2.0 and 100 days mission. https://cepi.net/cepi-20-and-100-days-mission
100. Key informant interview with Quantoom representatives. Of the US$178 million in savings, US$51 million will be realized during the commercial launch (assuming a volume of 15 million vaccine doses), US$52 million during production ramp up (already at 100 million doses scale with Ntensify solution), and US$74 million during final scale production (100 million doses). Ntensify offers immediate capacity to produce at final scale production. CoGs includes CAPEX depreciation.
101. Key informant interview with Quantoom representatives. Most of the savings result from the optimized process and an optimized reagents concentration. Note that the saving is US$74 million due to rounding.
102. Key informant interview with Quantoom representatives. See also: Rybicki EP. First WHO/MPP mRNA technology transfer programme meeting. Lancet Microbe 2023;4:e564-e566.
103. King ML. How manufacturing won or lost the COVID-19 vaccine race. Vaccine 2024;42:1004–1012.
104. Africa CDC. Current and planned vaccine manufacturing in Africa: results from a joint assessment by Africa CDC, CHAI, and PATH. October 3, 2023. https://africacdc.org/download/current-and-planned-vaccine-manufacturing-in-africa-results-from-a-joint-assessment-by-africa-cdc-chai-and-path/
105. Paun C. Moderna pauses plans to build vaccine plant in Kenya. Politico Pro. April 11, 2024. https://subscriber.politicopro.com/article/2024/04/moderna-pauses-plans-to-build-vaccine-plant-in-kenya-00151773.
106. U.S. Department of State. PEPFAR sets bold manufacturing targets for Africa. December 13, 2022. https://www.state.gov/pepfar-sets-bold-manufacturing-targets-for-africa/
107. Global Fund. PEPFAR and Unitaid collaboration paves way to accelerate approval of African-manufactured HIV rapid tests. August 8, 2023. https://unitaid.org/news-blog/global-fund-pepfar-and-unitaid-collaboration-paves-way-to-accelerate-approval-of-african-manufactured-hiv-rapid-tests/#en

108. Sarin S. G20 presidency: fostering global collaboration to accelerate regional manufacturing for diagnostics. August 17, 2023. https://www.finddx.org/publications-and-statements/opinion-piece/g20-presidency-fostering-global-collaboration-to-accelerate-regional-manufacturing-for-diagnostics/
109. Fleming KA, Horton S, Wilson M, et al. The Lancet Commission on diagnostics: transforming access to diagnostics. Lancet 2021;398:1997–2050.
110. PATH. Market failures and opportunities for increasing access to diagnostics In low- and middle-income countries. 2022. https://media.path.org/documents/Dx_MarketFailures_Report_2022_v1b.pdf
111. Greenhoe S, Guzman J. The role of regulation in advancing African vaccine manufacturing: policy options for Gavi. Center for Global Development. November 29, 2023. https://www.cgdev.org/blog/role-regulation-advancing-african-vaccine-manufacturing-policy-options-gavi
112. Policy Cures Research. A decade of R&D funding for platform technologies. 2022. https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2022/06/30024039/2022-Snapshot-Platform-Technology.pdf
113. Policy Cures Research. G-FINDER Database. 2024. https://gfinderdata.policycuresresearch.org/
114. Yamey G. Developing vaccines for neglected and emerging infectious diseases. BMJ; 2021;372:n373.
115. Hodgson J. The pandemic pipeline. Nat Biotechnol 2020;38:523–32.
116. Sparrow E, Hasso-Agopsowicz M, Kaslow DC, et al. Leveraging mRNA Platform Technology to Accelerate Development of Vaccines for Some Emerging and Neglected Tropical Diseases Through Local Vaccine Production. Front. Trop. Dis 2022; 3:844039.
117. National Institute of Allergy and Infectious Diseases. Strategic plan for COVID-19 research—2021 update. 2021. https://www.niaid.nih.gov/sites/default/files/NIAID-COVID-19-Strategic-Plan-2021.pdf
118. Whitley J, Zwolinski C, Denis C, et al. Development of mRNA manufacturing for vaccines and therapeutics: mRNA platform requirements and development of a scalable production process to support early phase clinical trials. Transl Res 2022;242:38-55.
119. Wellcome Trust, IAVI. Expanding access to monoclonal antibody-based products: a global call to action. 2020. https://wellcome.org/sites/default/files/expanding-access-to-monoclonal-antibody-based-products.pdf
120. Liu J. The history of monoclonal antibody development – Progress, remaining challenges and future innovations. Ann Med Surg (Lond) 2014;3: 113-116.
121. Gupta R, Purcell LA, Corti D, et al. Pandemic preparedness strategies must go beyond vaccines. Sci Transl Med 2023;15:eadd3055.
122. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19. JAMA 2021;325: 632-644.
123. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med 2021;384:238-251.
124. Taylor PC, Adams AC, Hufford MM, et al. Neutralizing monoclonal antibodies for treatment of COVID-19. Nat Rev Immunol 2021;21:382–393.
125. National Institutes of Health. Anti-SARS-CoV-2 monoclonal antibodies. February 29, 2024. https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/anti-sars-cov-2-monoclonal-antibodies/.
126. Zhou D, Ren J, Fry EE, et al. Broadly neutralizing antibodies against COVID-19. Curr Opin Virol 2023;61:101332.
127. Aleshnick M, Florez-Cuadros M, Martinson T, et al. Monoclonal antibodies for malaria prevention. Mol Ther 2022;30:1810-1821.
128. Gruell H, Vanshylla K, Tober-Lau P, et al. Safety and efficacy of a monoclonal antibody against malaria in Mali. N Engl J Med; 2022;387:1833-1842.
129. Gaudinski MR, Coates EE, Novik L, et al. Safety, tolerability, pharmacokinetics, and immunogenicity of the therapeutic monoclonal antibody mAb114 targeting Ebola virus glycoprotein (VRC 608): an open-label phase 1 study. Lancet 2019;393:889-898.
130. Rijal P, Donnellan FR. A review of broadly protective monoclonal antibodies to treat Ebola virus disease. Curr Opin Virol 2023;61:101339.
131. Nkuba-Ndayse A, Dilue-Keti A, Tovar-Sanchez T, et al. Effect of anti-Ebola virus monoclonal antibodies on endogenous antibody production in survivors of Ebola virus disease in the Democratic Republic of the Congo: an observational cohort study. Lancet 2023;24:3,266-274.
132. Corey L, Gilbert PB, Juraska M, et al. Two randomized trials of neutralizing antibodies to prevent HIV-1 acquisition. N. Engl. J. Med. 2021;384:1003–1014.
133. Gieber L, Muturi-Kioi V, Malhotra S, et al. Clinical and regulatory challenges and opportunities for monoclonal antibodies in low- and middle-income countries: lessons from COVID-19 and beyond. Pharmaceut Med 2023;37:203-214.
134. Jones JM, Fleming-Dutra K, Prill MM. Use of nirsevimab for the prevention of respiratory syncytial virus disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices—United States, 2023. MMWR Morb Mortal Wkly Rep 2023;72:920-925.
135. European Medicines Agency. First RSV vaccine to protect infants 6 months of age and older adults. July 21, 2023. https://www.ema.europa.eu/en/news/first-rsv-vaccine-protect-infants-6-months-age-and-older-adults
136. U.S. Food and Drug Administration. FDA approves first respiratory syncytial virus (RSV) vaccine). May 3, 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-first-respiratory-syncytial-virus-rsv-vaccine
137. Sharfstein J. Two new RSV products to protect infants. November 13, 2023. https://publichealth.jhu.edu/2023/two-new-rsv-products-to-protect-infants
138. Centers for Disease Control and Prevention. Healthcare providers: RSV prevention information. September 28, 2023. https://www.cdc.gov/vaccines/vpd/rsv/hcp/child.html
139. Kieffer A, Beuvelet M, Sardesai A, et al. Expected impact of universal immunization with nirsevimab against RSV-related outcomes and costs among all US infants in their first RSV season: a static model. J Infect Dis 2022; 226(Suppl 2):S282-S292.
140. Karron RA. Preventing respiratory syncytial virus (RSV) disease in children. Science 2021;372:686–687.
141. Sparrow E, Adetifa I, Chaiyakunapruk N, et al. WHO preferred product characteristics for monoclonal antibodies for passive immunization against respiratory syncytial virus (RSV) in infants—key considerations for global use. Vaccine 2022;40:3506-3510.
142. World Health Organization. WHO preferred product characteristics for respiratory syncytial virus (RSV) vaccines. January 1, 2017. https://www.who.int/publications/i/item/WHO-IVB-17.11
143. Azatyan S. Strengthening the regulation of health products through networking, cooperation, and harmonization. Technical briefing seminar on medicines and health products, May 8-12, 2023. https://shorturl.at/xIY19
144. World Health Organization. Saudi Arabia regulatory system becomes third to reach WHO maturity level 4. October 30, 2023. https://www.who.int/news/item/30-10-2023-saudi-arabia-regulatory-system-becomes-third-to-reach-who-maturity-level-4

145. World Health Organization. WHO Listed Authority (WLA). A framework for evaluating and publicly designating regulatory authorities as WHO Listed Authorities (WLAs). https://www.who.int/initiatives/who-listed-authority-reg-authorities

146. World Health Organization. List of National Regulatory Authorities (NRAs) operating at maturity level 3 (ML3) and maturity level 4 (ML4) (as benchmarked against WHO Global Benchmarking Tool (GBT)). As of October, 2023. https://cdn.who.int/media/docs/default-source/medicines/regulatory-systems/wla/list-of-nras-operating-at-ml3-and-ml4.v2.pdf?sfvrsn=ee93064f_14&download=true

147. Nkubito BM, Geysels Y. The African Medicines Agency: impacts on the continent's clinical trials regulation. Applied Clinical Trials. June 20, 2023. https://shorturl.at/jEFPX

148. Sharpe DJ. Shorter timelines, evolving strategies: four key trends in regulatory approvals of new medicines. Clarivate. August 2, 2022. https://clarivate.com/blog/shorter-timelines-evolving-strategies-four-key-trends-in-regulatory-approvals-of-new-medicines/

149. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. https://www.ich.org/

150. Ahonkhai V, Martins SF, Portet A, et al. Speeding access to vaccines and medicines in low- and middle-income countries: a case for change and a framework for optimized product market authorization. PLoS ONE 2016;16;11:e0166515.

151. Miller JE, Mello MM, Wallach JD, et al. Evaluation of drug trials in high-, middle-, and low-income countries and local commercial availability of newly approved drugs. JAMA Netw Open 2021;4:e217075

152. Sithole T, Mahlangu G, Capote V, et al. Evaluation of the review models and approval timelines of countries participating in the Southern African Development Community: Alignment and strategies for moving forward. Front Med 2021;8:742200.

153. Tanzania Medicines and Medical Devices Authority. The ZAZIBONA collaborative medicines registration procedure. https://www.tmda.go.tz/pages/the-zazibona-collaborative-medicines-registration-procedure

154. Compared to the review of new drugs (as assessed in the study by Miller et al – reference 151), the regulatory process for generics (assessed by Sithole et al – reference 12) should take less time and resources, i.e., the ZAZIBONA timelines should have been comparatively shorter.

155. U.S. Food and Drug Administration. International regulatory harmonization. March 26, 2020. https://www.fda.gov/drugs/cder-international-program/international-regulatory-harmonization

156. Ndomondo-Sigonda M, Miot J, Naidoo S, et al. Harmonization of medical products regulation: a key factor for improving regulatory capacity in the East African Community. BMC Public Health 2021; 21:187.

157. Mwangi JM. Towards African medicines regulatory harmonization: the case of the East African Community. Pharm Policy Law 2016;18:91–8.

158. Schofield I. Janssen pilot speeds up African approvals as harmonization project expands. February 6, 2017. http://pink.citeline.com/PS119980/Janssen-Pilot-Speeds-Up-African-Approvals-As-Harmonization-Project-Expands

159. PATH. Making the case: How regulatory harmonisation can save lives in Africa. December 2018. https://www.path.org/resources/making-case-how-regulatory-harmonisation-can-save-lives-africa/

160. Liberti L. Globally applicable facilitated regulatory pathways to improve equitable access to medicines. 2017. Utrecht University Repository. http://dspace.library.uu.nl/handle/1874/353474

161. Ndomondo-Sigonda M, Azatyan S, Doerr P, et al. Best practices in the African Medicines Regulatory Harmonization initiative: Perspectives of regulators and medicines manufacturers. PLOS Glob Public Health 2023; 26:3(4):e0001651.

162. Bolislis WR, de Lucia ML, Dolz F, et al. Regulatory Agilities in the Time of COVID-19: Overview, Trends, and Opportunities. Clin Ther 2021;43:124e139.

163. Rodier C, Bujar M, McAuslane N, et al. Use of the Certificate for Pharmaceutical Products (CPP) in 18 maturing pharmaceutical markets: comparing agency guidelines with company practice. Ther Innov Reg Sci. 2020:1–11.

164. Wellcome Trust. Strengthening regulatory systems in LMICs. 2022. https://cms.wellcome.org/sites/default/files/2022-07/strengthening-regulatory-systems-in-low-and-middle-income-countries-improving-the-sustainability-of-the-vaccine-innovation-ecosystem-in-africa.pdf

165. Rwanda Food and Drug Authority. Cooperation in the regulation of medical products. August 2021. https://rwandafda.prod.risa.rw/news-details/agreement-mou-was-signed-between-rwanda-and-tanzania-governments-for-collaboration-between-the-nras-of-the-2-countries-rwanda-fda-and-tmda

166. Guzman J, Prashant Y. To increase vaccine manufacturing in LMICs, we also need to strengthen regulatory capacity. Center for Global Development. May 25, 2021. https://www.cgdev.org/blog/increased-vaccine-manufacturing-lmics-we-also-need-strengthen-regulatory-capacity

167. Kearny B, McDermott O. The challenges for manufacturers of the increased clinical evaluation in the European Medical Device Regulations: A Quantitative Study. Ther Innov Regul Sci 2023; 57(4): 783–796. See also: VDE Health. The EU Medical Device Regulation (MDR): What is changing. February 29, 2024. https://www.vde.com/topics-en/health/consulting/the-eu-medical-device-regulation-mdr-what-changes

168. African Union Development Agency-NEPAD. African Union Smart Safety Surveillance (AU-3S). https://www.nepad.org/microsite/african-union-smart-safety-surveillance-au-3s

169. Chong SSF, Kim M, Limoli M, et al. Measuring progress of regulatory convergence and cooperation among Asia-Pacific Economic Cooperation (APEC) member economies in the context of the COVID-19 pandemic. Ther Innov Regul Sci. 2021;55:786-798.

170. European Commission. Strengthening Rwanda Food and Drug Authority's regulatory functions related to medicinal products including vaccine. https://international-partnerships.ec.europa.eu/news-and-events/stories/lessons-and-successes-rwanda-food-and-drug-authority-and-team-europe-twinning-project_en

171. Policy Cures Research. Neglected disease research and development: The higher costs of lower funding. 2023 Neglected Disease G-FINDER report. https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2024/01/08035109/2023-Neglected-Disease-G-FINDER-report.pdf

172. Policy Cures Research calculated that "in the absence of any inflation, global funding would have fallen by only 3.0%". See reference 171.

173. Policy Cures Research. G-FINDER Database. https://gfinderdata.policycuresresearch.org/

174. International Pandemic Preparedness Secretariat, Policy Cures Research. 100 days mission scorecard: Today's data to inform tomorrow's preparedness. January 2022. https://d7npznmd5zvwd.cloudfront.net/prod/uploads/2024/01/100-Days-Mission-Scorecard-Report.pdf

175. International Pandemic Preparedness Secretariat. 100 days mission: Therapeutics roadmap. January 2024. https://d7npznmd5zvwd.cloudfront.net/prod/uploads/2024/01/100-Days-Mission-Therapeutics-Roadmap.pdf

176. Policy Cures Research. Sexual and reproductive health research and development: Beyond spill-overs. 2023. https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2023/10/04050842/2023-SRH-G-FINDER.pdf

177. Access to Medicine Foundation. 2022 Access to Medicine Index. Special report: Women's health and SRHR. November 25, 2022. https://accesstomedicinefoundation.org/resource/what-is-the-role-of-r-and-d-in-addressing-srhr-needs-in-low-and-middle-income-countries

178. Access to Medicine Foundation. 2022 Access to Medicine Index. November 15, 2022. https://accesstomedicinefoundation.org/resource/2022-access-to-medicine-index

179. Merck for Mothers, Ferring Pharmaceuticals and WHO collaborated to support the advancement of Ferring's proprietary and investigational heat-stable carbetocin for the prevention of postpartum haemorrhage, which is better suited to use in LMICs as it can be stored and transported at much higher temperatures than oxytocin; however, it still needs to be administered intramuscularly.

180. Yamey G, Schäferhoff M, Moran M, et al. Developing an aggregator mechanism for late-stage clinical trials of neglected disease product candidates. The Center for Policy Impact in Global Health. Duke Global Working Paper Series 23. October 2020. http://centerforpolicyimpact.org/our-work/our-publications/developing-an-aggregator-mechanism-for-late-stage-clinical-trials/

181. CEPI. Global community comes together in support of 100 days mission and pledges over $1.5 Billion for CEPI's pandemic-busting plan. March 8, 2022. https://cepi.net/news_cepi/global-community-comes-together-in-support-of-100-days-mission-and-pledges-over-1-5-billion-for-cepis-pandemic-busting-plan/

182. Schäferhoff M, Chodavadia P, Martinez S, et al. International funding for global common goods for health: an analysis using the Creditor Reporting System and G-FINDER databases. Health Syst Reform 2019;5:350-365.

183. International Pandemic Preparedness Secretariat, FIND. Embedding diagnostic best practice to improve pandemic preparedness: An independent report from the International Pandemic Preparedness Secretariat and FIND. 2023. https://d7npznmd5zvwd.cloudfront.net/prod/uploads/2023/11/IPPS_Diagnostics-Report_2023.pdf

184. Xu M, Benn C, Reid-Henry S, Brown T, Zhou S, Yang J, Chen Y, Wang Z. Rethinking international financing for health to better respond to future pandemics. BMJ Glob Health 2023;8(11):e012988.

185. World Health Organization, World Bank. Analysis of pandemic preparedness and response (PPR) architecture, financing needs, gaps and mechanisms. 2022.

186. Ridley DB. Priority review vouchers. Durham (NC): Duke University Fuqua School of Business. https://sites.fuqua.duke.edu/priorityreviewvoucher and https://sites.fuqua.duke.edu/priorityreviewvoucher/awarded/

187. Ridley DB, Lasanta AM, Storer Jones F, et al. European priority review vouchers for neglected disease product development. BMJ Glob Health 2024;9:e013686

188. Valneva. Valneva gibt Verkauf seines Priority Review Vouchers für $103 Mio bekannt. February 5, 2024. https://valneva.com/press-release/valneva-announces-sale-of-priority-review-voucher-for-103-million/?lang=de

189. Ridley DB, Ganapathy P, Kettler HE. US tropical disease priority review vouchers: Lessons in promoting drug development and access. Health Aff 2021; 40(8).

190. U.S. Government Accountability Office. Drug development: FDA's priority review voucher programs (GAO-20-251). January 31, 2020. https://www.gao.gov/products/gao-20-251

191. Aerts C, Barrenho E, Miraldo M et al. The impact of the priority review voucher on research and development for tropical diseases. Pharmaceut Med 2022;36(3):189-197.

192. Ridley DB. Priorities for the Priority Review Voucher. Am J Trop Med Hyg 2017; 96:14–15.

193. Ridley DB, Sánchez AC. Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases. Lancet 2010;376:922-7.

194. Bank D. Guaranteed Impact. Stanford Social Innovation Review. Supplement. 2016. https://ssir.org/pdf/Summer_2016_Guaranteed_Impact.pdf

195. Reuters: Africa to get state-of-art HIV drugs for $75 a year. September 21, 2017. https://news.trust.org/item/20170921090612-zaslo/

196. Clinton Health Access Initiative. New high-quality antiretroviral therapy launched in South Africa and Kenya, available in 90 low- and middle-income countries at reduced price. September 21, 2017. https://www.clintonhealthaccess.org/news/new-high-quality-antiretroviral-therapy-launched-south-africa-kenya-90-low-middle-income-countries-reduced-price/

197. ReliefWeb. Bill & Melinda Gates Foundation commits $120 million to accelerate access to COVID-19 drug, lower prices for developing countries. October 19, 2021. https://reliefweb.int/report/world/bill-melinda-gates-foundation-commits-120-million-accelerate-access-covid-19-drug-lower

198. Yadav P. How the pandemic changed the future of work. Financial Times. October 15, 2023. https://www.ft.com/content/86acf796-3744-4924-9c78-57c291c2d833

199. The Global Fund. Global partnership to make available 120 million affordable, quality COVID-19 rapid tests. October 20, 2023. https://www.theglobalfund.org/en/news/2020/2020-09-28-global-partnership-to-make-available-120-million-affordable-quality-covid-19-rapid-tests/

200. World Health Organization. Global Health Expenditure Report 2023. https://www.who.int/news/item/11-12-2023-who-calls-on-governments-for-urgent-action-to-invest-in-universal-health-coverage

201. Reid M, Agbassi YJP, Arinaminpathy N, et al. Scientific advances and the end of tuberculosis: a report from the Lancet Commission on Tuberculosis. Lancet 2023;402:10411, 1473-1498.

202. Suleman F, Low M, Moon S, Morgan SG. New business models for research and development with affordability requirements are needed to achieve fair pricing of medicines. BMJ2020;368:10–2.

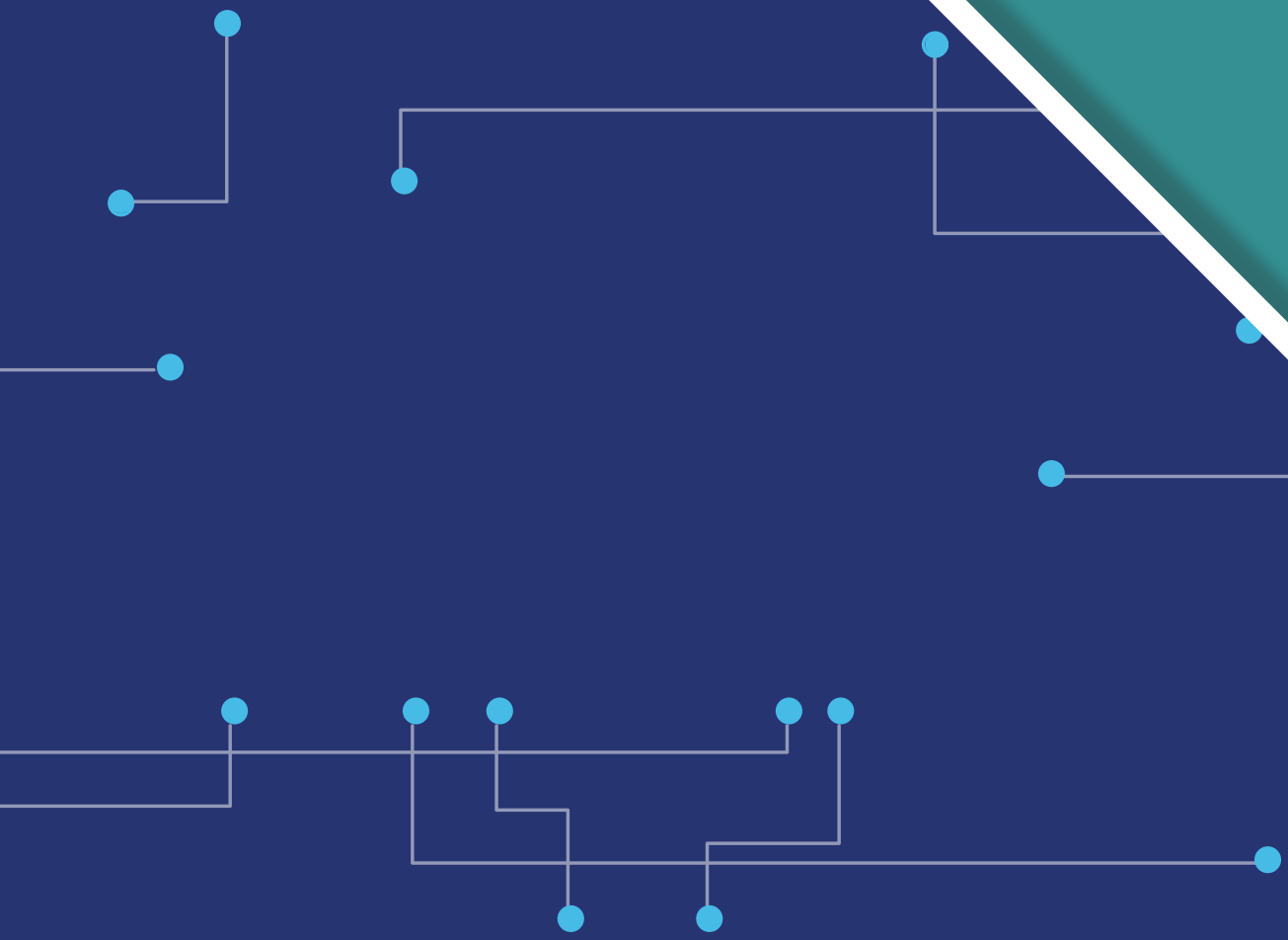
203. Adam T, Ralaidovy AH, Ross AL, et al. Tracking global resources and capacity for health research: time to reassess strategies and investment decisions. Health Res Policy Syst 2023;21:93.

204. Africa CDC. (2023). Risk ranking and prioritization of epidemic-prone diseases. February 26, 2023. https://africacdc.org/download/risk-ranking-and-prioritization-of-epidemic-prone-diseases/

205. In addition to Asian countries, APEC also includes several countries from North and Latin America and the Pacific.

206. Africa CDC. Meeting report: optimizing efficiency and impact in the African clinical trials ecosystem. November 8, 2023. https://africacdc.org/download/meeting-report-optimizing-efficiency-and-impact-in-the-african-clinical-trials-ecosystem/

207. Summers LH, Jamison DT, et al. Global health 2050: challenges and opportunities in the post-COVID world. Lancet, 2024. Forthcoming.



THE CENTER FOR POLICY IMPACT IN GLOBAL HEALTH

Gavin Yamey, Director
Trent Hall, Room 113
310 Trent Drive
Durham 27710
Twitter: @gyamey
centerforpolicyimpact.org

OPEN CONSULTANTS

Marco Schäferhoff, PhD
Managing Director
Jägerstr. 54/55
10117 Berlin, Germany
+49(0)17681037928
mschaeferhoff@openconsultants.org
openconsultants.org
linkedin.com/company/open-consultants