POLICY BRIEF

THE CENTER FOR POLICY IMPACT IN GLOBAL HEALTH

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

KEY MESSAGES

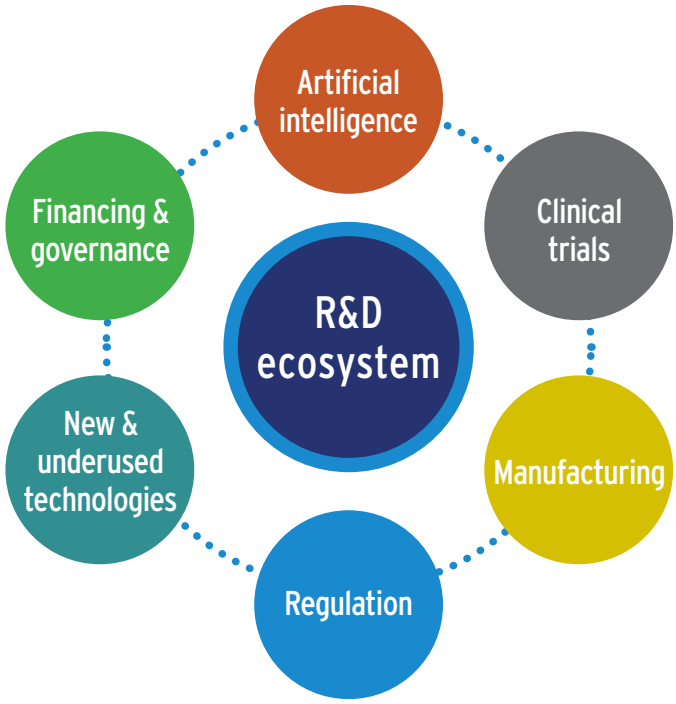
- The long timelines, high attrition rates, and high costs of global health research and development (R&D) are a barrier to bringing new medicines, vaccines, and diagnostics to the market
- Several promising innovations in the R&D ecosystem could help overcome these problems, accelerating the discovery and development of new health technologies
- Artificial intelligence can reduce discovery times to less than one year and costs by a factor of up to 50, while clinical trial networks and sharing control data can reduce trial costs by 40-60%
- Regulatory harmonization can reduce approval times down to 1-2 years
- Optimized mRNA production processes can reduce costs of goods by about 60%
- Widespread scale up of these innovations could transform the global health R&D landscape and accelerate progress in tackling a range of neglected diseases, emerging infectious diseases, and maternal health conditions

INTRODUCTION

The long timelines, high attrition rates, and high costs of global health R&D are impeding the development of new health technologies for neglected diseases (NDs), emerging infectious diseases (EIDs), and maternal health (MH). This **Policy Brief** synthesizes the key findings of a new analysis examining innovations across six key domains of the R&D ecosystem that could help tackle these barriers (Figure 1).[1] The analysis was based on insights and data from:

- Two **workshops** with over 30 senior policy actors engaged in global health R&D policymaking, with strong representation from low- and middle-income countries (LMICs)
- **Key informant interviews** with over 60 experts worldwide, including from academia, health and development agencies, pharmaceutical companies, research funders, regulators, product development partnerships, non-government organizations, foundations, and regional alliances
- **Regional consultations** with over 60 stakeholders in Africa, Asia, and Latin America
- **A review and synthesis** of the literature.

Figure 1: Six key dimensions of the R&D ecosystem



For each of the six innovation areas, this brief summarizes the benefits of the innovation, potential challenges, and recommendations for policy reform.

1. APPLYING ARTIFICIAL INTELLIGENCE TO PRODUCT DEVELOPMENT

BENEFITS

Artificial intelligence (AI) is already transforming the global health R&D ecosystem, including by speeding up drug discovery. The standard time for screening, identifying, and validating target molecules is 3-5 years; with AI, the discovery phase can be shortened to less than 12 months.[2] There are examples of AI tools that have lowered discovery costs by a factor of up to 50.[3] AI tools can improve screening and thus the quality of candidates, leading to less attrition during the clinical phase. There is a valuable role for AI platforms in drug repurposing and in identifying combination therapies.

CHALLENGES

If it is rolled out inequitably, AI could augment inequalities between LMICs and high-income countries (HICs). Researchers in LMICs have called for research on AI grounded in local contexts 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.

RECOMMENDATIONS FOR REFORM

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.
5. **Significantly strengthen existing regulatory frameworks for AI in global health.**

2. INNOVATIONS IN CLINICAL TRIAL CONDUCT

BENEFITS

Technological innovations, innovative trial designs, and trial networks are transforming clinical trial conduct. Digital clinical trials (DCTs) can reduce trial costs, timelines, and the number of patients needed in a trial and can improve recruitment and retention of participants. Platform trials can shorten trial duration, evaluate more treatments per trial, reduce the number of patients required per trial, and increase the proportion of programs that accurately recognize an effective treatment. 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.

CHALLENGES

DCTs have mostly been conducted in HICs, and it is unclear whether the findings can be generalized to LMICs. Capacity for conducting even traditional trials is currently limited in many 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).

RECOMMENDATIONS FOR REFORM

1. **Research funders and agencies should support sustained efforts to build clinical trial networks that have the capacity to adopt innovative approaches, leveraging capacities already built.**
2. **Adoption of platform trials and other master protocols in low-resource settings will require funding agencies, institutional review boards, 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. BUILDING MANUFACTURING CAPACITY IN LMICS

BENEFITS

Building the capacity of LMICs to manufacture health technologies has taken on new urgency—such capacity would ensure that in the next epidemic or pandemic these countries can manufacture medical countermeasures themselves rather than relying on donations from HICs. While traditional manufacturing is expensive, innovative modular manufacturing facilities have a smaller footprint, lowering capital costs. Optimized production processes for mRNA technologies have much lower operational costs because of high yields, reduced reagent use, and efficient design—the savings could lower mRNA vaccine production costs to US$0.5 per dose.[4] These processes also offer (i) flexibility to quickly switch from making one vaccine to another, (ii) scalable production, and (iii) integration of product development with large-scale manufacturing.

CHALLENGES

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.

RECOMMENDATIONS FOR REFORM

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. Donor agencies should subsidize manufacturing in LMIC regions and 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 in these regions.
2. **LMICs should also commit to buying products manufactured by LMICs**, such as through advanced purchase agreements, to help create sustainable markets.
3. **The 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).

4. ACCELERATING REGULATORY REFORMS

BENEFITS

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

CHALLENGES

Countries that do not have capacity to fulfill the range of necessary regulatory functions often also lack legislation for reliance. In addition, the implementation of reliance is often done poorly. There is still insufficient collaboration between national regulatory authorities (NRAs).

RECOMMENDATIONS FOR REFORM

1. **Regulatory capacity gaps need to be gradually and strategically addressed**. LMICs should assess their current regulatory systems using the WHO benchmarking tool[5] and allocate more funding to these systems. HICs should provide technical and financial support to NRAs 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. LMICs with more advanced NRAs should support less advanced countries.
2. **Any efforts to strengthen manufacturing capacity need to be accompanied by investments in regulatory systems.**
3. **WHO pre-qualification (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.

5. IMPROVING THE FINANCING OF R&D FOR NDS, EIDS, AND MH

BENEFITS

Several mechanisms have been used to improve the financing of product development for NDs, EIDs, and MH and to close the funding gap. In the United States, the priority review voucher (PRV), introduced in 2007, awarded more than 60 vouchers by 2024, contributing to the development of new medicines for NDs, such as Chagas and tuberculosis.[6] US vouchers were sold for US$100 million each, creating a substantial though insufficient financial incentive for developers. Volume guarantees have played an important role in creating sufficient incentive to manufacture health products, e.g., a volume guarantee in 2012 for production of the pentavalent vaccine by an Indian producer led to substantial cost savings for Gavi, the Vaccine Alliance. Increased domestic financing of R&D by LMICs would yield large health and economic returns.

CHALLENGES

There is still 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).[7] Funding for EIDs R&D has substantially increased, but the increase was mostly due to the COVID-19 pandemic. While funding for sexual and reproductive health R&D grew from 2018 to 2021 (totaling US$593 million in 2021), only a small share of this funding was for MH tools and the share declined over time. While there has been a recent increase in domestic LMIC funding for R&D for NDs, EIDs, and MH, the absolute amount remains very small.

RECOMMENDATIONS FOR REFORM

1. **A PRV should be created in Europe, hosted by the European Medicines Agency**. A European Union (EU) voucher would provide an additional incentive of US$100 million to US$200 million, which investors say would be a meaningful stimulus.[8] 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 the Priority Medicines Scheme.
2. **Volume guarantees should remain a key mechanism to promote access to new health tools.**

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.**

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

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. 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 non-communicable diseases. However, only seven mAbs were licensed for infectious diseases.

CHALLENGES

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. 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, and availability and affordability are two of the biggest barriers impeding global access to mAbs.

RECOMMENDATIONS FOR REFORM

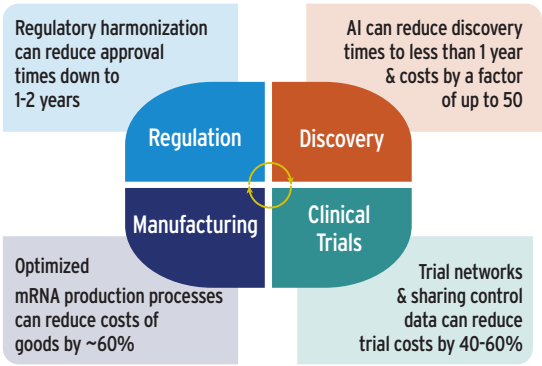
1. **Given that mRNA platforms have significant comparative advantages over more traditional technologies, investments should be scaled up in mRNA technologies for NDs, EIDs, and MH**.
2. **It is critical for LMICs to be able to produce their own mRNA technologies**. The global health community needs to support 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.
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**. A low-cost mAb for respiratory syncytial virus (RSV) is believed to be under development and could serve as a product for the global community to rally around.
5. **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.

CONCLUSION

There are key shifts and innovations now underway across six major domains of the R&D ecosystem for NDs, EIDs, and MH, which hold great potential for accelerating R&D, lowering its costs, and reducing attrition rates (Figure 2). 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.

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



1. The full analysis and supportive evidence is at https://centerforpolicyimpact.org/wp-content/uploads/sites/18/2024/05/reforming-research-and-development-ecosystem-final.pdf. It was conducted by researchers at Open Consultants, Berlin, Germany (Marco Schäferhoff); The Center for Policy Impact in Global Health, Duke University, Durham, North Carolina, USA (Gavin Yamey, Osondu Ogbuoji, Ayodamope Fawole, Armand Zimmerman, Ipchita Bharali, Ernesto J. Ortiz); the University of KwaZulu-Natal, Durban, South Africa (Mosa Moshabela); and Peking University, Beijing, China (Ming Xu); and by an independent global health consultant (Shingai Machingaidze). The work was funded by a grant from the Bill & Melinda Gates Foundation.
2. See, for example, Zhavoronkov A, Ivanenkov YA, Aliper A, et al. Deep learning enables rapid identifcation of potent DDR1 kinase inhibitors. Nat Biotechnol 2019;37:1038–1040. Additional examples are in the full report (reference 1).
3. For example, 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, rapidly identifying protein candidates for its candidate vaccine. It estimates that the entire costs for the drug discovery and preclinical phases totaled about US$215,000, a fraction of the cost of traditional screening studies.
4. Rybicki EP. First WHO/MPP mRNA technology transfer programme meeting. *Lancet Microbe* 2023;4:e564-e566.
5. https://www.who.int/tools/global-benchmarking-tools
6. See https://sites.fuqua.duke.edu/priorityreviewvoucher and https://sites.fuqua. duke.edu/priorityreviewvoucher/awarded
7. https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2024/01/08035109/2023-Neglected-Disease-G-FINDER-report.pdf
8. Ridley DB, Sánchez AC. Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases. *Lancet* 2010;376:922-7.