

# The Next Game Changers

## A Priority Innovation Agenda for Global Health

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### Abstract

Over the last century, scientific and technological innovation has led to unprecedented improvements in health outcomes—yet research and development (R&D) investments and progress to address health threats has been uneven. Commercial R&D has focused where investors can expect substantial financial returns: rich countries, the diseases that affect them, and high-tech solutions designed for the richest and most sophisticated systems. Despite supplemental funding from philanthropic and government grants, R&D to address many leading causes of death and disability—especially those that primarily affect low- and middle-income countries (LMICs) or insure against future risk—has been consistently underfunded relative to potential health gain. This implies that many untapped opportunities remain to dramatically improve global health and welfare via biomedical innovation.

In this paper, we report the results of a horizon-scanning exercise to source opportunities for global health R&D investment—that is, high-value potential biomedical innovations which are currently underfunded but which could be transformative for health, quality of life, and health security in LMICs and around the world. Drawing from a literature review and expert interviews with researchers, economists, funders, advocates, and implementers, we lay out an expansive and high-promise (though non-comprehensive) biomedical innovation agenda for global health spanning the unfinished MDG agenda; non-communicable diseases; and global health security. We conclude with a discussion of implications for research, funding, and practice.

## The Next Game Changers: A Priority Innovation Agenda for Global Health

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## Introduction

Over the last century, scientific and technological innovation has led to unprecedented improvements in health outcomes. New tools in the form of vaccines, therapeutics, and diagnostics have contributed to such public health successes as the eradication of smallpox and the transformation of HIV from a near death-sentence to a manageable chronic condition. The emergence of and response to COVID-19 offers another high-level illustration of the potential speed and power of biomedical innovation to transform killers into mostly manageable and/or preventable conditions. Yet at the global level, research and development (R&D) progress to address old and new health threats has been uneven.

The nature of innovation is unpredictable and high-risk, requiring front-loaded costs to support R&D. Much of R&D money—about 60% of all health R&D expenditure in wealthy countries<sup>1</sup>—flows from private investors and companies, who are in turn chasing returns on investment and profit. Broadly speaking, this dynamic can be characterized as a “pull” approach to financing innovation, whereby the promise of future sales and/or other revenue indirectly justify upfront expenditures in R&D, thereby “pulling” innovations to market. Most “pull” R&D dollars are laser-focused where investors can expect a substantial financial return: that is, rich countries, the diseases that affect them, and high-tech solutions designed for the richest and most sophisticated systems.

These market “pull” incentives are thus powerful, but incomplete. A parallel system of philanthropic and government grants supplements private sector R&D, and is often the only financing source for early-stage research; diseases that primarily affect low- and middle-income countries (LMICs)<sup>2</sup> or poor/marginalized populations; or other situations in which there is no clear path to profit. This approach can be characterized as “push financing” that directly subsidizes and defrays upfront R&D costs. The US government alone spends approximately \$135 billion each year on various forms of push funding to promote cross-sectoral R&D.<sup>3</sup>

Despite these public and philanthropic investments, overall R&D spending continues to largely neglect many LMIC needs. Countries classified as high-income receive the overwhelming majority of R&D expenditure<sup>4</sup>—both from the private sector and from biomedical research grants. Out of \$156.7 billion that pharmaceutical companies spent on overall health R&D in 2016, for example, only an estimated

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1 John-Arne Røttingen, Sadie Regmi, Mari Eide, Alison J Young, Roderik F Viergever, Christine Årdal, Javier Guzman, Danny Edwards, Stephen A Matlin, Robert F Terry (2013). Mapping of available health research and development data: what’s there, what’s missing, and what role is there for a global observatory? *Lancet* 382:1286–307.

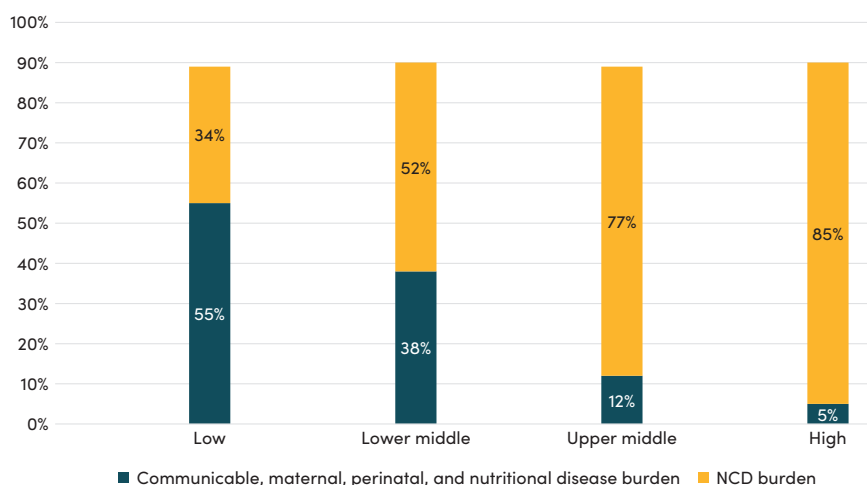
2 In this paper, we use the terminology of “low- and middle-income countries” to connote country income classification. We use this language to refer to country income groups and to contrast LMICs with HICs, which receive the bulk of R&D attention/investment given HICs’ market size. We are not implying that LMICs are homogenous (by income, disease burden, health care access, or any other characteristic). For more on the use of this category, see: Lencucha R, Neupane S. The use, misuse and overuse of the ‘low-income and middle-income countries’ category. *BMJ Global Health* 2022;7:e009067.

3 Congressional Research Service (2022). Federal Research and Development (R&D) Funding: FY2022. Available from: <https://sgp.fas.org/crs/misc/R46869.pdf>

4 JA Røttingen et al. Mapping of available health research and development data.

\$5.6 billion (3.6%) went towards drug and vaccine development that would primarily serve LMICs.<sup>5</sup> In 2019, US-based organizations alone received 90% of total global direct (primary) grant funding for biomedical research,<sup>6</sup> compared to less than one percent for all LMIC-based organizations combined.<sup>7</sup> And among eight of the largest primary grant recipients that reported collaborations—all of which are HIC-based, including the US National Institutes of Health—71% of their collaborations were with other HIC-based institutions.<sup>8</sup> The focus of grant funds show a similar skew toward rich country needs, as communicable, maternal, perinatal, and nutritional conditions account for just about a quarter of all grant funding and just nine percent of products in clinical development, despite this disease category comprising a significant disease burden in LMICs<sup>9</sup> (Figure 1, Figure 2).

**FIGURE 1. Disease burden by country income group**



Data source: Global Health Estimates 2019: Disease burden by Cause, Age, Sex, by Country and by Region, 2000–2019. Geneva, World Health Organization, 2020.

Note: Disease burden measured in disability-adjusted life years; percentages reflect total disease distribution per country income group. Percentages do not add up to 100% because Group III conditions, injuries, are omitted.

5 Darrell M. West, John Villasenor, and Jake Schneider. Private Sector Investment in Global Health R&D: Spending Levels, Barriers, and Opportunities. The Brookings Private Sector Global Health R&D Project. No. 2, September 2017. Available from: [https://www.brookings.edu/wp-content/uploads/2017/09/private-sector-investment-in-global-health-rd\\_final.pdf](https://www.brookings.edu/wp-content/uploads/2017/09/private-sector-investment-in-global-health-rd_final.pdf). The authors define global health R&D as “investments in drugs, vaccines, and therapeutics that emphasize the developing world” and state that “in 2016, we estimate that Western and non-Western pharmaceutical companies contributed \$5.6 billion in global health R&D targeting the developing world for drug and vaccine development.” We interpret their use of the phrase “developing world” as intended to indicate LMICs.

6 World Health Organization. Investments on grants for biomedical research by funder, type of grant, health category and recipient. January 2022. Available from: <https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/investments-on-grants-for-biomedical-research-by-funder-type-of-grant-health-category-and-recipient>. And: World Health Organization. Number of grants for biomedical research by funder, type of grant, duration and recipients (World RePORT). January 2022. Available from: <https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-grants-for-biomedical-research-by-funder-type-of-grant-duration-and-recipients>.

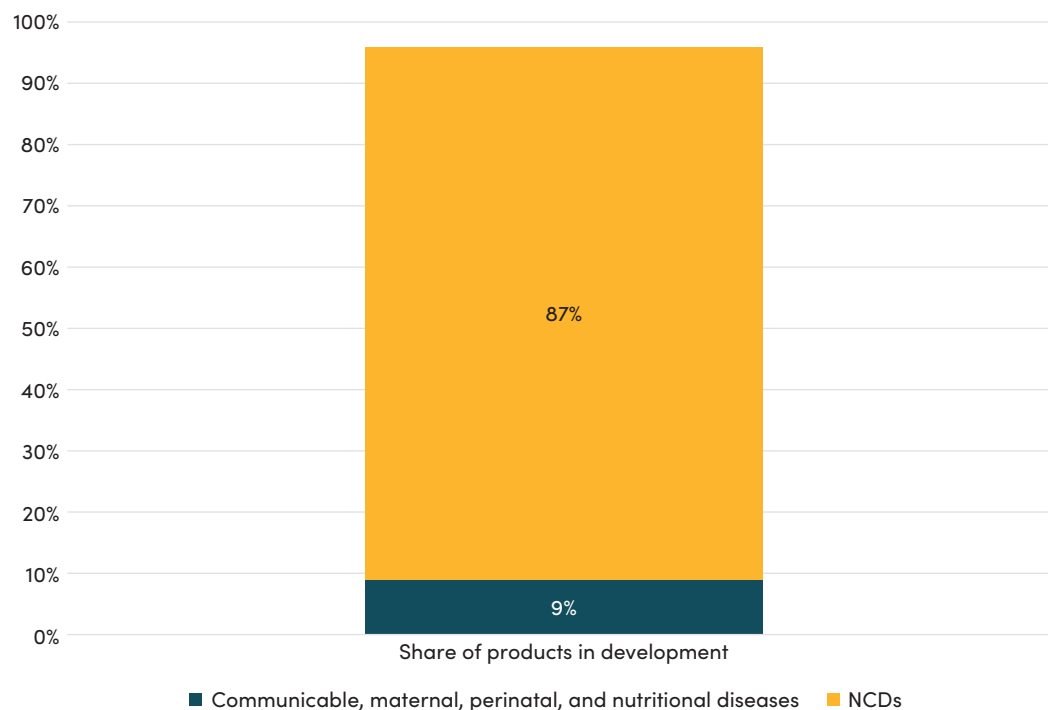
7 WHO. Investments on grants for biomedical research.

8 World Health Organization. Collaborations (between institutions) that resulted from grants for biomedical research. January 2022. Available from: <https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/collaborations-between-institutions-that-resulted-from-grants-for-biomedical-research>.

9 WHO. Investments on grants for biomedical research.

These skews in R&D expenditure directly translate to imbalances in the R&D pipeline and new medicine approvals. Between 2008 and 2018, 103 of 171 new medicine approvals launched by 20 of the largest pharmaceutical companies were for noncommunicable diseases (NCDs) such as diabetes and heart disease; in contrast, only one neglected tropical disease (NTD) medicine was approved during that ten-year period.<sup>10</sup> Likewise, 82% of all health products currently in the R&D pipeline (including in preclinical, clinical, and registration phases) are for noncommunicable diseases.<sup>11</sup> And among 211 health products the World Health Organization (WHO) and Policy Cures Research identified as priority innovations for LMICs, 149 are not in private sector development.<sup>12</sup>

**FIGURE 2. R&D attention per disease area measured by share of products in clinical development**



Data source: Adam T, Ralaidovy AH, Swaminathan S. Biomedical research; what gets funded where? *Bull World Health Organ.* 2019;97(8):516–516A.

Note: Percentages do not add up to 100% because Group III conditions, injuries, are omitted.

10 Access to Medicine Foundation (2019). Are pharmaceutical companies making progress when it comes to global health? Available from: <https://accesstomedicinefoundation.org/publications/are-pharmaceutical-companies-making-progress-when-it-comes-to-global-health>. See also: World Health Organization (2016). Health Product Research and Development Fund: A Proposal for Financing and Operation. Available from: [https://apps.who.int/iris/bitstream/handle/10665/204522/9789241510295\\_eng.pdf;jsessionid=1696A160A295B976D31E2849832F821C?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/204522/9789241510295_eng.pdf;jsessionid=1696A160A295B976D31E2849832F821C?sequence=1).

11 World Health Organization. Health products in the pipeline from discovery to market launch for all diseases. July 2022. Available from: <https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/health-products-in-the-pipeline-from-discovery-to-market-launch-for-all-diseases>.

12 Access to Medicine Foundation (2021). Access to Medicine Index 2021. Available from: <https://accesstomedicinefoundation.org/publications/2021-access-to-medicine-index>.

Taken together, these findings suggest serious gaps in the R&D pipeline for products that would benefit LMICs—and missed opportunities to improve health and welfare for the billions of people who live in them. These observations, alongside major access challenges for existing products, have led some academics and advocates to reconsider our global system of R&D funding and contemplate different financing models that could help address R&D inequities.

One potential approach is explicit “pull mechanisms”, which are designed to bring market incentives and the power of the private sector to health areas that would not otherwise receive enough private R&D investments. Pull mechanisms use either public or philanthropic financing/underwriting to increase either the expected size or predictability of revenue/sales for a health product, contingent on successful innovation. Pull mechanisms can de-risk emerging markets for pharmaceutical companies and encourage R&D expenditure to meet LMIC needs; they can also help LMIC governments and other payers lock-in locally affordable pricing, helping ensure that resultant innovations are broadly accessible to potential patients/users.

Starting in late 2021, we began a horizon-scanning exercise intended to source new opportunities for pull mechanisms—that is, high-value potential biomedical innovations which are currently underfunded but which could be transformative for health, quality of life, and health security in LMICs and around the world. That exercise has yielded several case studies, which will be shared and discussed extensively in a forthcoming working paper. However, the exercise also yielded a broader innovation agenda for global health, informed by expert interviews with researchers, economists, funders, advocates, and implementers working across disease areas and disciplines. In this paper, we share those findings with the dual goals of: (1) clarifying the global health innovation agenda; and (2) motivating further investments in the health technologies that could be transformative for the world’s poor and vulnerable.

This paper proceeds as follows. First, we describe our motivation for and approach to identifying high-value promising global health innovations as part of a broader initiative exploring potential use cases for pull mechanisms in global health innovation. Second, we report out on the global health innovation agenda raised by experts and stakeholders. We group the enormous agenda into the following three categories:

1. **The unfinished MDG agenda**—focusing specifically on HIV, tuberculosis, malaria, childhood pneumonia, contraception, and leishmaniasis
2. **The noncommunicable disease (NCD) agenda**—affordable and accessible tools to address the growing burden of NCDs such as cardiovascular disease, heavy metal poisoning, mental/brain health, diabetes, kidney failure, and cancer in LMICs
3. **The global health security agenda**—pandemic preparedness and response, surveillance, and antimicrobial resistance (AMR)



We conclude with a brief discussion of additional factors influencing and informing the future of global health innovation, including broader contextual considerations for accelerating progress in ensuring health for all.

Finally, we offer two appendices describing stakeholder views on pull mechanisms more broadly. In Appendix A, we report out on stakeholder familiarity with and perceptions of pull mechanisms as a tool for driving global health innovation, including a brief overview of types of pull mechanisms that have either been applied or proposed to address global health challenges. We also highlight in Appendix B design considerations that would inflect the application of pull mechanisms to any of these high-priority innovation areas.

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## Methods

Starting in late 2021, we conducted a horizon-scanning exercise that explored how and when pull mechanisms could best be applied to address global health challenges. We conducted a literature review and 24 interviews with 33 experts, including biomedical researchers, funders, advocates, and economists, all broadly considering different disease areas, technology types, and stages in the R&D pipeline.<sup>13</sup> The horizon-scanning exercise was not designed or powered to identify the “best” or “most important/needed” innovations. Instead, our goal was to source a handful of promising innovations that would offer high global health value while also offering illustrative value about a range of potential pull mechanism applications.

Our analytic criteria for this exercise included:

1. **Potential health impact** (i.e., save and/or improve lives) vis-à-vis globally important health challenges, with an emphasis on:
  - a. Global public goods, such as antimicrobials or pandemic preparedness
  - b. Health problems that mostly affect LMICs
  - c. Health problems that are broadly shared, but where existing health technologies are not affordable or otherwise accessible in most LMICs (e.g., cancer or kidney disease)
2. **Existence of a market failure** that prevents or otherwise limits R&D, market entry, and/or widespread health product access
3. **Opportunity for a well-designed pull mechanism** to address the market failure described in (2).

Though the methodology was originally intended only to source pull mechanism case studies,<sup>14</sup> a review of our preliminary findings in early-2022 suggested that the results of the horizon-scanning

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<sup>13</sup> We were not able to consult patient groups/directly affected individuals as part of this horizon-scanning exercise; we acknowledge this missing perspective as a limitation. We view advocates’ perspectives with whom we consulted as helpful in filling in this gap.

<sup>14</sup> A complementary paper on pull mechanism case studies, also drawing from the horizon-scanning exercise, will be published by end-2022.

exercise could also be broadly informative for understanding the overall innovation agenda for global health, without prejudice to a specific R&D financing model. We thus expanded upon/modified our original exercise along the following parameters for the purposes of this paper:

- We eliminated criteria [2] and [3] listed above—that is, we considered all potentially impactful innovations without prejudice to optimal R&D financing approach or underlying cause of R&D neglect.
- We constrained our analysis to focus narrowly on R&D—that is, global health innovations that do not yet exist but which have the potential to transform global health if developed. We thus omit discussion of health products that already exist but which are not available at scale globally, such as certain NCD diagnostics and therapeutics, and water, hygiene, and sanitation interventions.
- We constrained our analysis to focus narrowly on *biomedical innovation* specifically (i.e., biomedical innovations such as medicines or diagnostic tests); we thus exclude potential innovations in service delivery, financing, or logistics, as well as in telecommunications and energy access. This choice should not be interpreted as a reflection of relative value; in many cases, service delivery bottlenecks may be far more important barriers to health improvement than the lack of biomedical innovation. However, they are beyond the scope of this paper.
- We conducted additional literature review to better understand the specific innovations under consideration, including development stage and existing constraints to R&D.
- We conducted three additional interviews after the initial innovation list had been selected to ensure the ultimate selections were broadly representative and inclusive of stakeholder perspectives.

Finally, we caution that while our findings reflect the content of stakeholder interviews, they are necessarily filtered through our own interpretations and contextualization. The absence of a potential innovation from this list should *not* be interpreted as a negative statement about its importance or potential. All errors, omissions, and ultimate editorial responsibility are our own.

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## On the Agenda: Promising and Necessary Innovations for Global Health

The following section outlines three priority health innovation agendas that emerged during our horizon-scanning exercise. Each innovation agenda includes discrete challenges that contribute to poor health outcomes/premature deaths, and accompanying opportunities for addressing each identified challenge. Given the broad scope of this research, our findings similarly span a broad range of health areas (e.g., malaria, contraception, diabetes) and innovation types (e.g., diagnostics, therapeutics, vaccines). The innovations described below do not reflect an exhaustive or complete list

of all health areas warranting greater investment; rather, they comprise a sampling of necessary and important health innovations for global health.<sup>15</sup>

**TABLE 1. Summary of the global health innovation agenda**

Innovation	Health Area	Innovation Type
<b>The Unfinished MDG Agenda</b>		
Rapid POC TB diagnostic test	Tuberculosis	Diagnostic
Universal short-course TB regimen	Tuberculosis	Therapeutics
Next generation antimalarials	Malaria	Therapeutics
Longer lasting prevention tools	Malaria	Vaccine, preventative therapeutics
Longer lasting, scalable HIV prevention	HIV/AIDS	Vaccine, preventative therapeutics
Rapid antigen test	Leishmaniasis	Diagnostic
New treatment options	Leishmaniasis	Therapeutics
Nonhormonal, male, and multipurpose contraceptives	Contraception & reproductive health	
Rapid POC diagnostic test	Pneumonia	Diagnostic
<b>The Noncommunicable Disease Access Agenda</b>		
Rapid diagnostic test capable of detecting all forms of SCD	Sickle cell disease	Diagnostic
More safe, effective, affordable, and scalable SCD treatment options	Sickle cell disease	Therapeutic
Cheaper, thermostable, quality-assured biosimilar insulin products	Diabetes	Therapeutic
Better, more affordable, less resource-intensive dialysis options	Kidney disease	Therapeutic
Intuitive, accurate, and accessible self-testing/self-sampling tools	Cancer care	Diagnostic
More reliable and affordable diagnostics for POC lead testing	Lead poisoning	Diagnostic
Safe, inexpensive chelation therapy	Lead poisoning	Therapeutic
<b>The Global Health Security Agenda</b>		
Pan-coronavirus and pan-influenza vaccines	Pandemic preparedness	Vaccines
New classes of antimicrobials	Antimicrobial resistance (AMR)	Therapeutics
Multiplex genomic sequencing	Outbreak surveillance, pandemic preparedness, & AMR	Diagnostics

Note: POC = point-of-care.

15 For a more thorough listing of global health innovations in the pipeline, see: <https://www.who.int/observatories/global-observatory-on-health-research-and-development/resources/databases/databases-on-processes-for-r-d/health-products-in-the-pipeline> and <https://www.policycuresresearch.org/pipeline-database/>. For a list of USAID's ready-to-launch innovations, see: <https://www.usaid.gov/cii/global-health-innovation-index>.

## 1. The unfinished MDG agenda

In 2000, the United Nations launched the Millennium Development Goals (MDGs)—an ambitious agenda to improve health and quality of life for all people, everywhere. The MDGs called for eradicating global poverty and hunger, improving global health and education outcomes, promoting gender equality, ensuring environmental sustainability, and strengthening global partnerships in service of achieving these goals—all by 2015.<sup>16</sup> Despite progress, the MDG agenda remains unfinished several years after the intended end-date. Even before COVID-19, progress had stalled in efforts to fight entrenched scourges (i.e., HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases) while also improving reproductive health, maternal and child health, and water and sanitation.<sup>17</sup> The COVID-19 pandemic has exacerbated the challenge by disrupting financing, economic growth, supply chains, and routine health services, leading to backsliding across many health areas—eroding and in some cases reversing decades of hard-won progress.

The following section lays out a selection of challenges and opportunities in fully realizing the MDGs.

### Tuberculosis

Behind COVID-19, tuberculosis (TB) remains the deadliest infectious disease in the world, claiming about 1.5 million lives every year.<sup>18</sup> Annual TB deaths have hovered between 1.2–1.7 million since at least the early nineties, and the number of people who died from TB increased in 2020.<sup>19</sup> While some progress has been made in therapeutics, the suite of tools to prevent, detect, and treat TB is outdated and unable to address the entirety of the disease burden.<sup>20</sup>

*The Challenge: Every year, millions of people develop active TB infections but are not diagnosed. About 45% of these people will die without treatment.*<sup>21</sup>

Of the estimated 10 million people who developed active TB infections in 2020, only 5.8 million received a diagnosis.<sup>22</sup> Although TB cases have been reported in over 84 countries, 86% of all new cases occurred in 30 “high burden” countries, with about 66% of all cases in just eight countries.<sup>23</sup>

16 See: <https://www.un.org/millenniumgoals/bkgd.shtml>

17 See: [https://www.un.org/millenniumgoals/2015\\_MDG\\_Report/pdf/MDG%202015%20PR%20Transitioning.pdf](https://www.un.org/millenniumgoals/2015_MDG_Report/pdf/MDG%202015%20PR%20Transitioning.pdf) and: [https://www.who.int/news-room/fact-sheets/detail/millennium-development-goals-\(mdgs\)](https://www.who.int/news-room/fact-sheets/detail/millennium-development-goals-(mdgs)).

18 World Health Organization. Tuberculosis. January 2021. Available from: <https://www.who.int/news-room/fact-sheets/detail/tuberculosis>.

19 IHME GBD Results Tool. And: World Health Organization. Global tuberculosis report 2021.

20 Madhukar Pai, Tereza Kasaeva, and Soumya Swaminathan. Covid-19's Devastating Effect on Tuberculosis Care—A Path to Recovery. *N Engl J Med* 2022;386:1490–1493. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMp2118145>. See also: WHO, Investing in new TB vaccines: It's time to end the century-long wait! July 2021. <https://www.who.int/news/item/16-07-2021-investing-in-new-tb-vaccines>.

21 WHO. Tuberculosis.

22 World Health Organization. Global tuberculosis report 2021. Available from: <https://www.who.int/publications/i/item/9789240037021>.

23 WHO. Tuberculosis. The eight countries are, in order of share of the global TB burden: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa.

Without diagnosis—and thus without receiving adequate treatment—about 45% of HIV-negative patients and almost all HIV-positive patients will die.<sup>24</sup> Undiagnosed patients also continue to unknowingly transmit TB in their households and communities, potentially infecting 5–15 others within a year and perpetuating the cycle of disease.<sup>25</sup>

The inadequacy of TB diagnostic tools is one important root cause of under-diagnosis. Standard of care for TB diagnosis requires a blood, sputum, or skin test, requiring either laboratory analysis or multiple visits to a healthcare facility. Active case finding programs can use mobile x-ray to identify probable TB cases among high-risk groups, but they can be difficult and expensive to deploy at scale in the highest burden countries as they are also equipment-intensive; they also cannot be readily deployed at the moment a potential patient develops symptoms and a confirmatory test is still required for diagnosis.<sup>26</sup> There is no fit-for-purpose TB rapid test for community screening or self-testing. Recent diagnostic innovations (e.g., portable battery-powered x-rays, rapid molecular drug susceptibility testing,<sup>27</sup> and rapid LAM tests<sup>28</sup>) have helped around the edges, but have had only marginal impact in identifying missing cases and connecting patients to prompt, appropriate treatment. Drug sensitivity testing is needed to ensure appropriate treatment given the growing threat of drug resistance, yet approaches to doing so often greatly delay diagnosis—sometimes by as long as 16 weeks.<sup>29</sup> Service delivery disruptions caused by the COVID pandemic have further exacerbated access challenges TB-related diagnostic services.<sup>30</sup>

*The Innovation Agenda: A rapid, inexpensive, and simple point-of-care diagnostic test for TB to support easy self-testing, community screening at scale, and break the transmission cycle.*

Within a year of COVID-19's emergence, companies and governments had developed an enormous array of rapid antigen diagnostics to support the COVID-19 response. When used correctly, these antigen tests allow individuals to quickly determine whether or not they are infected and prevent onward transmission; they also empower communities to screen their populations at scale and with regularity, helping enable the safe re-opening of schools, medical services, and other public spaces. With the emergence of effective therapeutics, these tools are also helping patients secure prompt access to treatment that reduces their likelihood of hospitalization and death.

24 WHO. Tuberculosis.

25 WHO. Tuberculosis.

26 Optimizing active case-finding for tuberculosis: Implementation lessons from South-East Asia. New Delhi: World Health Organization, Regional Office for South-East Asia; 2021. Available from: <https://apps.who.int/iris/rest/bitstreams/1371366/retrieve>.

27 See: <https://www.cephid.com/en/tests/Critical-Infectious-Diseases/Xpert-MTB-XDR>.

28 See: <https://www.ghitfund.org/investment/portfoliodetail/detail/126>.

29 World Health Organization. Tuberculosis: Extensively drug-resistant tuberculosis (XDR-TB) FAQ. [https://www.who.int/news-room/questions-and-answers/item/tuberculosis-extensively-drug-resistant-tuberculosis-\(XDR-TB\)](https://www.who.int/news-room/questions-and-answers/item/tuberculosis-extensively-drug-resistant-tuberculosis-(XDR-TB)).

30 Eleni Smitham and Rachel Silverman. Another Year and Another Respiratory Infection: 2022 Prospects for Tuberculosis Control in the Shadow of COVID-19. Center for Global Development: April 2022. Available from: <https://www.cgdev.org/blog/another-year-and-another-respiratory-infection-2022-prospects-tuberculosis-control-shadow>.

A similar tool for TB diagnosis could be transformational,<sup>31</sup> enabling mass testing, timely diagnosis, and prompt linkage to care. (Subsequent confirmatory testing and drug sensitivity testing would still be required, but the overall time from disease onset to diagnosis/treatment initiation would be substantially reduced.) Together, these measures would both dramatically decrease individual patients' morbidity and chance of death, while also helping to cut onward transmission and reduce the long-term disease burden at the population level. Such a test would be most impactful if it were highly affordable, enabling mass deployment and repeat testing; it should also be simple enough for use by a layperson (e.g., a non-health-worker), and ideally even authorized for self-testing in the comfort and privacy of a patient's own home.

*The Challenge: Long and toxic treatment regimens make it difficult for patients to complete the entirety of TB treatment, leading to preventable deaths and further development of drug resistance.*

First-line therapy for TB involves a six-month course of four different antibiotics, at about US\$40/complete course.<sup>32</sup> For poor and mobile populations, this treatment duration, complexity, and cost can be prohibitive. And before treatment even begins, drug sensitivity testing is needed to determine the existence and extent of drug resistance; this has implications for whether the disease can be treated with first-line drugs, or whether second or third-line treatments are required. This testing can delay the start of treatment and reduce patients' likelihood of beginning appropriate treatment. For drug-resistant TB, treatment regimens are even longer and more complex, with regimens sometimes exceeding two years and requiring costlier drugs with more side effects—though there have been some recent advancements to simplify and reduce the toxicity of treatment regimens.<sup>33</sup> Low adherence to these challenging treatment regimens can be dangerous for both the patient and community by lowering the likelihood of treatment success and increase the likelihood that further drug resistance will develop and spread.

*The Innovation Agenda: A universal, short-course TB treatment regimen.*

A short-course TB treatment regimen universally applicable across drug resistance levels would eliminate the need for drug sensitivity testing (which delays treatment initiation), improve treatment adherence and by extension patient outcomes, and reduce community TB spread. The WHO published a target product profile (TPP) in 2016 for a universal drug regimen that could tackle both drug-sensitive and drug-resistant TB strains within a two-month or shorter treatment course.<sup>34</sup> The TPP also specifies that a new product should ideally avoid drug interactions or toxicity, aspects of

31 Rapid antigen tests (RATs) for COVID are only widely available in North America, Europe, and Australia. By "available," we mean affordable, accessible, and deployed at scale in LMICs (unlike COVID RATs currently).

32 WHO. Tuberculosis.

33 World Health Organization. Rapid communication: Key changes to the treatment of drug-resistant tuberculosis. May 2022. Available from: <https://www.who.int/publications/i/item/WHO-UCN-TB-2022-2>.

34 Kalipso Chalkidou, Martina Garau, Rachel Silverman, and Adrian Towse. Blueprint for a market-driven value-based advance commitment for tuberculosis. Center for Global Development and Office of Health Economics. 2020.

existing TB regimens that serve to disincentivize or disqualify patients from starting or completing treatment. As with a rapid TB diagnostic, a universal regimen would decrease individual patients' morbidity and chance of death. Without a new TB regimen, global TB treatment costs are projected to increase by about one-third before 2025, primarily driven by increased expenditure on second-line therapies as drug resistance continues to grow. While some progress has been made recently by the TB Alliance in addressing this challenge, a universal drug regimen capable of treating all resistance levels would eliminate the need for second- and third-line drugs.<sup>35</sup> A safe, universal, short-course TB treatment regimen would limit opportunities for drug-resistant TB to spread, thereby reducing the population-level TB burden.

## **Malaria**

Malaria control requires evidence-based application of a complex suite of interventions. Together, artemisinin-based combination therapies (ACTs), insecticide-treated nets, seasonal chemoprevention, and vector control have reduced malaria deaths by about one-third over the past two decades.<sup>36</sup> Yet despite the availability of these prevention and treatment tools at scale, global cases have hovered around 241 million<sup>37</sup> across 85 malaria endemic countries and just under half a million children continue to die from malaria each year.<sup>38</sup> Most malaria deaths (77%) occur among children younger than five.<sup>39</sup> Ninety-six percent of all malaria cases and deaths occur in only 29 malaria endemic countries, almost all of which are on the African continent.<sup>40</sup>

*The Challenge: Emerging signs of resistance to artemisinin-based combination therapies, the main drugs used globally to treat malaria, indicate that next generation antimalarials are needed now, before malaria becomes incurable.*

ACTs have been the main approach to treating malaria since the mid-2000s; they are broadly very effective at treating malaria. Yet early signs of partial artemisinin resistance (e.g., delayed parasite clearance time) in the Greater Mekong subregion in Asia and in eastern Africa may threaten existing treatment/management approaches.<sup>41</sup> If and when ACTs become ineffective at treating malaria, hundreds of thousands to millions of additional malaria deaths are likely to occur each year, mostly among young children.

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35 For more on TB Alliance's work on developing effective treatments for drug-resistant TB such as BPaL, see: <https://www.tballiance.org/portfolio>.

36 World Health Organization. World malaria report 2021. <https://apps.who.int/iris/rest/bitstreams/1398397/retrieve>.

37 WHO, World malaria report 2021.

38 WHO, World malaria report 2021.

39 WHO, World malaria report 2021.

40 WHO, World malaria report 2021. Nigeria and the Democratic Republic of the Congo experience the most malaria cases and deaths out of these 29 countries.

41 See: <https://www.who.int/news-room/questions-and-answers/item/artemisinin-resistance>.

### *The Innovation Agenda: Next generation antimalarial drugs.*

To counteract the relative overreliance on just a handful of ACTs, next generation antimalarials—both new combination therapies and new classes of drugs—are necessary to mitigate the growing threat of drug resistance and ensure malaria does not become an incurable disease. Some promising drugs are currently in development (e.g., tafenoquine<sup>42</sup> and KAF/lumefantrine<sup>43</sup>); other novel compounds and additional therapeutic strategies, such as monoclonal antibodies (early trial results of monoclonal antibody L9LS in Kenya and Mali, for example, show promising signs of protection<sup>44</sup>), would further bolster the toolkit for effective malaria management.

### *The Challenge: Despite extensive efforts to control malaria, about a quarter billion people contract malaria every year. High endemicity constrains life chances.*

About 241 million people contract malaria each year.<sup>45</sup> Certain groups, including people living with HIV, young children, and migrant workers, face a heightened risk of severe disease from a malaria infection.<sup>46</sup> Chronic, repeated bouts of malaria can devastate individual households and drain national economic prospects. Vector control tools, including insecticide-treated bed nets and indoor residual spraying of insecticides, have been delivered at scale across many malaria-endemic areas, yet this high case burden remains. Seasonal chemoprevention campaigns for young children can also prevent many malaria cases, but require substantial coordination and resources to administer. The COVID-19 pandemic has made it more difficult to deliver both vector control programs and seasonal chemoprevention campaigns in some contexts. The WHO-endorsed RTS,S/AS01 vaccine is the first vaccine found to be at all effective against malaria in young children, but its 30% efficacy level leaves many children still at risk. New approaches are still needed to reduce the frequency of malaria infection, especially in vulnerable populations.

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42 Tafenoquine is the newest drug to treat *P. vivax* malaria (see: James A Watson, Narimane Nekkab, Michael White (2021). Tafenoquine for the prevention of *Plasmodium vivax* malaria relapse. *The Lancet Microbe* Vol 2, 5, e175–e176). While promising, tafenoquine is not indicated for people who have glucose-6-phosphate dehydrogenase (G6PD) deficiency; a G6PD deficiency diagnostic test must be administered prior to tafenoquine use. Accessible G6PD deficiency diagnostics is another innovation priority (see: Pal S, Bansil P, Bancone G, Hrutkay S, Kahn M, Gornawun G, Penpitchaporn P, Chu CS, Nosten F, Domingo GJ. Evaluation of a Novel Quantitative Test for Glucose-6-Phosphate Dehydrogenase Deficiency: Bringing Quantitative Testing for Glucose-6-Phosphate Dehydrogenase Deficiency Closer to the Patient. *Am J Trop Med Hyg* 2019 Jan;100(1):213–221).

43 See: <https://www.mmv.org/newsroom/interviews/kaflumefantrine>.

44 See: [https://www.niaid.nih.gov/news-events/monoclonal-antibody-prevents-malaria-us-adults-nih-trial-shows?utm\\_campaign=+52863386&utm\\_content=&utm\\_medium=email&utm\\_source=govdelivery&utm\\_term=](https://www.niaid.nih.gov/news-events/monoclonal-antibody-prevents-malaria-us-adults-nih-trial-shows?utm_campaign=+52863386&utm_content=&utm_medium=email&utm_source=govdelivery&utm_term=)

45 World Health Organization. Malaria. May 2022. Available from: <https://www.who.int/news-room/fact-sheets/detail/malaria>.

46 WHO. Malaria.



### *The Innovation Agenda: Longer lasting, more effective malaria prevention tools.*

Next generation malaria vaccines with greater efficacy are still very much needed to curb malaria case counts and save hundreds of thousands of lives—especially among infants and young children. Other prevention tools—for example, longer-lasting prophylactic medications—could also help extend protection throughout the entire malaria high season. In the context of emerging drug resistance, preventing malaria cases outright also helps protect future generations from the risk of untreatable malaria. Strengthening local manufacturing capacity and ensuring affordable pricing would help ensure maximal impact of longer lasting, more effective malaria prevention tools.

## **HIV/AIDS**

Advances in HIV treatment have allowed HIV-positive individuals to survive and thrive—so long as they learn their status and initiate antiretroviral treatment (ART). Millions of lives have indeed been saved through ART scaleup: AIDS-related mortality has nearly halved since 2010.<sup>47</sup> Medical science has demonstrated that ART is also extraordinarily effective at preventing onward transmission of HIV, meaning treatment protects both HIV-positive individuals *and* their sexual partners. Yet new infections and preventable deaths continue. In 2021, there were an estimated 1.5 million new HIV infections and 650,000 deaths from HIV/AIDS.<sup>48</sup> Among people living with HIV, 71% live in MICs, where HIV financing is expected to dwindle in coming years because of donor transitions.<sup>49</sup>

### *The Challenge: HIV continues to spread and kill—primarily among groups who do not know their status and initiate treatment. And despite major advances in HIV prevention technology, existing tools still leave some communities vulnerable to infection.*

Many people still do not know they have HIV: an estimated 15% of people living with HIV do not know their HIV status.<sup>50</sup> Treatment accessibility compounds the magnitude of this problem: a quarter of people living with HIV (about 9.6 million of 38.3 million) are not on treatment, including an estimated 800,000 children.<sup>51</sup> Because symptoms of HIV can take years to develop, people living with HIV may unknowingly transmit HIV to others. Socioeconomic inequities can also concentrate the risk of acquiring HIV in marginalized and vulnerable communities.

Better prevention tools are still needed to protect communities at higher risk from HIV infection, including female sex workers, people who inject drugs, and men who have sex with men.

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47 UNAIDS. “Confronting Inequalities: Lessons for pandemic responses from 40 years of AIDS.” Global AIDS Update 2021. Available from: [https://www.unaids.org/sites/default/files/media\\_asset/2021-global-aids-update\\_en.pdf](https://www.unaids.org/sites/default/files/media_asset/2021-global-aids-update_en.pdf).

48 UNAIDS. “In Danger.” Global AIDS Update 2022. Available from: [https://www.unaids.org/sites/default/files/media\\_asset/2022-global-aids-update\\_en.pdf](https://www.unaids.org/sites/default/files/media_asset/2022-global-aids-update_en.pdf).

49 UNAIDS, “In Danger.”

50 UNAIDS, “Confronting Inequalities.”

51 UNAIDS, “Confronting Inequalities” and UNAIDS, “In Danger.”

There have been some steps forward in this area, including expansion of highly effective pre-exposure prophylaxis (PrEP)<sup>52</sup>; recent approval of a longer-lasting (two-month) injectable form of PrEP; the dapivirine vaginal ring, shown to reduce risk of HIV infection by about a third; and other longer lasting multipurpose innovations currently in the pipeline.<sup>53</sup> While important, these tools may still be out of reach for mobile, poor, vulnerable, and/or stigmatized populations who may lack sustained access to health care facilities or pharmacies.<sup>54</sup>

### *The Innovation Agenda: Longer lasting and scalable HIV prevention methods—including a safe and effective HIV vaccine—to eliminate HIV transmission.*

To truly achieve an AIDS-free generation, people at risk of HIV infection need better, longer-lasting protection—and, ideally, a highly protective and long-lasting vaccine. The NIH recently announced three Phase I clinical trials for HIV vaccines using mRNA technology, expected to be completed in July 2023.<sup>55</sup> Although a handful of other vaccines are in the pipeline as well, the speed at which multiple safe, effective COVID-19 vaccines were developed demonstrates that with the requisite investment and commitment, developing a safe and effective HIV vaccine should be within reach.<sup>56</sup>

### **Leishmaniasis**

The 20 diseases/disease groups categorized as neglected tropical diseases (NTDs) affect nearly a quarter of the world's population.<sup>57</sup> NTDs disproportionately burden impoverished communities and exacerbate social, economic, and health harms. Despite the wide-ranging impact of these diseases, investments in R&D for NTD prevention and treatment decreased for the fourth consecutive year in 2020, by 6.3 percent.<sup>58</sup> Some of these infectious diseases lack any suitable medical toolkit for prevention, diagnosis, and/or treatment.

One such NTD is leishmaniasis, an insect-borne parasitic disease that affects as many as one million people every year.<sup>59</sup> There are three main forms of leishmaniasis: visceral, cutaneous, and mucocutaneous. Without treatment, visceral leishmaniasis (VL) is deadly 95% of the time, while

52 In 2020, only about 845,000 people used PrEP globally, just 8% of the 2025 target. Source: UNAIDS, "Confronting Inequalities."

53 See: <https://www.hiv.gov/blog/fda-approves-first-injectable-treatment-hiv-pre-exposure-prevention> and [https://www.ipmglobal.org/sites/default/files/attachments/publication/ipm\\_ring\\_background\\_dec\\_2021.pdf](https://www.ipmglobal.org/sites/default/files/attachments/publication/ipm_ring_background_dec_2021.pdf).

54 UNAIDS, "Confronting Inequalities."

55 See: <https://www.nih.gov/news-events/news-releases/nih-launches-clinical-trial-three-mrna-hiv-vaccines>. Exploration of mRNA technology for HIV immunization contributed to the speed at which scientists were able to develop an mRNA-based COVID vaccine: <https://www.nature.com/articles/d41586-021-02483-w>.

56 See: <https://www.iavi.org/our-science/pipeline>.

57 World Health Organization. "Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030." 2020. <https://apps.who.int/iris/rest/bitstreams/1326801/retrieve>.

58 Policy Cures Research. "Neglected Disease Research and Development: New Perspectives." G-FINDER 2021 report. <https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2022/01/02212458/2021-G-FINDER-Neglected-Disease.pdf>.

59 World Health Organization. Leishmaniasis. January 2022. Available from: <https://www.who.int/news-room/fact-sheets/detail/leishmaniasis>.

other forms can cause permanent, debilitating damage.<sup>60</sup> About 600 million people globally live in at risk areas for VL<sup>61</sup> while cutaneous leishmaniasis (CL) is endemic in 87 countries.<sup>62</sup>

### *The Challenge: Prevailing methods for diagnosing leishmaniasis rely on clinical signs and lab-based tests.*

Diagnosing leishmaniasis is complicated and challenging: health care workers must assess clinical signs such as fever and anemia in VL and lesions or ulcers on the skin in CL.<sup>63</sup> Relying on signs of illness necessarily has limitations, as other diseases may manifest similar clinical signs (e.g., malaria and tuberculosis also commonly present with fevers).<sup>64</sup> VL diagnosis also involves serological or parasitological tests, which usually requires sending results to a lab or a health facility.<sup>65</sup> The time it takes to collect and analyze specimens, however, can make the difference between life and death. For people living with HIV in particular, leishmaniasis is especially lethal, making timely intervention of paramount importance.<sup>66</sup> No rapid diagnostic test exists for CL. Several countries most at risk of leishmaniasis, such as Iraq and Yemen, are experiencing entrenched conflict, making prompt diagnosis of leishmaniasis a challenge.

### *The Innovation Agenda: A rapid antigen test to more easily diagnose leishmaniasis.*

An accurate rapid diagnostic test would make it easier for people with leishmaniasis infections to get a confirmatory diagnosis earlier on in the course of infection. Prompt diagnoses for VL are necessary to prevent death, which is virtually guaranteed without treatment. For all forms, though, faster diagnosis prevents progression to more serious forms of disease and reduces the likelihood of lasting, disabling damage. Early diagnosis also supports efforts to curb incidence of leishmaniasis by breaking chains of transmission. A rapid test deployable in community settings further increases the likelihood of reaching people who may be at risk of developing leishmaniasis by bringing diagnostics closer to where they are.

### *The Challenge: Available treatment options for leishmaniasis are expensive, difficult to administer, and sometimes toxic.*

Diagnostics are of limited use without effective treatment options. Existing treatment options for leishmaniasis carry significant challenges. Treatment for VL is long (at least one month), costly,

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60 WHO. Leishmaniasis.

61 Drugs for Neglected Diseases Initiative. Visceral leishmaniasis. <https://dndi.org/diseases/visceral-leishmaniasis/>.

62 Drugs for Neglected Diseases Initiative. Cutaneous leishmaniasis. <https://dndi.org/diseases/cutaneous-leishmaniasis/>.

63 WHO. Leishmaniasis.

64 Thakur S, Joshi J, Kaur S. Leishmaniasis diagnosis: an update on the use of parasitological, immunological and molecular methods. *J Parasit Dis* 2020;44(2):253–272. doi:10.1007/s12639-020-01212-w.

65 WHO. Leishmaniasis.

66 WHO. Leishmaniasis.

complex, and occasionally toxic/not well tolerated among patients.<sup>67</sup> No effective oral or topical treatment exists for CL,<sup>68</sup> while available CL treatment's effectiveness is suboptimal. Treatment for CL requires injections, which must be administered by trained health care workers. Growing resistance to first-line drugs for treating leishmaniasis has necessitated the use of second- and third-line drugs; resistance to some and high rates of toxicity in others has further contracted the treatment toolkit.<sup>69</sup> The long duration of existing treatments, moreover, makes it more difficult for people to fully clear the parasitic infection, which in turn heightens the risk of morbidity and mortality, as well as onward transmission and drug resistance.<sup>70</sup>

### *The Innovation Agenda: More effective, safer, and easier to administer leishmaniasis treatment options.*

There have been some recent advances in drug discovery for treating leishmaniasis, particularly in individuals living with HIV.<sup>71</sup> This prioritization makes sense, as people living with HIV are far more at risk of developing severe leishmaniasis infections. A well tolerated, safe, effective, and easy to administer treatment for all forms of leishmaniasis could ensure that no one dies from VL; it would also ensure that everyone at risk of developing leishmaniasis has access to effective treatment that they can maintain until the parasite is cleared without the risk of toxic side effects.<sup>72</sup>

## **Contraception and reproductive health**

Contraceptives help all people achieve bodily autonomy, healthy birth spacing, and desired family size; contraceptives are also linked to better education outcomes and long-term economic opportunity, both at the individual and population level.<sup>73</sup> However, an estimated 270 million sexually active women around the world who do not currently wish to become pregnant are not using modern contraception.<sup>74</sup>

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67 See: <https://dndi.org/diseases/visceral-leishmaniasis/facts/>.

68 Policy Cures Research, "Neglected Disease Research and Development."

69 Ghorbani, Masoud, and Ramin Farhoudi. "Leishmaniasis in humans: drug or vaccine therapy?" *Drug Design, Development and Therapy* vol. 12:25–40. 22 Dec. 2017, doi:10.2147/DDDT.S146521.

70 WHO. Leishmaniasis.

71 See, for example: <https://www.ghitfund.org/investment/portfolio>, <https://dndi.org/diseases/visceral-leishmaniasis/target-product-profile/>, and <https://dndi.org/diseases/cutaneous-leishmaniasis/target-product-profile/>. See also: <https://www.who.int/news/item/08-06-2022-visceral-leishmaniasis-and-hiv-coinfection-who-publishes-new-guideline-with-region-specific-treatment-recommendations>.

72 For more on ideal TPPs for leishmaniasis treatment, see: <https://dndi.org/diseases/visceral-leishmaniasis/target-product-profile/> and <https://dndi.org/diseases/cutaneous-leishmaniasis/target-product-profile/>.

73 See, for example: <https://www.cgdev.org/publication/reproductive-choices-life-chances-new-and-existing-evidence-impact-contraception-women> and <https://www.cgdev.org/publication/family-planning-program-effects-review-evidence-microdata-working-paper-422>.

74 Kantorová V, Wheldon MC, Ueffing P, Dasgupta ANZ (2020) Estimating progress towards meeting women's contraceptive needs in 185 countries: A Bayesian hierarchical modelling study. *PLoS Med* 17(2):e1003026.

*The Challenge: Hormonal contraceptive methods fail to meet some people's contraceptive needs. Limited choices in the contraceptive product market contributes to unintended pregnancies worldwide.<sup>75</sup>*

Hormonal contraceptive products carry a long list of possible side effects; some, such as blood clots, can be potentially life-threatening. Many people cannot or will not tolerate hormonal methods, but find non-hormonal methods also fail to meet their needs. There are few investments in drug development that would expand contraceptive options,<sup>76</sup> and most products currently in the pipeline rely on the same hormones as contraceptives already on the market. While new delivery mechanisms for drugs with established safety and efficacy may address some unmet contraceptive needs, they are unlikely to address the troublesome side effects that deter some people from contraceptive use.

*The Innovation Agenda: Nonhormonal, male, and multipurpose contraceptives could help close the gap in unmet need for family planning and ensure everyone in the world has reproductive autonomy.*

Nonhormonal contraceptive methods (for everyone) and male contraceptives would fill important gaps in global unmet need for contraception. Investments in market research around male contraceptives and several new products in the pipeline demonstrate some momentum around developing male and nonhormonal contraceptives,<sup>77</sup> though effective nonhormonal compounds and male reproductive pathway targets still need to be identified.<sup>78</sup> People who use contraceptives also frequently use products for multiple purposes: hormonal pills are prescribed to treat dysmenorrhea, endometriosis, and other conditions, for example. And preventing sexually transmitted infections (STIs), including HIV and cancer-causing HPV,<sup>79</sup> is also a concern for most sexually active people. A third innovation category, an easy-to-use nonhormonal contraceptive for people of all genders that could also prevent HIV and other STIs, would help people exercise control over bodily autonomy while also helping curb STIs, both at the individual and population levels.

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75 Bearak JM, Popinchalk A, Beavin C, et al. Country-specific estimates of unintended pregnancy and abortion incidence: a global comparative analysis of levels in 2015–2019. *BMJ Global Health* 2022;7:e007151.

76 Callahan, Rebecca L et al. "The new contraceptive revolution: developing innovative products outside of industry." *Biology of Reproduction* vol. 103,2 (2020): 157–166. doi:10.1093/biolre/ioaa067.

77 See: <https://www.malecontraceptive.org/>. See also: <https://www.nature.com/articles/d41586-020-03534-4> on a promising male contraceptive gel currently in clinical development. For a comprehensive list of contraceptive products currently in the R&D pipeline, see: <https://pipeline.ctiexchange.org/products>.

78 Anke Hemmerling, Emily Christopher, Bethany Young Holt, Towards a roadmap to advance non-hormonal contraceptive multipurpose prevention technologies: strategic insights from key stakeholders, *Biology of Reproduction*, Volume 103, Issue 2, August 2020, Pages 289–298, <https://doi.org/10.1093/biolre/ioaa092>.

79 Not all strains of HPV are cancer-causing; however, the several strains of HPV that do cause cancer account for 90% of cervical cancer cases in the US alone (see: <https://www.cdc.gov/hpv/parents/cancer.html>).

## ***Pneumonia***

Pneumonia is easily preventable and treatable, yet globally it is still the leading infectious disease killer of children younger than five. Over 740,000 children died from pneumonia in 2019 alone.<sup>80</sup> As with many health conditions described in this paper, deaths from childhood pneumonia are largely attributable to the inequitable distribution of resources: relative to children in high-income countries, children in countries with high pneumonia mortality burdens face a 60-fold greater risk of contracting and dying from pneumonia.<sup>81</sup>

***The Challenge: Effective tools to prevent and treat childhood pneumonia exist, but there is still no quick, easy way to diagnose it.***

Most pneumonia can be prevented (with vaccines) and/or effectively treated (with antibiotics and oxygen). Yet rapid diagnostics are still lacking, and childhood pneumonia is primarily diagnosed through physical examination.<sup>82</sup> Bacteria, viruses, and fungi can all cause pneumonia; it is important to know which pathogen underlies any given infection to properly treat it.<sup>83</sup> Delayed or inaccurate diagnoses delay proper treatment, which compounds the risk of more serious disease and death. Treating viral or fungal pneumonia with antibiotics, if a confirmatory test is not possible, also risks amplifying antimicrobial resistance while simultaneously leaving the underlying causes of pneumonia untreated, thereby increasing the risk of death.

***The Innovation Agenda: Better diagnostic tests to catch childhood pneumonia sooner, support timely and appropriate treatment, counteract antimicrobial resistance, and save young lives from preventable death.***

Development of a rapid point-of-care test for childhood pneumonia would help enable quick, accurate diagnosis—and, in turn, inform timely treatment initiation and appropriate antimicrobial prescribing. A timely *negative* diagnosis would also prove useful, as it could rule out pneumonia as the cause of a child's fever and turn health worker attention toward other potential etiologies, such as malaria. Faster access to accurate diagnosis and appropriate treatment would in turn help prevent thousands of childhood deaths.

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80 World Health Organization. Pneumonia. November 2021. Available from: <https://www.who.int/news-room/fact-sheets/detail/pneumonia>.

81 UNICEF. Every Child's Right to Survive: An Agenda to End Pneumonia Deaths. 2020. Available from: [https://data.unicef.org/wp-content/uploads/2020/01/Every-childs-right-to-survive-pneumonia-brochure-English\\_2020-final.pdf](https://data.unicef.org/wp-content/uploads/2020/01/Every-childs-right-to-survive-pneumonia-brochure-English_2020-final.pdf).

82 UNICEF. Childhood pneumonia: Everything you need to know. November 2020. Available from: <https://www.unicef.org/stories/childhood-pneumonia-explained>.

83 WHO. Pneumonia.

## 2. The noncommunicable disease access agenda

Lack of access to quality health care in LMICs contributes to nearly eight million deaths annually from treatable causes.<sup>84</sup> Innovations for addressing cardiovascular disease, mental/brain disorders, diabetes, kidney disease, cancers, asthma, heavy metal poisoning, and other noncommunicable diseases (NCDs) are not available at scale in LMICs. While effective tools for preventing, diagnosing, and treating most NCDs do exist, widespread access to such tools is concentrated in resource-rich settings. The innovation agenda for NCD access, then, is two-fold: both to make existing products more accessible in LMICs, and to develop new and more affordable/appropriate approaches for care in LMIC settings. Within the scope of this paper, we focus on the latter.

### *Sickle cell disease*

Sickle cell disease (SCD) is a genetic disorder that affects hemoglobin, a protein in red blood cells that transports oxygen throughout the body.<sup>85</sup> There are two main hemoglobin disorders, SCD and thalassemia. In SCD, abnormal mutations in hemoglobin cause red blood cells to be crescent-shaped rather than disc-shaped, resulting in more rigid red blood cells. This increased cell rigidity makes it more difficult for red blood cells to move through vessels, resulting in diminished blood flow and potentially blockages or clots.<sup>86</sup> These impairments can lead to low blood oxygen levels and anemia, which in turn can result in chronic severe pain, tissue damage and death, and severe fatigue.<sup>87</sup> Because SCD is a systemic, chronic illness, over time it can lead to even more serious complications, including organ failure, bone damage, and death.<sup>88</sup>

An estimated 20 million people worldwide have SCD (though data are lacking, so the actual number may be much higher).<sup>89</sup> Both parents must carry the genetic variation for SCD to pass it down; while the global estimated prevalence of carriers is 5%, carrier prevalence can be as high as 45% in some parts of Africa.<sup>90</sup>

*The Challenge: Early detection of SCD is paramount for improving childhood survival rates, yet prevailing diagnostic methods require laboratory-based blood or genetic tests, which are not feasible on the scale required to detect all SCD cases.*

While people living with SCD can live relatively long lives with adequate access to health services and other resources, SCD significantly contributes to under-five mortality in countries without robust

84 Kruk ME et al. High-quality health systems in the Sustainable Development Goals era: time for a revolution.

*Lancet Glob Health* 2018 Nov;6(11):e1196–e1252. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7734391/>.

85 World Health Organization. "Sickle Cell Disease." <https://www.afro.who.int/health-topics/sickle-cell-disease>.

86 WHO. "Sickle Cell Disease."

87 WHO. "Sickle Cell Disease."

88 Johns Hopkins Medicine. "Sickle Cell Disease." <https://www.hopkinsmedicine.org/health/conditions-and-diseases/sickle-cell-disease>.

89 National Heart, Blood, and Lung Institute. "Sickle Cell Disease: What Is Sickle Cell Disease?" <https://www.nhlbi.nih.gov/health/sickle-cell-disease>.

90 WHO. "Sickle Cell Disease."

health systems. Available evidence suggests that as few as 1 in 10 children with SCD lives to see their fifth birthday in some LMIC contexts.<sup>91</sup> Infections (including, for example, bacterial and malarial) and complications from severe anemia most commonly contribute to these premature deaths. Many if not most children in resource-limited contexts die without having received an SCD diagnosis.<sup>92</sup> Standard of care for SCD diagnosis currently involves using blood or genetic tests that require use of a laboratory facility, trained health workers, and infrastructure for storing, transporting, and analyzing samples.<sup>93</sup> This technical capacity may not be available across all contexts, thereby limiting the ability of the most affected countries from deploying widescale screening efforts.

*The Innovation Agenda: A rapid diagnostic test for SCD, capable of detecting all forms of SCD, that can be rolled out feasibly, affordably, and at scale in newborn screening programs in LMICs.*

Because early detection is critical for ensuring people—newborns particularly—with SCD can access appropriate care, barriers to prompt diagnosis must be reduced. Relatively sophisticated lab-based tests are not currently scalable to meet the need. Within the past decade, however, advances have been made in developing accurate point-of-care rapid diagnostic tests that do not require lab equipment, electricity, or trained health staff. Sickle SCAN, for example, is a point-of-care immunoassay capable of detecting hemoglobin A, S, and C.<sup>94</sup> HemoTypeSC is another rapid test that can detect hemoglobin A, S, and C.<sup>95</sup> While these innovations fill a vital gap, additional R&D attention is needed in developing scalable rapid tests for detecting hemoglobin D, E, and O. Ideally, one single point-of-care rapid test could detect all six hemoglobin variations and be accessible for even the most rural and remote communities.

*The Challenge: While a suite of interventions exists for managing SCD, some components can be costly, high-tech, and/or come with toxic/intolerable side effects.*

As discussed elsewhere in this paper, the health benefits of reliable, fast diagnostics depend on linkages to appropriate care and treatment. For SCD, treatment primarily revolves around preventing organ damage, infections, and complications from anemia while also managing symptoms such as pain and fatigue. Gold standard approaches include: prophylactic use of antibiotics and antimalarials to prevent infection in the earliest years of life; hydroxyurea, an anticancer drug shown to be effective in attenuating anemia and other resulting conditions/symptoms; nutritional supplements

91 Wastnedge, et al. The global burden of sickle cell disease in children under five years of age.

92 Oron, A.P., Chao, D.L., Ezeanolue, E.E. et al. Caring for Africa's sickle cell children: will we rise to the challenge? *BMC Med* 18, 92 (2020).

93 Williams TN. An accurate and affordable test for the rapid diagnosis of sickle cell disease could revolutionize the outlook for affected children born in resource-limited settings. *BMC Med* 2015;13:238. Published 2015 Sep 23.

94 See: <https://www.biomedomics.com/products/hematology/sicklescan/>.

95 See: <https://www.nhlbi.nih.gov/news/2019/rapid-result-test-track-transform-sickle-cell-disease-screening-millions> and: <https://www.hemotype.com/>.



(e.g., folic acid); and blood transfusions.<sup>96</sup> While antibiotics, antimalarials, and nutritional supplements are generally accessible at scale, hydroxyurea and blood transfusions are not. And although hydroxyurea has been shown to be a safe and effective therapy for SCD, it may come with significant side effects, and additionally requires regular contact with a health facility for treatment monitoring and administration.<sup>97</sup>

### *The Innovation Agenda: Expanding the options for safe, effective, affordable, and scalable SCD treatment.*

Recent high-level political<sup>98</sup> and financial<sup>99</sup> commitments to address and even cure SCD suggest growing awareness of the need to find solutions. While curative therapies would be groundbreaking if developed, there is another critical innovation agenda to be found in improving the suite of tools used to treat SCD. As mentioned, hydroxyurea can be a suitable treatment option, but the development of even safer, simpler treatment options could also help ensure more people with SCD, particularly young children who live far away from health facilities, have access to suitable therapeutic options. Recent progress in exploring novel approaches to treating SCD shows some promise;<sup>100</sup> greater investments in expanding the treatment arsenal for SCD would help ensure infants and young children diagnosed with SCD in resource-limited settings have access to safe, effective, feasible treatment.

## **Diabetes**

Diabetes is a chronic, incurable condition that impairs production or regulation of the hormone insulin, which regulates blood glucose levels. People with diabetes who are unable to produce or no longer able to regulate insulin effectively require continual administration of insulin and glucose monitoring. About 17% of people with diabetes require life-long insulin treatment.<sup>101</sup> Without insulin or other forms of diabetes management, chronic elevated blood glucose levels can lead to serious and sometimes fatal health outcomes. About 75% of the estimated 537 million people who have either type 1 or type 2 diabetes live in LMICs and over 100 million additional people are projected to develop

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96 Oron et al. "Caring for Africa's sickle cell children."

97 Agrawal RK, Patel RK, Shah V, Nainiwal L, Trivedi B. Hydroxyurea in sickle cell disease: drug review. *Indian J Hematol Blood Transfus* 2014;30(2):91–96.

98 WHO Africa. "African health ministers launch drive to curb sickle cell disease toll." August 23, 2022. <https://www.afro.who.int/news/african-health-ministers-launch-drive-curb-sickle-cell-disease-toll>.

99 National Institutes of Health. "NIH launches new collaboration to develop gene-based cures for sickle cell disease and HIV on global scale." October 23, 2019. <https://www.nih.gov/news-events/news-releases/nih-launches-new-collaboration-develop-gene-based-cures-sickle-cell-disease-hiv-global-scale>.

100 National Heart, Blood, and Lung Institute. "Researchers study a new way to treat sickle cell disease." June 16, 2022. <https://www.nhlbi.nih.gov/news/2022/researchers-study-new-way-treat-sickle-cell-disease>.

101 World Health Organization. Keeping the 100-year-old promise: making insulin access universal. Geneva: World Health Organization; 2021. Available from: <https://apps.who.int/iris/rest/bitstreams/1389748/retrieve>.

diabetes in the next eight years alone.<sup>102</sup> Diabetes prevalence has been rising over the last several decades, in part due to environmental and social risk factors.

*The Challenge: When left untreated, diabetes can lead to severe health problems including kidney failure, cardiovascular disease/thrombotic events, blindness, amputations, and death. Yet millions of people who require insulin to survive are unable to access it.*

Just half of the 63 million people with type 2 diabetes worldwide who require insulin are able to access it,<sup>103</sup> while three-quarters of children with type 1 diabetes are unable to maintain an appropriate blood glucose level.<sup>104</sup> Insulin is currently available in human and analogue forms, the latter of which is typically more expensive. Appropriate dosing and administration of insulin may require the assistance of health care workers and a cold chain for insulin transportation and storage (which may require traveling to a health facility as well, as many people globally lack continuous electricity or cold storage at home<sup>105</sup>), an option not available in every LMIC context. Insulin administration can be done with a syringe or with reusable pens; supply chain problems/stockouts can further impede people's ability to safely and regularly administer insulin. People with diabetes must also regularly undertake blood glucose monitoring, which generally involves procuring or accessing monitoring devices and testing strips on a routine basis. Just three pharmaceutical companies dominate the insulin market, which contributes to unaffordability and stalled innovation in diabetes management products.<sup>106</sup>

*The Innovation Agenda: Cheaper, thermostable, quality-assured biosimilar insulin products.*

More affordable, shelf-stable insulin that does not require a cold chain would make it easier to administer insulin to those who need it everywhere, but especially for people living in tropical/hotter climates (also of growing importance in the context of climate change and rising global temperatures). While existing insulin products can survive extended periods of being left unrefrigerated after opening, the upper temperature limit may be below actual "room" temperatures

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102 International Diabetes Federation. IDF Diabetes Atlas. 10th edn. International Diabetes Federation, Brussels 2021. <https://diabetesatlas.org/>.

103 WHO, "Keeping the 100-year-old promise."

104 Lancet Editorial. 100 years of insulin: a technical success but an access failure. *The Lancet* 2021; Vol 398. Beyond insulin, numerous other pharmacological and non-pharmacological interventions may be indicated for diabetes management. Yet as with insulin, these tools are out of reach: fewer than one in ten people in LMICs with diabetes are able to access adequate treatment. See: David Flood et al. (2021). The state of diabetes treatment coverage in 55 low-income and middle-income countries: a cross-sectional study of nationally representative, individual-level data in 680102 adults. *Lancet Healthy Longev*; 2:e340–51.

105 Sharmila Devi. Cold comfort: getting insulin to those who need it. *The Lancet* 2021; Vol 398.

106 WHO, "Keeping the 100-year-old promise."

in some contexts, and unopened insulin still requires refrigeration.<sup>107</sup> Cheaper human<sup>108</sup> or biosimilar thermostable insulin products could also potentially combat the market distortion around analogue insulin, which can cost as much as eight times more than human insulin per vial.<sup>109</sup> Paired with non-pharmacological interventions (i.e., diet and exercise adjustments) where feasible and better pricing and procurement policies (including around syringes and pen devices), more affordable thermostable insulin products would enable people to more effectively manage diabetes, particularly in tropical and conflict-affected environments. In turn, this shift would prevent people with diabetes from developing more serious and debilitating health problems or dying prematurely.

## **Kidney disease**

An estimated 697.5 million people were living with chronic kidney disease (CKD) in 2017; 1.2 million people died from kidney disease that same year (though estimates for both figures vary considerably due to a lack of data).<sup>110</sup> China and India account for about one-third of these cases and most people (81.4%) with CKD live in low and middle socio-demographic index (SDI) countries.<sup>111</sup> Deaths from kidney disease increased by 32% between 2005 and 2015 and are projected to continue rising.<sup>112</sup> Diabetes and hypertension most commonly cause kidney disease, though multiple other factors can contribute to its onset,<sup>113</sup> including rising global temperatures.<sup>114</sup> CKD can progress to end-stage kidney disease, which is most frequently treated with hemodialysis (a process by which a person's blood is mechanically transferred from their body, cycled through a machine to remove waste products, and cycled back into their body) or a kidney transplant.

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107 WHO, "Keeping the 100-year-old promise."

108 The WHO recently launched a prequalification program for human insulin aimed at lowering prices and expanding access. See: <https://www.who.int/news/item/13-11-2019-who-launches-first-ever-insulin-prequalification-programme-to-expand-access-to-life-saving-treatment-for-diabetes>.

109 WHO, "Keeping the 100-year-old promise."

110 GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020;395(10225):709–733. doi:10.1016/S0140-6736(20)30045-3.

111 GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017. Unlike income groupings (e.g., low, middle, high), the socio-demographic index categorizes countries using a composite measure based on income per capita, education, and fertility rates. It is another, more nuanced approach to classifying countries.

112 Yeung E, Bello A, Levin A, et al. Current status of health systems financing and oversight for end-stage kidney disease care: a cross-sectional global survey. *BMJ Open* 2021;11:e047245. doi: 10.1136/bmjopen-2020-047245.

113 Luyckx VA, Al-Aly Z, Bello AK, et al. Sustainable Development Goals relevant to kidney health: an update on progress [published correction appears in *Nat Rev Nephrol*. 2021 Oct;17(10):704]. *Nat Rev Nephrol* 2021;17(1):15–32. doi:10.1038/s41581-020-00363-6.

114 Bo Wen et al. Association between ambient temperature and hospitalization for renal diseases in Brazil during 2000–2015: A nationwide case-crossover study. *The Lancet Regional Health—Americas* 2022: Vol. 6, 100101.

*The Challenge: Over a million people with kidney disease die every year because dialysis—while generally available in rich countries—is virtually impossible to access in some LMIC contexts.*

Dialysis is completed as either hemodialysis (HD) or peritoneal dialysis (PD), both of which can be prohibitively expensive in resource-constrained contexts; HD, for example, is estimated to cost nearly 23,000 international dollars<sup>115</sup> per year on average globally and between 10,000 and 18,000 international dollars on average in LMICs.<sup>116</sup> HD machines have been on the market for seven decades, yet innovations in ease of use, cost, and efficiency have not kept pace in that time.<sup>117</sup> Relative to HD, PD is less invasive and involves adding fluid to a person's abdomen via a catheter; both treatments can be done at home.<sup>118</sup> Although estimates vary widely due to insufficient data, existing evidence suggests that dialysis access is concentrated among rich, privately insured individuals;<sup>119</sup> only 4% of people with end-stage kidney disease have access to treatment in LICs.<sup>120</sup> Dialysis also involves extensive monitoring, and the effectiveness of dialysis treatment depends on quality, dose, frequency, and other factors, requiring sustained linkages to medical care and oversight from multiple kinds of health care providers. Shortfalls in the health workforce make delivering this kind of care especially challenging. Access to kidney transplants is similarly constrained: fewer than half of the estimated 4.9–9.7 million people who qualified for a kidney transplant received one in 2010 and only between about 4–30% of people in LMICs requiring a transplant received one that year.<sup>121</sup> Without treatment, people with end-stage kidney disease will almost certainly die.

*The Innovation Agenda: Better, more affordable, less resource-intensive dialysis options.*

The Affordable Dialysis Prize was awarded in 2016 for a solar panel-powered PD machine concept intended to improve accessibility of low-tech alternatives to existing dialysis options; however, the idea has not moved beyond the design stage.<sup>122</sup> Innovations in both PD and HD are critically needed to meet the significant and growing unmet demand for end-stage kidney disease treatment. More comfortable, affordable treatment options would also benefit everyone with kidney disease. Further advances in solar or battery powered machines for purifying water used in PD devices would be

115 Equal to 2016 USD value.

116 International Society of Nephrology. Global Kidney Health Atlas: A Report by the International Society of Nephrology on the Global Burden of End-stage Kidney Disease and Capacity for Kidney Replacement Therapy and Conservative Care Across World Countries and Regions. [https://www.theisn.org/wp-content/uploads/2021/05/GKHAtlas\\_2019\\_WebFile-1.pdf](https://www.theisn.org/wp-content/uploads/2021/05/GKHAtlas_2019_WebFile-1.pdf).

117 John Knight and Vlado Perkovic. The Affordable Dialysis Prize steams ahead. *The Lancet* 2016. Vol 387.

118 Global Kidney Health Atlas.

119 Gloria Ashuntantang et al. Outcomes in adults and children with end-stage kidney disease requiring dialysis in sub-Saharan Africa: a systematic review. *The Lancet Global Health* Apr 2017; Vol 5, Issue 4. [https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(17\)30057-8/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(17)30057-8/fulltext).

120 Global Kidney Health Atlas.

121 Thurlow JS, Joshi M, Yan G, Norris KC, Agodoa LY, Yuan CM, Nee R. Global Epidemiology of End-Stage Kidney Disease and Disparities in Kidney Replacement Therapy. *Am J Nephrol* 2021;52(2):98–107. doi: 10.1159/000514550. Epub 2021 Mar 22. PMID: 33752206; PMCID: PMC8057343.

122 See: <https://www.dialysisprize.org/> and: <https://www.georgeinstitute.org/projects/the-affordable-dialysis-project>.

potentially helpful, but may also be limited to short-term cases of acute kidney failure. PD is generally cheaper and easier to administer relative to HD, yet still requires a sufficiently strong health system infrastructure to support its ongoing implementation and is not indicated in every case of end-stage kidney disease.<sup>123</sup> Innovations in both HD and PD machines that simplify and streamline the dialysis process and bring down costs of administering treatment, particularly in non-clinical/home-based settings, would help make it easier to scale up dialysis access and ensure people with end-stage kidney disease are able to maintain treatment for as long as they need it.

## **Cancer care**

Cancer is among the leading causes of death worldwide. In 2020, 10 million people died from cancer, accounting for one in six global deaths.<sup>124</sup> About 19.3 million people were newly diagnosed with cancer in 2020.<sup>125</sup> In LMICs, cases of cancer disproportionately lead to death relative to cases in HICs for a variety of reasons, including delayed diagnosis and inaccessible treatment options. For example, while not a leading cause of cancer deaths overall, cervical cancer nevertheless makes up a sizable portion of the cancer burden in LMICs: 90% of the 340,000 women who died in 2020 from cervical cancer were women in LMICs.<sup>126</sup> Cervical cancer, like numerous other forms of cancer, is curable when detected early on in the course of disease and promptly treated. Although 82% of overall childhood cancer cases in 2017 occurred in LMICs; 95% of the estimated 142,300 cancer deaths among children were in LMICs.<sup>127</sup> These figures suggest that cancer diagnoses in LMICs are disproportionately more likely to result in death relative to those in HICs.

*The Challenge: Without early detection and prompt treatment, cancer spreads in the body and frequently causes premature death. Yet many people around the world lack access to cancer screening tools.*

One reason cancer deaths are disproportionately concentrated in LMICs is the lack of fast, accurate, and accessible cancer screening tools available at scale. While people in rich countries generally enjoy comparatively accessible cancer screening options such as colonoscopies and mammograms for common cancers such as colon/rectal and breast cancers, respectively, access to such diagnostic tools remains constrained in many LMICs. Many of these screening tools, including also biopsies of abnormal growths and blood tests, may also require trained health care providers to administer and interpret results. Early detection, however, is vital for catching the disease before it metastasizes

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123 PD requires safe disposal methods for waste, regular medical supervision/monitoring, and medical supplies.

124 World Health Organization. "Cancer." February 2022. <https://www.who.int/news-room/fact-sheets/detail/cancer>.

125 Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. *Int J Cancer* 2021 Apr 5. doi: 10.1002/ijc.33588. Epub ahead of print. PMID: 33818764.

126 World Health Organization. "Cervical Cancer." February 2022. <https://www.who.int/news-room/fact-sheets/detail/cervical-cancer>.

127 GBD 2017 Childhood Cancer Collaborators. "The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017." *Lancet Oncol* 2019;20:1211–25. Available from: [https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(19\)30339-0/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30339-0/fulltext).

(i.e., spreads to other parts of the body) or otherwise causes more severe illness and possibly death. Prompt, accurate diagnosis is especially important in resource-constrained contexts where cancer care may be deprioritized relative to other health areas such as malaria, TB, and HIV, and more intensive cancer treatment options may be limited. Some cancers have well-established etiologies; for example, HPV causes more than 95% of all cervical cancer cases.<sup>128</sup> Understanding this link has enabled effective prevention (an HPV vaccine) and screening methods (an HPV test). To better reach people at risk of developing cervical cancer, the WHO now recommends HPV self-sampling to improve global cervical cancer screening.<sup>129</sup> This move is an important stride in global cancer control efforts. Yet the majority of cancers lack similarly easy to use self-sampling or self-testing tools.

### *The Innovation Agenda: Intuitive, accurate, and accessible self-testing/self-sampling tools to diagnose multiple types of cancer sooner and improve prognoses.*

There have been recent advances in cancer diagnostics/early detection, such as HPV self-sampling and a new platform capable of detecting multiple kinds of cancers simultaneously.<sup>130</sup> Aside from the HPV test, however, there is limited evidence that such tools are being adapted for affordable, scalable use in LMICs, where they are needed most. The causes and prevalence of different kinds of cancers also varies by context; in many LMICs, for example, viral and bacterial infections such as HPV, HIV, *Helicobacter pylori*, and hepatitis contribute to excess cancer mortality.<sup>131</sup> As has been done with HPV testing as a means of screening for cervical cancer, screening approaches tailored to infection-driven cancers when also paired with prevention efforts could help support individuals in accessing diagnoses earlier in the course of disease. This shift would in turn support faster linkages to care, thereby increasing likelihood of survival.

## **Lead poisoning**

Lead is a dangerous neurotoxin that impedes normal brain development and harms human health, even in very small quantities. At high concentrations, acute lead poisoning can lead to encephalopathy, colic, seizures, sterility, paralysis, and death. More commonly, chronic lower-level lead exposure impedes normal brain development, causes neurological disorders, and substantially increases the risk of heart and kidney disease. Lead poisoning in young children permanently impairs their ability to learn and thrive, with lifelong consequences for earnings and welfare.

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128 WHO. "Cervical Cancer."

129 Several specific strains of HPV can cause cervical cancer, making HPV testing an important component of cervical cancer screening. For more on WHO's guidance around HPV self-sampling, see: <https://www.who.int/publications/i/item/WHO-SRH-2012>.

130 See, for example, CancerSEEK, discussed in <https://hub.jhu.edu/2019/06/03/cancerseek-blood-test/> and <https://www.science.org/doi/full/10.1126/science.aar3247>.

131 Shailja C. Shah, Violet Kayamba, Richard M. Peek Jr, and Douglas Heimburger. Cancer Control in Low- and Middle-Income Countries: Is It Time to Consider Screening? *Journal of Global Oncology* 5 (2019) 1–8. Published online March 25, 2019.

Since the 1970s, efforts to reduce human lead exposure—including the phase-out of leaded petrol, efforts to replace lead pipes, and the gradual reduction of lead use in paint—have dramatically reduced the burden of lead poisoning, at least in HICs. Yet even today, estimates suggest that almost half of children in LMICs have blood-lead levels that would merit medical intervention by HIC standards.<sup>132</sup> Lead remains pervasive and invisible, reaching children via contaminated cookware, spices, toys, and contaminated industrial/informal battery recycling sites. While data is sparse, lead poisoning may be one of the most impactful yet overlooked challenges in global health, education, and economic development. Estimates suggest that lead poisoning contributes to 900,000 premature deaths<sup>133</sup> and almost one trillion dollars in economic losses each year—accounting for 2–4% of LMIC GDP.<sup>134</sup>

*The Challenge: Few LMICs are able to systematically monitor the prevalence or severity of lead poisoning, perpetuating a cycle of neglect and inaction.*

Underlying the dramatic figures about global lead poisoning is great uncertainty; many estimates of the burden have been constructed over an almost complete data vacuum. A recent systematic review found zero recent data on blood-lead levels in about two-thirds of LMICs,<sup>135</sup> while just a handful of countries have conducted nationally representative prevalence surveys. The two most prominent sets of estimates often show dramatic disagreement with each other, leaving national policymakers with little reliable information to guide prioritization or intervention.<sup>136</sup>

Though part of this data vacuum is attributable to political neglect and lack of awareness, there are also technological barriers to better surveillance. At present, the “gold standard” of blood lead testing is a venous blood draw, which is then sent to a laboratory for analysis. Venous blood draws are expensive and often impractical as they require a trained medical practitioner to administer; advanced laboratory capacity (that may not exist in many LMICs) to analyze; and days or weeks to produce results. Venous blood draws are also relatively invasive and uncomfortable for the children or adults being tested. An alternative approach uses capillary blood draws (“finger-pricks”); at present, however, only one company manufactures a point of care (POC) system for capillary

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132 UNICEF and Pure Earth. The toxic truth: Children’s exposure to lead pollution undermines a generation of future potential. July 2020. Available from: <https://www.unicef.org/reports/toxic-truth-childrens-exposure-to-lead-pollution-2020>.

133 UNICEF and Pure Earth. The toxic truth.

134 New York University. Economic Costs of Childhood Lead Exposure in Low- & Middle-Income Countries. Available from: <https://med.nyu.edu/departments-institutes/pediatrics/divisions/environmental-pediatrics/research/policy-initiatives/economic-costs-childhood-lead-exposure-low-middle-income-countries>.

135 Bret Ericson, Howard Hu, Emily Nash, Greg Ferraro, Julia Sinitzky, Mark Patrick Taylor. Blood lead levels in low-income and middle-income countries: a systematic review. *Lancet Planet Health* 2021;5:e145–53. [https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196\(20\)30278-3/fulltext](https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196(20)30278-3/fulltext).

136 Lee Crawford, Susannah Hares, Justin Sandefur, and Rachel Silverman. Time to Get Serious About Measuring Childhood Lead Poisoning. Center for Global Development: May 2022. <https://www.cgdev.org/blog/time-get-serious-about-measuring-childhood-lead-poisoning>.

blood-lead testing.<sup>137</sup> Though the device itself is reasonably priced (at about \$2,000), test kits cost about \$8 each—a price point far too high for routine testing in most LMICs. There have also been concerns about the reliability of the device, including a product recall from 2020–2021 due to inaccurately low results.<sup>138</sup>

### *The Innovation Agenda: More reliable and affordable diagnostics for POC lead testing.*

Proof of concept for a POC lead test is already established, but greater competition and innovation could help produce more fit-for-purpose options to serve LMIC markets at an affordable price. This would enable much broader and more frequent testing, both for population-level surveillance to help remediate broad sources of lead exposure and to diagnose and treat potentially vulnerable children in a clinical setting. Total sales for the existing POC system are around \$18 million annually<sup>139</sup>—a relatively modest overall market size, but one which could expand dramatically if LMIC providers began broader surveillance efforts and routine lead testing in children. For example, routine annual testing of children under five in India would target about 115 million kids each year; at a cost of \$1 per test, that alone could 6x the existing POC market size (by revenue).

### *The Challenge: Chelation agents to treat poisoning with lead and other heavy metals often require injection/hospitalization, and/or are not widely available in LMICs.*

For lead poisoning, prevention is almost always the best treatment; children will generally eliminate lead from their blood with a half-life of a few weeks if ongoing lead exposure is halted. In cases of severe acute lead poisoning, however, other treatment may be needed to prevent life-long negative outcomes or death. Chelation agents, which bind to heavy metals, can be administered to adults and children with acute lead poisoning to help more quickly flush the toxins from their bodies; chelation therapy is typically indicated in children with blood lead levels above 45 micrograms/deciliter.<sup>140</sup> Yet chelation therapy often requires either inpatient care (injection/intravenous administration) or outpatient oral administration over a long duration, and chelating agents are not always widely available in LMICs.<sup>141</sup>

137 See: <https://www.magellandx.com/leadcare-products/leadcare-ii/>.

138 Advancing Health in America. LeadCare blood lead tests recall expanded due to risk of falsely low results. October 2021. <https://www.aha.org/news/headline/2021-10-14-leadcare-blood-lead-tests-recall-expanded-due-risk-falsely-low-results>.

139 See: <https://investor.meridianbioscience.com/media/document/ec09ffab-f23e-4e3b-87ab-a81a8d9d2cc3/assets/Meridian%20Q2%202022%20Earnings%20Presentation%20vFinal.pdf>.

140 World Health Organization. Guideline for clinical management of exposure to lead. October 2021. <https://www.who.int/publications/i/item/9789240037045>.

141 WHO. Guideline for clinical management of exposure to lead.



### *The Innovation Agenda: Safe and inexpensive chelation therapy for better clinical management of lead exposure.*

The limited indication of chelation therapy is in part a function of its cost, side effects, and safety concerns, constraining the frequency with which the benefits will outweigh the risks of its administration. Better chelation agents—for example, long-lasting oral therapies without safety risks or side-effects—could potentially be administered regularly to children at elevated risk of lead poisoning, perhaps even as a prophylactic measure. These agents would allow for wider and more aggressive treatment of children with confirmed and/or suspected lead poisoning, and potentially even population-wide administration in areas with widespread environmental contamination while mitigation activities are ongoing.

## **3. The global health security agenda**

The COVID-19 pandemic illustrated the critical importance of robust outbreak surveillance systems, effective public health messaging, and global cooperation—and the high cost of the “panic and neglect” cycle for pandemic preparedness and response.<sup>142</sup> Our existing toolkit to fight evolving microbes and known pathogens of pandemic potential needs reinforcement, while tomorrow’s still unfamiliar threats will require new and improved tools. Yet even after our recent experience with COVID-19, investments in bolstering surveillance capacity, developing new antimicrobials, and fortifying pandemic preparedness all fall short of projected needs.

### ***Pandemic preparedness: next generation vaccines***

#### *The Challenge: Experts estimate even odds of another deadly global pandemic comparable to COVID occurring within the next 25 years (47–57 percent).*<sup>143</sup>

Wildlife habitat destruction and impacts from climate change, along with the natural tendency of microbes to evolve, have led to an increase in zoonotic spillover events over the last several decades. In the past 20 years alone, two novel coronaviruses have made the jump from animals to humans. Experts agree that we will more than likely experience another severe pandemic in our lifetime.

Despite international commitments to better prepare for future pandemics, however, current preparedness and response infrastructure and investments are insufficient.<sup>144</sup> The ongoing

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142 While the scope of this paper is limited to important and necessary biomedical innovations, we again caveat that underlying social conditions that exacerbate collective vulnerability to pandemics must also be addressed. See: <https://law.yale.edu/yys-today/yale-law-school-videos/ed-yong-normal-led-two-years-covering-pandemic>.

143 Eleni Smitham and Amanda Glassman. The Next Pandemic Could Come Soon and Be Deadlier. CGD Blog. August 2021. <https://www.cgdev.org/blog/the-next-pandemic-could-come-soon-and-be-deadlier>.

144 Wenham C, Kavanagh M, Torres I, Yamey G. Preparing for the next pandemic. *BMJ* 2021;373:n1295. <https://www.bmj.com/content/373/bmj.n1295>.

COVID-19 pandemic highlights the disruptive consequences of poor preparedness: most of the world is still experiencing economic, health, and social fall-out from the pandemic, including economic stagnation or recession.<sup>145</sup> Costs associated with pandemic response are estimated to be 10 to 25 times the “cumulative additional investments in prevention and preparedness.”<sup>146</sup> Without adequate preparation, pandemics can close economies, borders, trade, and schools—in addition to their impact on death and disability.

### *The Innovation Agenda: Safe, effective pan-coronavirus and pan-influenza vaccines to protect against future variants—and the next pandemic.*

The speed of developing and deploying an effective vaccine against COVID-19 disease was historically unprecedented.<sup>147</sup> With similar resources and dedication—plus modern biotechnology, like the mRNA platform—it may also be possible to develop pan-coronavirus and pan-influenza vaccines. A pan-coronavirus vaccine would protect against COVID-19 variants, but also future (as yet unknown) coronaviruses; likewise, a pan-influenza vaccine would protect against “normal” seasonal influenza and also the threat of a future flu pandemic. Together, these tools could potentially avert millions of deaths and pandemic-related disruptions.<sup>148</sup> As with all medical technologies, however, a universal influenza vaccine would need to be widely accessible and acceptable to generate the potential health effects. This situation is often not the case; well under half of LICs and LMICs have policies for routine vaccination against seasonal influenza even though the vast majority of pediatric influenza deaths occur in low- and middle-income countries.<sup>149,150</sup>

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145 World Bank Group. Global Economic Prospects. June 2022. <https://www.worldbank.org/en/publication/global-economic-prospects>.

146 A Global Deal for our Pandemic Age: Report of the G20 High Level Independent Panel on Financing the Global Commons for Pandemic Preparedness and Response, 2021. Available from: <https://pandemic-financing.org/wp-content/uploads/2021/07/G20-HLIP-Report.pdf>.

147 Amanda Glassman, Charles Kenny, and George Yang. COVID-19 Vaccine Development and Rollout in Historical Perspective. CGD Working Paper. February 2022. <https://www.cgdev.org/publication/covid-19-vaccine-development-and-rollout-historical-perspective>.

148 Sabin-Aspen Vaccine Science & Policy Group. Powering Vaccine R&D: Opportunities for Transformation. 2021. <https://www.sabinaspengroup.org/app/uploads/2021/05/Sabin-Aspen-Report-2021.pdf>.

149 World Health Organization. Global action plan for influenza vaccines: global progress report 2006–2016. Geneva: World Health Organization; 2019. Available from: <https://apps.who.int/iris/bitstream/handle/10665/329300/9789241515634-eng.pdf?sequence=1&isAllowed=y>.

150 Harish Nair et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 2011;378:1917–30. <https://www.thelancet.com/action/showPdf?pii=S0140-6736%2811%2961051-9>.

## ***Antimicrobial resistance and pandemic response***

*The Challenge: The world is losing its ability to effectively treat/cure common illnesses. Without effective antimicrobials, once treatable illnesses are becoming lethal again. Yet the existing R&D pipeline does not come close to meeting this innovation need.<sup>151</sup>*

The “antibiotic revolution” of the 20th century, together with other important strides in public health, rendered many once life-threatening infections into easily curable transient illnesses.<sup>152</sup> Available tools for fighting infection, however, are losing their potency, partly because of over- and misuse in health and agricultural settings.<sup>153</sup> Antimicrobial resistance (AMR)—both the natural tendency of microbes to evolve over time and the ability of illness-causing microbes to evade available treatments such as antibiotics, antivirals, antifungals, and antiparasitics—presents one of the main health challenges threatening humanity.<sup>154</sup> AMR now contributes to premature mortality on par with the leading causes of infectious disease; a recent analysis estimated that bacterial AMR contributed to nearly five million deaths in 2019 alone.<sup>155</sup> If resistance continues to develop and expand, some experts fear a “nightmare scenario” in which surgeries, transplants, and chemotherapy become prohibitively risky. Yet four decades have elapsed since scientists last developed a new class of antibiotics.<sup>156</sup> Without coordinated efforts to develop next generation antimicrobials, once manageable infections could once again become lethal.

*The Innovation Agenda: New classes of antimicrobials, including broad-spectrum antibiotics, to protect against AMR and some future pandemics.*

New classes of antivirals, antibiotics, and other antimicrobials are needed to preempt the growing threat of AMR; they could also serve as counter-measures against future, as yet unknown pandemic pathogens. Six bacteria have been identified as “priority pathogens” based on their resistance-induced lethality; these six bacteria alone contributed to nearly three-quarters of AMR-related

151 The Review on Antimicrobial Resistance. May 2015. “Securing New Drugs for Future Generations: The Pipeline of Antibiotics.” [https://amr-review.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20GENERATIONS%20FINAL%20WEB\\_0.pdf](https://amr-review.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20GENERATIONS%20FINAL%20WEB_0.pdf). This report found that among 41 drugs then in development, only three were rated as “high priority.”

152 Adedeji WA. The Treasure Called Antibiotics. *Ann Ib Postgrad Med* 2016;14(2):56–57. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5354621/>.

153 Aditi Sriram, Erta Kalanxhi, Geetanjali Kapoor, Jessica Craig, Ruchita Balasubramanian, Sehr Brar, Nicola Criscuolo, Alisa Hamilton, Eili Klein, Katie Tseng, Thomas Van Boeckel, Ramanan Laxminarayan. 2021. State of the world’s antibiotics 2021: A global analysis of antimicrobial resistance and its drivers. Center for Disease Dynamics, Economics & Policy, Washington DC. <https://cddep.org/wp-content/uploads/2021/02/The-State-of-the-Worlds-Antibiotics-in-2021.pdf>.

154 See, for example: <https://cgdev.org/blog/antimicrobial-resistance-advances-we-need-action-stop-predictable-catastrophe/>; <https://amr.solutions/pathogens-and-pipelines/>; and <https://amr-review.org/>.

155 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022;399:629–55. <https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2902724-0>.

156 Matthew I Hutchings, Andrew W Truman, Barrie Wilkinson. “Antibiotics: past, present and future.” *Current Opinion in Microbiology*, Volume 51, 2019, Pages 72–80. Available from: <https://www.sciencedirect.com/science/article/pii/S1369527419300190>.

deaths in 2019.<sup>157</sup> Broad-spectrum antibiotics capable of treating infections caused by these bacteria would, therefore, significantly curb future AMR-related deaths and offer “enablement” value for continued use of surgery, transplant, and chemotherapy, among other foundational treatments in modern medicine whose viability is dependent on antimicrobial efficacy.

## ***Next generation diagnostics***

*The Challenge: Our current diagnostic and surveillance toolkit may not be sophisticated enough to identify outbreaks and drug resistance as they happen, increasing response time and vulnerability.*

Accurate, fast diagnostics, together with other elements of outbreak surveillance, comprise a critical component of pandemic preparedness and response. Although the COVID-19 pandemic helped expand and fortify the diagnostic infrastructure across much of the world, it has also illustrated persistent blind spots in global surveillance. These blind spots include the time required to develop and scale testing infrastructure for any given emerging pathogen, as well as the need for rapid genetic sequencing (and sharing) to facilitate development of countermeasures and identify variants of concern. These exact challenges are playing out with the emerging global monkeypox outbreak; in the US, for example, problems with testing prevented case detection and very likely contributed to community spread during the initial phase of the outbreak.<sup>158</sup> Increasingly, sophisticated diagnostic capabilities with genetic sequencing capability may also be needed at the individual level—for example, to determine the extent of drug resistance and inform appropriate antimicrobial prescribing.<sup>159</sup>

*The Innovation Agenda: Multiplex genomic sequencing to rapidly identify—and respond to—new and evolving pathogens.*

Next-generation sequencing technologies could be capable of rapidly identifying the genetic composition (i.e., DNA or RNA sequence) of a previously-unknown pathogen,<sup>160</sup> enabling scientists/other experts to quickly investigate outbreaks and develop tailored countermeasures. Prompt containment measures are vital for preventing pathogenic infections from reaching pandemic-scale. Next-generation sequencing, including multiplex point-of-care testing, is also crucial for monitoring drug resistance and understanding how pathogens evade and respond to vaccines and therapeutics. This understanding would help enable the development of better, more effective medical toolkits for treating new and existing infectious diseases, potentially on an expedited timeline. When paired

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157 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019.

158 Helen Branswell and Andrew Joseph. ‘Testing bottleneck’ for monkeypox puts hope of containment at risk, experts warn. STAT News: June 2022. <https://www.statnews.com/2022/06/07/testing-bottleneck-for-monkeypox-jeopardizes-containment-experts-warn/>.

159 See: <https://amr-review.org/sites/default/files/Paper-Rapid-Diagnostics-Stopping-Unnecessary-Prescription-Low-Res.pdf>.

160 See: <https://www.finddx.org/sequencing/>.

with reliable rapid point-of-care diagnostics that are also optimized for resource-limited, remote, rural contexts, these innovations would significantly improve localized, regional, and global disease outbreak surveillance efforts.<sup>161</sup>

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## Discussion and Conclusion

Overall, our landscaping effort suggests an unfinished agenda for biomedical innovation to advance global health priorities. We see a chronically underfunded global health innovation ecosystem, with substantial “absorptive capacity” for potentially high-impact R&D investments. The global health “wish-list” is diverse across disease areas, innovation types, and levels of technological sophistication. Unsurprisingly, however, opportunities are clustered in health areas vulnerable to market failure—diseases of poverty, antimicrobial resistance, and global health security. Our hypothesis—though still speculative, at least within the scope of this paper—is that many (though not all) of these proposed innovations would be discovered/developed/brought to market if R&D were fully funded, commensurate with the level of funding dedicated to diseases that primarily affect rich countries.

This exercise was motivated by an interest in potential opportunities for pull mechanisms—and pull mechanisms do indeed offer one promising avenue for addressing some of the relevant market failures. At the same time, pull mechanisms may not always be an appropriate or optimal approach, and we do not presuppose here the correct way to fund R&D priorities. (Pull mechanism design will be considered further in a complementary working paper.) We reflect stakeholder views on funding approach, with a particular focus on pull mechanisms, in Appendix A.

Notwithstanding choice of funding *mechanism*, there is also, of course, the question of funding *source*; which governments, organizations, or individuals should have the mandate and resources to financially support this R&D agenda? As discussed in the introduction, most of the innovations described in this paper are neglected by market R&D due to perceived insufficient profit potential. That leaves three groups of potential funders: governments; philanthropists; and international organizations. The latter category is itself directly funded by governments and philanthropists, and their involvement in R&D is determined by the mandate and direction of their constituent funders; we therefore exclude them from direct consideration here.

Given the wealth of high-value opportunities for biomedical advance—and the market failures that prevent sufficient private-sector R&D for these areas—governments have an important role to play in mobilizing R&D financing. As discussed in the introduction, HIC government financing for R&D is already substantial, but generally focused on noncommunicable disease threats. Biomedical

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<sup>161</sup> DIATROPIX of Institut Pasteur de Dakar is currently leading efforts to develop and produce rapid diagnostic tests for largely neglected diseases at scale. For more information, see: <https://www.pasteur.sn/en/news/actualite-covid/launch-rapid-diagnostic-test-production-platform-institut-pasteur-dakar>.

research for pandemic preparedness and other health security threats is chronically underfunded relative even to domestic importance within the US—and many neglected tropical diseases or emerging diseases, like Ebola or monkeypox, also have the potential to threaten HICs domestically. We argue, therefore, that HIC governments consider a substantial increase in R&D financing—at minimum focused on threats with domestic health relevance, but ideally contributing to the global commons of biomedical technology to counter the full compendium of infectious disease threats, which ultimately are just that—global.

Beyond traditional HIC government funders, LMIC governments should consider allocating targeted R&D funding from their own budgets to address local health threats. In the wake of the COVID-19 pandemic, many LMICs have signaled a commitment to increase local manufacturing capabilities for vaccines and other pharmaceuticals. It is argued that such capabilities, if locally held, would protect LMICs from reliance on wealthy country “charity” during future pandemics—thereby preventing the recurrence of severe vaccine access inequities experienced during 2021–2022. That argument could be logically extended: LMICs should not have to rely exclusively on wealthy donors to finance locally relevant R&D, but should build domestic innovative biotech industries to serve local health needs, perhaps subsidized by the governments under industrial policy. Alternatively, or as a complement, LMICs governments could also consider more strategic payer policy to drive desired innovation outcomes.<sup>162</sup>

Philanthropy is the other potential source of additional R&D financing. Disease research has long been a focus of private giving and philanthropy; however, most individual donors contribute to causes that are of personal importance to their families and communities, e.g., diseases including cancer, cystic fibrosis, heart disease, and Alzheimer’s, or even contributions to local hospitals where they or their family member(s) received treatment. While such giving patterns are understandable, they also definitionally exclude R&D for disease areas that do *not* directly affect wealthy individuals with disposable resources. Most innovations discussed in this paper fall into that category, and therefore would benefit from additional philanthropic support for R&D.

This R&D agenda, therefore, may be most attractive to philanthropists whose giving is motivated by a desire to do good, broadly speaking, versus contributing specifically to a cause of personal import. We suggest that this R&D agenda may be of particular interest to the rapidly growing philanthropic community aligned with Effective Altruism (EA), “a philosophy and community focused on maximizing the good you can do through your career, projects, and donations.”<sup>163</sup> Though the returns on investment are more uncertain than EA-endorsed service delivery interventions (e.g. malaria

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162 Kalipso Chalkidou, Adrian Towse, and Rachel Silverman Bonnifield. Unpacking the Black Box of Payer Policy: A Demand-Side Approach for Equitable Uptake of Cost-Effective Health Innovation. CGD Note. February 2020. Available from: <https://www.cgdev.org/publication/unpacking-black-box-payer-policy-demand-side-approach-equitable-uptake-cost-effective>.

163 See: <https://www.effectivealtruism.org/>.

bed-net distribution or seasonal chemoprevention),<sup>164</sup> targeted investments in biomedical R&D are likely to perform very well on the prioritization criteria used in the EA community: importance, tractability, and neglectedness.<sup>165</sup> Our third innovation category—the Global Health Security Agenda—is also well-aligned with EA concerns about long-term existential risks, including pandemics.<sup>166</sup> EA funders should consider increasing their investments in targeted R&D as a neglected cause with very high return on investment potential.

It is important to acknowledge, however, the limits of biomedical innovation alone to solve entrenched health problems. Yes, the innovations discussed above all have the potential to transform lives, accelerate progress in neglected health areas, and/or insure against both individual and collective health risks. At the same time, many of the problems contributing to premature death and disability are structural and require policy action. Existing life-saving innovations such as dialysis and cancer care are virtually inaccessible in many countries. Pharmacies endure frequent stockouts of basic health commodities such as contraceptives and HIV antiretroviral drugs because of inconsistent or inefficient supply chains. Technological/biomedical solutions do not change the need for addressing these systemic, structural failures.

Policymakers and regulators must address these basic problems in health systems alongside the introduction of any new health technology, as health technologies can only save and improve lives if they reach people in the places and times of need.<sup>167</sup> Similarly, biomedical innovation is useful only when efforts are taken to ensure access at scale among affected communities. Such efforts include early incorporation of access and scaleup feasibility considerations within the R&D cycle, plus creation of an enabling policy environment for widespread, ongoing adoption and diffusion (see Appendix B). Adopting systems thinking and conceiving of the innovation ecosystem as just that—an interconnected *system*—could also help. For example, several different interviewees emphasized the transformative potential of a digital link between diagnostic results and the broader digital infrastructure to improve overall surveillance, data collection, and case management—especially if paired with broader investments to bolster digitalization and routine collection and use of health data.

Despite our focus here on biomedical innovation, we also want to be clear that any given biomedical advance is unlikely to serve as a silver bullet across complex, context-specific health challenges. Addressing the social and structural determinants of health—poverty, nutrition, housing quality,

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164 See: <https://www.givewell.org/charities/top-charities>.

165 See: <https://forum.effectivealtruism.org/topics/itn-framework>.

166 William Macaskill. The Case for Longtermism. *The New York Times*. August 2022. <https://www.nytimes.com/2022/08/05/opinion/the-case-for-longtermism.html>.

167 Better R&D coordination, information sharing, and public interest alignment are all other necessary components of improving the global health innovation ecosystem. See: Soumya Swaminathan et al. (2022). Reboot biomedical R&D in the public interest. *Nature*. <https://www.nature.com/articles/d41586-022-00324-y> and: Beyeler N, Fewer S, Yotebieng M, Yamey G. Improving resource mobilisation for global health R&D: a role for coordination platforms? *BMJ Global Health* 2019;4:e001209.

environment, sanitation, inequity, and access to quality PHC services—are all foundational for long-term health improvement. Biomedical innovation (and delivery) must be accompanied by measures to address the underlying drivers of collective vulnerability; it is not a *substitute* for social and economic development. Yet for the challenges discussed in this paper, we argue that transformational progress is possible if focused, strategic biomedical innovation is paired with a sufficient investment of time, resources, and effort.

Finally, in addition to our earlier caution that this should not be considered “the” definitive agenda for priority global health innovation, we also note that no prioritization should be static, but instead subject to constant revision alongside evolving circumstances and understanding of underlying disease dynamics. The emergence of SARS-CoV-2 fundamentally transformed the prioritization landscape and appropriately so; it is difficult to anticipate what the “next” emerging or re-emerging priority might be, though we can anticipate some likely effects from climate change. Likewise, technological advances in gene therapy and mRNA have expanded the potential for biomedical innovation beyond what was once thought possible; given the unknowns of near- and long-term biomedical advances more generally, it is difficult to project what might join the frontier of the innovation agenda.

While we have also taken efforts to source ideas from a broad range of experts—and while we are confident in the relevance and importance of the innovation agenda laid out in this paper—we also acknowledge the potential for oversight, bias, and/or other limitations based on our own positions. Priority innovations selected for investment must be identified in partnership with affected countries and populations, and reflective of their own policy priorities and health needs. The biomedical innovation agenda must also be tailored to or borne from locally and regionally developed R&D strategies, such as the African Union’s Health Research and Innovation Strategy for Africa (HRISA): 2018–2030<sup>168</sup> and the WHO’s Research for Health: A Strategy for the African Region, 2016–2025.<sup>169</sup>

We urge funders and policymakers to prioritize biomedical innovation commensurate with its importance as a facilitator and enabler of potentially transformative health improvement—alongside the health system improvements and structural changes needed to ensure effective delivery and address the underlying drivers of poor health.

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168 African Union Development Agency-NEPAD. Health Research and Innovation Strategy for Africa (HRISA): 2018–2030. May 2019. <https://www.nepad.org/publication/health-research-and-innovation-strategy-africa-hrisa-2018-2030>.

169 World Health Organization. Research for health: A strategy for the African region, 2016–2025. November 25, 2015. <https://www.afro.who.int/publications/research-health-strategy-african-region-2016-2025>.



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## Appendix A. Perceptions and applications of pull mechanisms as a tool for driving global health innovation

Our conversations suggested a wide range of familiarity with and enthusiasm for pull mechanisms as a tool to drive global health innovation. Global health stakeholders were most familiar with advance market commitments (AMCs, e.g., by Gavi for pneumococcal disease<sup>170</sup>) and volume guarantees (e.g., Bill & Melinda Gates Foundation for contraceptive implants<sup>171</sup>), but had mixed perceptions of their effectiveness. Many seemed more receptive to “non-traditional” pull mechanisms, including prizes, priority review vouchers, subscription models, milestone payments, and advance purchase agreements, especially if complemented by targeted “push” investments upstream. Enthusiasm was generally highest for health areas perceived as global public goods with high relevance even in high-income countries—antimicrobials, pandemic preparedness and response, and diagnostics/surveillance—and lower for those perceived as primarily relevant to LMICs, like NTDs—where many stakeholders appeared to favor a continued push/grant funding approach. For some experts with whom we spoke, moreover, the critiques against push mechanisms we have outlined elsewhere<sup>172</sup> did not resonate; they pointed to their own institutions’ vetting and approval processes for research projects as counterfactuals to the claimed inefficiencies of push mechanisms.

Beyond the specifics of *how* to fund particular health areas, some experts framed innovation gaps as a problem of political will more broadly. In the US context especially, embedding sustained attention and investment in areas such as pandemic preparedness and response at the policy level has been a persistent challenge. Some experts we spoke with thought the central problem limiting innovation was a lack of political leadership necessary to raise the profile of some issues in the first place. “Diseases of poverty” and antimicrobial resistance (AMR) are two examples of this constrained prioritization. The focus on individual patient outcomes that characterizes biomedical research, moreover, feeds into the under-prioritization of health areas such as AMR; the societal benefits of investing in new antimicrobials, while potentially enormous, may be masked by difficult-to-capture benefits to the individual patient.

Undergirding this characterization in many instances was an acknowledgement of the role of commercial incentives in shaping or inhibiting investment in particular health areas, and the varying risk tolerances of different kinds of innovators. Prevailing commercial incentives are based on short-term investor profits; in most cases, pharmaceutical companies do not perceive

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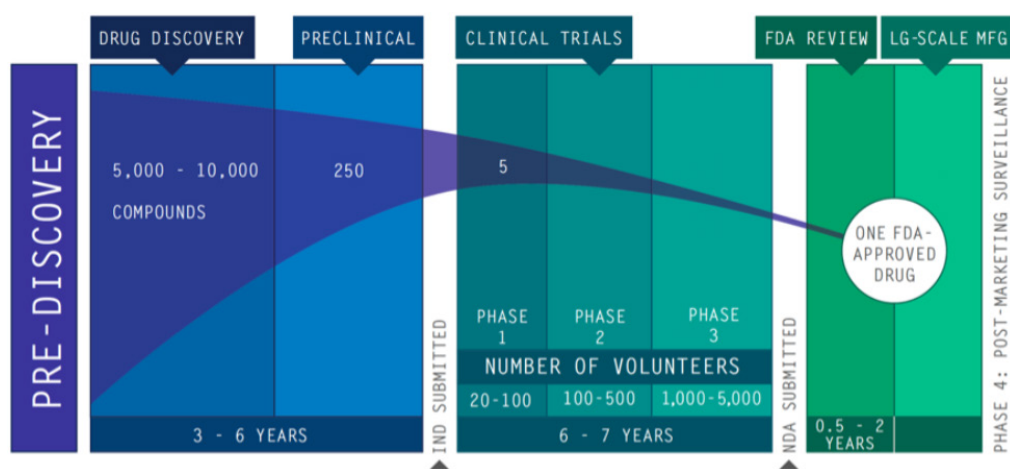
170 Vaccine AMC (Really) Launched Today. Center for Global Development: 2009. <https://cgdev.org/blog/vaccine-amc-really-launched-today>.

171 Amanda Glassman and Prashant Yadav. Demand Forecasting Takes Off. Center for Global Development: 2013. <https://cgdev.org/blog/demand-forecasting-takes>.

172 Steven Kosiak and Rachel Silverman. “Enabling US Government Participation in Pull Mechanisms for Social Impact Innovation: A Survey of Federal Authorities, Budgetary Barriers, and Potential Solutions.” CGD Policy Paper. August 2021. <https://www.cgdev.org/publication/enabling-us-government-participation-pull-mechanisms-social-impact-innovation-survey>.

LMIC markets as attractive or viable for profitmaking. Yet larger companies may have R&D capacity (e.g., clinical site access/coordination, provider network access, and regulatory knowledge/experience) and/or financial “cushions” that smaller, newer companies may lack, enabling larger companies to have higher risk tolerances and greater ability to set the R&D agenda. Consequently, experts we spoke with pointed to the need for designing pull mechanisms in a way that is sensitive to, but not dominated by, the reality that companies capable of developing and producing new products are above all concerned with returns on investment. To that end, some experts we spoke with expressed enthusiasm about using pull mechanisms to help build “onramps” for smaller, potentially more innovative companies, particularly in the early stages of R&D where the risk of failure is much higher (relative to stages farther along the pipeline). This approach could be especially helpful for more globally and/or regionally distributed innovative companies, which would also in turn help disrupt the existing concentration of pharmaceutical companies in HICs.

At the same time, other experts’ enthusiasm for pull mechanisms was tempered by the prospect of designing such a mechanism for the earliest stages; in their view, push funding makes more sense for basic research and drug discovery phases where the chance of failure is highest (see figure below). A pull mechanism at the front-end would need to account for the substantial risk of not identifying a viable compound (even the most carefully designed pull mechanism cannot completely overcome the risk of not coming up with a product at all). One strategy suggested to us to counteract this risk would be to design the pull mechanism with multiple prizes or payouts, especially if the resulting product would be privately held/patented. An expert we spoke with shared an experience working on a pipeline of products for HIV testing and noted how multiple products were developed that matched the target product profile (TPP), yet would be more or less appropriate depending on the context in which the product was used. A well-designed pull mechanism, then, particularly if targeting earlier phases in the R&D pipeline, should build in adaptability to account for both the inherent uncertainty in earlier innovation pipeline stages and the need for contextual specificity of products (i.e., similar innovations may be better suited to different contexts).



Source: Hery Chung. Drug Development and Discovery. Medium. 2019. Available from: <https://medium.com/bioai/drug-discovery-and-development-31758bf6cc72>.

To maximize likelihood of impacting health outcomes, such a pull mechanism would also ideally need to have some sort of follow through plan or otherwise account for phase I-III clinical trials and product launch, manufacturing, and distribution. Some companies may be well-equipped to manufacture products but not develop new ones and vice versa. A well-designed pull mechanism would involve some degree of harmonization of funding structures across the R&D pipeline to help promising innovations make it all the way to the end user. The earlier in the pipeline, moreover, the costlier investments tend to be (potentially billions of dollars<sup>173</sup>), which can crowd out smaller firms that may otherwise be willing to pursue neglected health areas. And in terms of where R&D infrastructure is most robust, the US dominates the innovation ecosystem, which means the US market disproportionately shapes incentives. To better balance market shares and resulting influence over the innovation agenda, experts we spoke with recommended aggregation across markets/regions for volumes (e.g., regional associations in Africa as opposed to individual countries).

At the other end of the pipeline, some experts endorsed a market intervention that would reduce product prices and/or identify models of distribution that improve access. However, others expressed concern that artificially low prices, subsidized by donors via pull mechanisms, could deter market entry of potential competitors and unintentionally entrench monopoly control of the market—perversely leading to higher prices in the long run after direct subsidy had expired.

Some experts also viewed industry secrecy as a major inhibitor of innovation and thought that greater transparency in pricing—both product development and markup—and R&D/production agreements must come before making any decision about funding mechanisms or investment approach. Moderna, for example, received nearly \$10 billion from the US Government to develop a COVID vaccine, yet has not made its mRNA vaccine technology available.<sup>174</sup> One expert we spoke with suggested making all production agreements available, similar to the registration process for all clinical trials.<sup>175</sup>

### *Examples of pull mechanisms in global health*

As mentioned, the most familiar type of pull mechanism to stakeholders were AMCs, which promise a guaranteed market for products meeting a specific TPP, and advance purchase agreements/commitments (APCs). Enthusiasm for AMCs varied significantly; some experts viewed AMCs favorably, while others did not think AMCs or APCs were realistic in LMIC contexts (only the US market has the requisite scale, in this view). Several experts we spoke with thought that pull mechanisms, particularly APCs, would only make sense in areas where there is reasonable

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173 Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009–2018. *JAMA* 2020;323(9):844–853. doi:10.1001/jama.2020.1166.

174 Carrie Teicher. What Moderna owes the world. *STAT News*: November 2021. <https://www.statnews.com/2021/11/04/what-moderna-owes-the-world/>.

175 See: <https://www.clinicaltrials.gov/>. See also: <https://www8.gsb.columbia.edu/articles/chazen-global-insights/patents-vs-pandemic> on the argument for open science.

assurance the product can be developed, or where markets can be aggregated (such as at the scale of the African Union). Pfizer, for example, agreed to produce Prevenar 13, built on its established pneumococcal conjugate vaccine Prevenar, under an AMC with Gavi.<sup>176</sup>

COVID-19 Vaccines Global Access (COVAX), a pooled procurement vehicle aimed at ensuring equitable access to COVID vaccines, showcases mixed results for advance procurement. The mRNA platform technology's path to market further showcases the inherent uncertainty and inevitability of some failure on the way towards technological progress and scientific breakthroughs. While scientists have been exploring potential applications of mRNA technology for over 40 years (including for HIV and influenza vaccines), mRNA was considered too risky, and so did not receive substantial commercial interest or investment until only around the turn of the century.<sup>177</sup>

Vouchers—regulatory incentives that expedite the regulatory approval process—comprised the other type of pull mechanism with which stakeholders were most familiar. The Federal Drug Administration's Priority Review Voucher (PRV) program, established in 2007, targets tropical diseases.<sup>178</sup> The transferable exclusivity voucher is a proposed voucher program that would enable an innovator to transfer exclusivity to another product, pending their development of a product that matches the TPP of the voucher program.<sup>179</sup> It has primarily been explored in the context of developing new drugs for neglected diseases and developing new antimicrobials.<sup>180</sup> The Innovative Vector Control Consortium recently proposed a similar voucher program modeled on the PRV focused on developing new insecticides and other vector control products: the vector expedited review voucher (VERV).<sup>181</sup> Although the agrochemical sector is smaller than the pharmaceutical sector in absolute terms, the proposed VERV has the potential to incentivize a non-health sector to develop new tools for addressing global health challenges.

While promising, experts nevertheless expressed some hesitation around vouchers, primarily in terms of accessibility of new products and incentivizing the wrong thing. Miltefosine, for example, a drug used to treat leishmaniasis since 2002, was acquired by Knight Therapeutics in 2014 and awarded a PRV; however, the PRV appears to have little impact on improving access, as the drug

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176 See: [https://www.pfizer.com/news/press-release/press-release-detail/pfizer\\_signs\\_long\\_term\\_agreement\\_to\\_supply\\_prevenar\\_13\\_to\\_the\\_world\\_s\\_poorest\\_countries](https://www.pfizer.com/news/press-release/press-release-detail/pfizer_signs_long_term_agreement_to_supply_prevenar_13_to_the_world_s_poorest_countries).

177 For a detailed history of mRNA technology, see: Elie Dolgin, "The tangled history of mRNA vaccines." *Nature*. 22 October 2021. <https://www.nature.com/articles/d41586-021-02483-w>.

178 See: <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/tropical-disease-priority-review-voucher-program>.

179 Beth Boyer, Adam Kroetsch, and David Ridley. "Design of a Transferable Exclusivity Voucher Program: Incentives for Drug and Vaccine Development for Neglected Diseases." Duke Margolis Center for January 2022. *Health Policy*. <https://healthpolicy.duke.edu/publications/design-transferable-exclusivity-voucher-program>.

180 On the latter, see: Seth Seabury, Neeraj Sood. "Toward A New Model For Promoting The Development Of Antimicrobial Drugs." May 2017. *Health Affairs*. <https://www.healthaffairs.org/doi/10.1377/forefront.20170518.060144>.

181 See: <https://www.ivcc.com/vector-control/vector-expedited-review-voucher-verv/#vector-expedited-review-voucher-verv>.

remains inaccessible within countries that would most benefit from it.<sup>182</sup> Experts we spoke with underscored the need for clearer enforcement mechanisms for ensuring access to products developed or licensed with PRVs (including, for example, requiring in-country sponsors) and for designing pull mechanisms with equitable access in mind from the beginning. This approach would mean also defining the terms of the program from the point of view of end users (i.e., metrics of success reflect public health goals).

Beyond AMCs, APCs, and voucher programs, experts were familiar with a range of other examples of pull or pull-like funding approaches for financing global health innovation. The proposed “3P project” for tuberculosis, for example, sought to produce an affordable one-month treatment regimen using “prizes, grants and the pooling of intellectual property (pull, push, pool).”<sup>183</sup> The proposed launch date of 2017 never materialized, however; an expert we spoke with attributed this failure, in part, to the level of risk smaller companies would have to take on to participate. Beyond specific initiatives, some organizations have departments dedicated to market analytics and understanding market entry dynamics, such as PATH.<sup>184</sup> Other organizations have been established for the express purpose of overcoming market failures that have led to chronic neglect of particular health areas, such as the Drugs for Neglected Diseases Initiative<sup>185</sup> and Japan’s Global Health Innovative Technology (GHIT) Fund, a public-private partnership focused on increasing investments in health technologies for malaria, TB, and NTDs.<sup>186</sup> Gavi’s Innovation for Uptake, Scale and Equity in Immunisation (INFUSE) mechanism provides financing and technical expertise to countries to help accelerate vaccine access.<sup>187</sup> MedAccess uses volume and procurement guarantees to lower prices of certain products such as mosquito nets and TB treatment for LMICs.<sup>188</sup> Experts we spoke with also shared familiarity with government programs and strategies aimed at accelerating investments in innovation, such as the US Government’s Biomedical Advanced Research and Development Authority (BARDA) Ventures<sup>189</sup> and Advanced Research Projects Agency for Health (ARPA-H).<sup>190</sup>

Beyond push/pull funding, experts listed market access (particularly access to new, bigger markets), market/consumer research/intelligence, and commercial/regulatory knowledge as other potentially

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182 Sunyoto T, Potet J, Boelaert M. “Why miltefosine—a life-saving drug for leishmaniasis—is unavailable to people who need it the most.” *BMJ Glob Health* 2018;3:e000709.

183 See: <https://imedproject.org/proposals-database/3p-project/>.

184 See: <https://www.path.org/programs/market-dynamics/about/>.

185 See: <https://dndi.org/about/>.

186 See: <https://www.ghitfund.org/>.

187 See: <https://www.gavi.org/investing-gavi/infuse>. Gavi’s three-year Vaccine Innovation Prioritization Strategy (VIPS) (see: <https://www.gavi.org/our-alliance/market-shaping/vaccine-innovation-prioritisation-strategy>) and Cold Chain Equipment Optimization Platform (CCEOP) (see: <https://www.gavi.org/our-impact/evaluation-studies/cceop-evaluation>) are two other examples experts cited of ways Gavi has attempted to incentivize, and influence the market in favor of, innovation.

188 See: <https://medaccess.org/>.

189 See: <https://drive.hhs.gov/ventures.html>.

190 See: <https://www.nih.gov/arpa-h>.

compelling innovation incentives, especially for smaller innovators. Grants or discount schemes that make it easier for young researchers to access research funding could also support greater innovation in the long-run. Greater visibility and more systematic use of indices such as the Access to Medicines Index, which ranks pharma companies' performance on product accessibility and other global health-related metrics, could also incentivize companies to ensure their products reach people in LMICs.<sup>191</sup> Developing better “connective tissue” across the innovation ecosystem that supports innovators and product developers throughout the entire lifecycle of product development was seen as yet another way to accelerate global health innovation.<sup>192</sup> Poverty reduction would also help accelerate innovation by expanding the perceived market for diagnostics and therapeutics, particularly for NCDs (the top contributor to deaths worldwide<sup>193</sup>).

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191 See: <https://accesstomedicinefoundation.org/access-to-medicine-index>.

192 See, for example, Global Health Technology Coalition's policy proposal for the Supporting Innovations in Global Health Technologies (SIGHT) Fund: <https://www.ghtcoalition.org/resources-item/the-supporting-innovative-global-health-technologies-sight-fund-a-new-proposal-to-drive-inclusive-global-health-innovation-at-usaid>.

193 See: <https://ourworldindata.org/causes-of-death>.

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## Appendix B. Considerations for using pull mechanisms in global health

While the health areas outlined in this paper would all benefit from increased investment, pull mechanisms may not be appropriate in all cases. If decision-makers opt to use pull funding, the selected mechanism must be highly context-specific, supported by an enabling ecosystem, and carefully designed to avoid perverse unintended outcomes. Successful implementation of pull funding approaches broadly requires agreed upon criteria for what the pull mechanism is intended to achieve and clear guidance for how resources should be allocated across the global innovation ecosystem. The following design and contextual considerations were highlighted in our stakeholder interviews:

- **How do we ensure access considerations are incorporated early in the R&D pipeline, and directly addressed within any pull mechanism design?** Several stakeholders suggested that access considerations should be embedded within pull mechanism design from its earliest stages—for example, via well-defined and enforceable access clauses in contracts with meaningful penalties for delayed or fragmented product delivery. Depending on the size and scope of the pull mechanism, the specific approach to drive access might require country- or even district-specific access solutions.
- **How do we ensure direct and meaningful participation from affected communities and the health workforce in product specification—which is essential to ensure the innovation actually responds to local needs?** Clinical trials run by HIC-based institutions frequently do not involve LMIC-based innovators. To ensure global health innovations are fit-for-purpose and designed with the needs and priorities of affected populations in mind, end users and LMIC-based experts need to be centered in innovation investment decision-making processes. One possible strategy would include co-application requirements that outline direct, non-tokenistic participation of LMIC researchers and impacted communities. Engagement of local clinical advisory boards in the design process could also help.
- **Are health systems ready and fit-for-purpose to deploy the targeted innovation? And if not, can investments in system strengthening/adaptation now ensure appropriate and timely regulatory review plus readiness upon regulatory approval?** Experts pointed to supply chain and health system challenges across the board, including in areas of demand forecasting, procurement, health workforce preparation, and availability of basic medical supplies (e.g., syringes, vials, and other commodities). Where any new innovation or technology is introduced, innovators must consider the readiness of the health system and regulatory environment; pull mechanism design should factor in not just the product/innovation, but the entire package of care and how it will integrate with the existing health system. This approach could also look like better integration of traditionally siloed programs with PHC systems. Cross-cutting innovations that span health areas, for example, could

help reduce inefficiencies in the health system, maximize the health impact of available resources, and lead to more innovative, patient-centered approaches.

- **How does pull mechanism design reflect the stage of development within the R&D pipeline? Should pull mechanisms be used to drive drug discovery—and if so, how? Or exclusively used for later-stage commercial development? How does the pull mechanism fit within the entire R&D pipeline—from drug discovery to clinical development and commercial deployment?** The whole ecosystem should be considered for maximizing likelihood of success of new health technologies. Research organizations searching for new therapeutic compounds, for example, may not have marketing and commercialization strategy capabilities needed for the launch phase of a product. Regulatory approval, particularly WHO prequalification, can be time-intensive, thereby delaying revenue generation for a product. The entire R&D process for a new product may exceed a decade, necessitating thoughtful, responsive planning.
- **How do we design evaluation/assessment criteria against the target product profile (TPP) that are sufficiently clear/predictable to drive investments, but also sufficiently adaptable/flexible to accommodate an ever-shifting innovation landscape?** The disease landscape is continually evolving, necessitating an adaptive, nimble approach to R&D. Finding suitable treatments for diseases can often be complex. The right dosage/dose regimen may take time and experimentation to determine. All these factors make clear criteria essential.
- **How do we set and design the incentive level? How do we balance the risk of “over-paying” against the risk of innovation failure/benefit of the target innovation—and how should “over-payment” be defined in context? Would required remuneration be lower/different for different kinds of innovators (e.g., SMEs versus “big pharma”), or LMIC-based companies versus those based in HICs?** To make incentives meaningful and compelling, they will need to be tailored to where in the R&D pipeline pull mechanisms target. Earlier stages in the pipeline, including drug discovery and proof of concept, are inherently riskier (i.e., greater chance of failure and investments not yielding returns), while later stage projects may be easier to pitch to potential partners as “surer bets.”
- **How do we avoid unintended effects on market competition and new product entry?** Very low prices, subsidized by donors via a pull mechanism, may artificially entrench the position of the incumbent firm and prevent market entry of potential competitors, particularly SMEs and firms based in low- and middle-income countries. In the long run, this can lead to *higher* prices after the subsidy expires because the incumbent firm will face less price pressure from competitors. To the greatest extent possible, pull mechanisms should be carefully designed to encourage competition and avoid market monopolization.