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Operation Warp Speed, Encore

A Case for US Leadership to Drive Market-Based Global Health Innovation

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Abstract

The experience of the COVID-19 pandemic—both in the US and around the world—has helped highlight the potential feasibility and importance of biomedical R&D for global health and welfare. In the midst of a very large, focused expansion of public expenditure for R&D on COVID-19—both direct (e.g. supporting trials) and indirect (e.g. promised revenue via advanced purchase agreements)—dramatic and rapid advancements in biomedical science took place, with very large commensurate social and health benefits.

Drawing from this experience and momentum, this paper argues that the US should deepen its engagement and ambition in global health R&D to drive other similarly transformative improvements in global health outcomes and security—protecting American citizens from global health threats while also helping save and improve lives and livelihoods around the world. To provide illustrative evidence about the potential of such investment, it lays out three indicative case studies where US government investment, at least partially in the form of a pull mechanism, could help incentivize and drive high-value innovation: for new antimicrobials; a rapid, low-cost TB test; and for next-generation, accessible whole genome sequencing. Using clear and generally conservative assumptions, the case studies describe how such biomedical innovation could generate large returns on investment—in two of three cases exclusively from the perspective of US domestic welfare—while also saving and improving lives around the world. It concludes with a discussion of implications for research funders, emphasizing the need for large R&D investments to tackle commensurately large global health threats.

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Operation Warp Speed, Encore: A Case for US Leadership to Drive Market-Based Global Health Innovation

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This Policy Paper draws from case studies developed in partnership with Adrian Towse, Rory Todd, Stasha Mamotra, Christian Hauck, David Tordrup, Jorge Mestre-Ferrandiz, and Christine Leopold. (The case study with Adrian Towse will be published in full as a CGD Policy Paper under separate cover). This paper is also informed by previous co-authored work with Cordelia Kenney and Steven Kosiak, as well as review/input from Cordelia Kenney, Steven Kosiak, Cordelia Kenney, Kevin Outterson, John Rex, Erin Collinson, Ranil Dissanayake, Willo Brock, Emma Hannay, and anonymous peer reviewers. I am grateful to Schmidt Futures and Founders Pledge for their financial support of this work. All errors and omissions are my own.

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Introduction

In recent years, the experience of the COVID-19 pandemic—both in the US and around the world—has helped highlight the potential feasibility and importance of biomedical R&D for global welfare. In its first year, COVID-19 paralyzed social, educational, and economic life across most of the world—illustrating the potentially enormous and multisectoral costs of disease and health-related disruption, as well as the concrete and quantifiable risk posed by heretofore largely abstract "global health security" threats in the US context. More recently, the return to mostly "normal" life can be attributed in large part to the historically rapid development and at-scale deployment of novel vaccines and antiviral therapeutics, which in turn have dramatically reduced COVID-19 mortality, morbidity, and healthcare utilization.

One key plank in COVID-19 R&D was Operation Warp Speed—the flagship initiative of the Trump Administration to speed countermeasure development and roll-out. Support to vaccine and therapeutic R&D under Operation Warp Speed was multi-faceted, including advanced purchase agreements for vaccine candidates but also some direct support to at-risk manufacturing expansion; clinical trials; and other R&D inputs. Given its use of vaccine advance purchase agreements to drive vaccine development, some argue that Operation Warp Speed should be primarily conceptualized as a "pull" funding initiative—that is, an approach to funding R&D that works by increasing the expected size or predictability of expected revenue contingent on successful product development, thereby leveraging the profit-motive of private sector companies to pursue socially utile objectives. This is contrasted to "push" funding approaches that directly finance or subsidize input costs for R&D, e.g., traditional grants that pay scientists directly for their time, materials, and so forth.

Operation Warp Speed clearly involved both substantial push and pull aspects. Companies benefitted from public funding and de-risking, though they also made profit-driven decisions to apply their most promising development platforms to the COVID-19 response specifically. Likewise, persistent debates surround many related topics in pharmaceutical and innovation policy during the COVID-19 pandemic response, including pharmaceutical pricing; equity in international procurement/distribution; the role of intellectual property; transparency of development and trial costs; appropriate compensation for pharmaceutical executives and investors; and "open science" versus proprietary R&D.

Yet despite these disagreements, one learning from the COVID-19 pandemic is indisputable: in the midst of a very large, focused expansion of public expenditure for R&D on COVID-19—both direct (e.g. supporting trials) and indirect (e.g. promised revenue via advanced purchase agreements)—dramatic and rapid advancements in biomedical science took place, with very large commensurate social and health benefits.[1] As of late-2021, governments had invested about $93 billion total in developing and

1 Many advocates would argue that costs would be lower and/or social benefits substantially higher under alternative R&D/IP paradigms, e.g. open/non-profit pharmaceutical development, IP waivers, or forced tech transfer. This paper does not take a position on that question one way or the other, but simply notes that the absolute social return on investment was very large even if it *could have* been larger and/or more equitably distributed.

procuring vaccines and therapeutics[2]—but those investments had enormous returns. Around the world, COVID-19 vaccines saved an estimated 20 million lives in their first year of roll-out;[3] in the US alone, vaccines prevented an estimated 1.1 million deaths and 10.3 million hospitalizations through November 2021.[4] Given the economic devastation caused by the virus, economic benefits of the vaccine likely total many trillions.[5]

Accordingly, some global health leaders have argued for a step-change in spending on R&D for pandemic preparedness. Writing in *Science*, for example, Pecetta et al. suggest a $680 billion program to support vaccine development for 20 pathogens of pandemic preparedness; this level of spending would represent roughly a 10-fold increase compared even with Operation Warp Speed total outlays on countermeasure R&D and procurement.[6] More generally, the unprecedented speed and success of COVID-19 countermeasure development, in large part based on the novel mRNA platform, has inspired renewed optimism about the prospects of well-funded life science R&D to address persistent causes of disease and disability—including HIV,[7] malaria,[8] and tuberculosis[9]—as well as pandemic threats like influenza[10] and other zoonotic coronaviruses.[11]

Drawing from this experience and momentum, this paper is a call to action for the United States government, including Congress and the Biden Administration. It argues that the US should deepen its engagement and ambition in global health R&D to drive transformative improvements in global health outcomes and security—protecting American citizens from global health threats while also helping save and improve lives and livelihoods around the world. Building on the success of the Operation Warp Speed approach, it illustrates the potential value of such engagement with three indicative case studies where US government investment, at least partially in the form of a pull

2 Madeleine Hoecklin, "€93 Billion Spent By Public Sector On COVID Vaccines And Therapeutics In 11 Months, Finds New Research," Health Policy Watch, January 12, 2021, https://healthpolicy-watch.news/81038-2/.

3 Oliver J Watson et al., "Global Impact of the First Year of COVID-19 Vaccination: A Mathematical Modelling Study," *The Lancet Infectious Diseases* 22, no. 9 (September 2022): 1293–1302, https://doi.org/10.1016/S1473-3099(22)00320-6.

4 Eric C. Schneider et al., "The U.S. COVID-19 Vaccination Program at One Year: How Many Deaths and Hospitalizations Were Averted?," 2021, https://doi.org/10.26099/3542-5N54.

5 David M. Cutler and Lawrence H. Summers, "The COVID-19 Pandemic and the $16 Trillion Virus," *JAMA* 324, no. 15 (October 20, 2020): 1495, https://doi.org/10.1001/jama.2020.19759; Simone Pecetta et al., "The Trillion Dollar Vaccine Gap," *Science Translational Medicine* 14, no. 638 (March 30, 2022): eabn4342, https://doi.org/10.1126/scitranslmed.abn4342.

6 Pecetta et al., "The Trillion Dollar Vaccine Gap."

7 "NIH Launches Clinical Trial of Three MRNA HIV Vaccines," Press Release, National Institutes of Health (NIH), March 14, 2022, https://www.nih.gov/news-events/news-releases/nih-launches-clinical-trial-three-mrna-hiv-vaccines.

8 Helen Mendes, "Hunting the 'Perfect Protein' for Malaria MRNA Vaccine," Gavi, the Vaccine Alliance, April 25, 2022, https://www.gavi.org/vaccineswork/hunting-perfect-protein-malaria-mrna-vaccine.

9 Sanjeet Bagcchi, "Can MRNA Vaccine Tech Take on Tuberculosis?," Gavi, the Vaccine Alliance, April 14, 2022, https://www.gavi.org/vaccineswork/can-mrna-vaccine-tech-take-tuberculosis.

10 Ranmali Kavishna et al., "A Single-Shot Vaccine Approach for the Universal Influenza A Vaccine Candidate M2e," *Proceedings of the National Academy of Sciences* 119, no. 13 (March 29, 2022): e2025607119, https://doi.org/10.1073/pnas.2025607119.; Bob Woods, "A Universal Flu Vaccine May Be the next Big MRNA Breakthrough for Moderna, Pfizer," CNBC, January 10, 2022, https://www.cnbc.com/2022/01/10/universal-flu-vaccine-may-be-next-big-moderna-pfizer-mrna-development.html.

11 Elie Dolgin, "Pan-Coronavirus Vaccine Pipeline Takes Form," *Nature Reviews Drug Discovery* 21, no. 5 (April 19, 2022): 324–26, https://doi.org/10.1038/d41573-022-00074-6.

mechanism, could help incentivize and drive high-value innovation, potentially generating very high returns on investment. Each case study addresses an important health area for which R&D is otherwise chronically underfunded, at least in part due to well-understood market failures; all focus on infectious disease threats; and two of the three offer clear and direct benefits for Americans' health security.

Importantly, these case studies are constructed as indicative examples; this paper does not argue that they are necessarily the *best* use cases of pull mechanisms from the perspective of the US government. Instead, its purpose is simply to demonstrate the high estimated returns on investment (ROIs) from plausible examples to motivate broader US engagement in this space. Likewise, the proposed mechanism designs are for illustrative use only, and in some cases have been deliberately simplified for ease of estimation and illustration. Any actual deployment of a pull mechanism by the US government should include design and review through a consultative, transparent, multi-stakeholder and multi-disciplinary process, including participation from economists, disease-specific experts, industry, and industrial organization/mechanism design specialists.

The focus on pull mechanisms specifically is motivated by potential benefits elaborated in an earlier paper: "Pull funding maintains incentives for innovation success; removes (or at least reduces) the government's role in "picking winners"; and allows the funder to serve as a more impartial arbiter of whether the resultant innovation is socially valuable."[12,13] However, these funding mechanisms remain somewhat controversial, and the jury is still out on the relative cost-effectiveness of pull mechanisms and conditions under which they are best used.[14] The argument made here is that there is enough promise in these approaches that we should be more forthcoming in using and experimenting with them—and in dramatically scaling the scope and magnitude of those experiments, especially given that even the cumulative cost of all three proposals would comprise just a tiny portion of overall USG funding for health R&D. Likewise, the paper does not argue that pull mechanisms will *always* be optimal to drive global health innovation goals; however, for these case studies specifically, there are reasons to believe that a well-designed pull mechanism would be well-suited to the observed challenge and market failures.

12 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," Policy Paper (Washington, D.C.: Center for Global Development, August 11, 2021), https://www.cgdev.org/publication/enabling-us-government-participation-pull-mechanisms-social-impact-innovation-survey.

13 See also discussion here here and here: Alice Albright et al., eds., *Making Markets for Vaccines: Ideas to Action: Report of the Center for Global Development Working Group* (Washington, D.C.: Center for Global Development, 2005), https://www.cgdev.org/sites/default/files/archive/doc/books/vaccine/MakingMarkets-complete.pdf; Kalipso Chalkidou et al., "In the Race to Develop a Vaccine For COVID-19, Is a Pull for R&D Essential or Optional?," Center for Global Development | Ideas to Action, June 8, 2020, https://www.cgdev.org/blog/race-develop-vaccine-covid-19-pull-rd-essential-or-optional; Kalipso Chalkidou et al., "Blueprint for a Market-Driven Value-Based Advance Commitment for Tuberculosis" (Washington D.C.: Center for Global Development, 2020), https://www.cgdev.org/sites/default/files/MVAC-Blueprint-Final_2.pdf.

14 See appendix of complementary paper on global health innovation for a discussion of stakeholder views on this issue.

The paper proceeds as follows. First, it describes the methodology for sourcing, selecting, and developing the three case studies contained in this paper. Second, it lays out three investment cases for US participation in global health pull mechanisms: a subscription model for new antimicrobials; an advance market commitment (AMC) for rapid TB diagnostics; and a moonshot prize plus manufacturing support to develop and scale next-generation whole genome sequencing for global genomic surveillance. Each case study includes background on the nature and magnitude of the global health threat; analysis of the market failure that has prevented sufficient R&D investment to this point; a description of a proposed pull mechanism design; and a return on investment (ROI) calculation to illustrate the potential value of each research program. The paper concludes with a discussion of overall findings and implications for the governmental and philanthropic financing of pull mechanisms specifically and global health innovation more broadly.

Methods

From late 2021 to early 2022, CGD conducted a horizon-scanning exercise to explore how and when pull mechanisms have been used in health, and ultimately to identify three promising innovations that could potentially be incentivized and developed through use of a well-designed, US-led pull mechanism. The exercise included a literature review and 29 expert/stakeholder interviews, including with biomedical researchers, funders, advocates, and economists.

The horizon-scanning exercise resulted in a long list of potentially promising innovations, though it was not powered or designed to identify the "best" or "most important/needed" innovations. (The full results of this horizon-scanning exercise, including a resultant innovation agenda for global health, are reported via a separate policy paper with Cordelia Kenney.[15]) From that list, CGD considered the following analytic criteria to select promising and important innovations that could also serve as useful case studies/test cases for broader US government use of pull mechanisms:

1. Potential to save/improve lives—potential health impact vis-à-vis globally important health challenges, focusing specifically on the following three categories:
    a. Global public goods, such as antimicrobials or pandemic preparedness;
    b. Health problems that mostly affect low- and middle-income countries (LMICs), such as neglected tropical diseases;
    c. Health problems that are broadly shared, but where existing health technologies are not affordable or accessible in most LMICs, such as cancer or kidney disease.
2. Existence of a market failure that prevents limits R&D, market entry, and/or widespread access to high-value health technologies.

15 Cordelia Kenney and Rachel Silverman Bonnifield. 2022. "The Next Game Changers: A Priority Innovation Agenda for Global Health." CGD Policy Paper 269. Washington, DC: Center for Global Development. https://www.cgdev.org/publication/next-game-changers-priority-innovation-agenda-global-health.

3. Opportunity for a well-designed pull mechanism to address the market failure described in (2).

Using these criteria, CGD selected the following three innovations for further exploration:

1. New antimicrobials to combat the growing threat of antimicrobial resistance;
2. A rapid, low-cost test for tuberculosis (TB) that could be deployed for at-scale screening, with a focus on ending the scourge of TB in India, the most-affected country; and
3. Next-generation whole genome sequencing in the field, to dramatically expand the coverage of genomic surveillance capabilities and strengthen pandemic preparedness.

CGD then commissioned investment cases for the three selected innovations; these were developed between March to July, 2022, with close oversight and direction. The first, on new antimicrobials, was developed by Adrian Towse and Rachel Silverman Bonnifield with data assistance from Rory Todd. The other two case studies (on rapid TB diagnostics and whole genome sequencing) were developed by a team at Triangulate Health Ltd., including Stasha Mamotra, Christian Hauck, David Tordrup, Jorge Mestre-Ferrandiz, and Christine Leopold. The final case studies, presented below, include some content from these inputs but differ substantially in several ways, e.g., they are shortened; the latter two include some different data inputs/parameters/modelling approaches, and therefore generate different ROI calculations; and some (but not all) of the text has been modified or rewritten. All errors and omissions are therefore entirely my own.

The case studies are largely tailored to a US government audience, and therefore center the US perspective and national interest as the primary motivation for action. Only the second case study, on TB in India, would involve a more traditional foreign aid approach; the other two are justified entirely by American self-interest, e.g. returns on investment that accrue to the United States population and welfare. However, all three case studies generate very large global benefits in addition to US-specific ROI.

The assumptions and approach behind the ROI modelling are explained in full within each case study. In general, the ROI approach is preliminary and conservative, e.g., it includes only direct effects on health and health expenditure and excludes more speculative impacts via transmission reduction, economic productivity, or enablement value, for example. Where possible, parameters were selected from the literature and clearly cited; however, in several cases the literature lacked consensus or precision, requiring judgement calls on defensible/plausible inputs.

Case study 1: The PASTEUR act for new antimicrobials[16]

Background

Antibiotics form the backbone of modern medicine. The discovery and global distribution of these drugs,[17] alongside global introduction of effective childhood vaccinations, has helped dramatically decrease the global burden of infectious disease. In addition, the widespread availability and high efficacy of antibiotics facilitate surgeries, chemotherapy, organ transplants, and other treatments for non-communicable diseases—all of which would be far riskier, and perhaps impossible, if not for effective antibiotics.

Yet exposure to antibiotics creates selective pressure; microbes will randomly mutate over time, and drug-resistant variants will be more likely to survive exposure to an antimicrobial drug. This phenomenon is generally referred to as "antimicrobial resistance", or AMR. Humans are engaged in a race against this resistance—we need to ensure that novel antimicrobials are available to replace old therapies as their efficacy wanes.

Already, drug resistance is a major cause of disease and death, both in the US and around the world. The US CDC estimates that drug-resistant bacterial and fungal infections cause 36,000 deaths per year in the US;[18] a recent global estimate pegged the global death toll from antibiotic-resistant bacterial infections at 1.27 million[19] for 2019.[20] And mortality and morbidity rates, naturally, will rise as resistance increases. At present, estimates suggest that six pathogens account for over 70% of global deaths attributable to antibiotic resistance.[21]

16 This section is a shortened version of a case study co-developed with Adrian Towse, which was published in full as a CGD Policy Paper under separate cover. See Towse and Silverman Bonnifield (2022). An Ambitious USG Advanced Commitment for Subscription-Based Purchasing of Novel Antimicrobials and Its Expected Return on Investment. CGD Policy Paper 277. Washington, DC: Center for Global Development. Available at: https://www.cgdev.org/publication/ambitious-usg-advanced-commitment-subscription-based-purchasing-novel-antimicrobials.

17 Sulphonamides were introduced in 1932. Penicillin was discovered in 1928, initially developed for medical use in the 1940s, when it was produced in substantial quantities to treat sick and wounded soldiers. Streptomycin, discovered in 1943, an aminoglycoside, was the first antibiotic effective against tuberculosis (TB) in humans. Other important classes of antibiotics include macrolides, first introduced in 1952, cephalosporins in 1962, and carbapenems in 1975. No new classes have been discovered since the 1980s. (CDC, 1999; Davies, 2013).

18 CDC (2019). Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA, US. Department of Health and Human Services, CDC, 2019.

19 Antimicrobial Resistance Collaborators (ARC) (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet; published online Jan 20. https://doi.org/10.1016/S0140-6736(21)02724-0.

20 There is some controversy about estimation techniques, discussed in further detail in Appendix A of the complementary CGD policy paper.

21 Antimicrobial Resistance Collaborators (ARC) (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet; published online Jan 20. https://doi.org/10.1016/S0140-6736(21)02724-0.

Despite this large and growing burden, the R&D pipeline for new antimicrobials remains sparse.[22] As of June 2019, Pew Charitable Trusts reported that just 42 antibiotics were in clinical development globally, with about half (24) targeting bacteria on CDC or World Health Organization (WHO) priority lists.[23] In the last five years, 12 new antibacterial drugs have been approved globally, but only one belongs to a new bacterial class, and only one is targeted at a gram-negative priority pathogen.

The market failure

The large and growing burden of AMR, paired with the insufficient R&D pipeline for new antimicrobials, begs an obvious question: why are market mechanisms failing to address this challenge? At the most basic level, the market failure arises because private companies are unable to capture a sufficient private ROI, despite the very high social value of new antimicrobials. Underlying this disconnect are several distinct challenges:

- *Initial Sales Volumes Are Low:* Given the imperative to conserve novel antimicrobial efficacy, new antimicrobials should only be used for the small subset of patients where existing first-, second-, and third-line therapies have failed. This keeps initial sales volumes low, even though they are expected to rise substantially over time.
- *Most Social Value is Incurred After Patent Expiry:* For new antimicrobials, usage of the drug will increase over a long time horizon—with most social value realized after patent expiry.[24] This means that the expected ROI for a private developer is low relative to the long-term social value of the new antimicrobial.
- *Clinical Value is Difficult to Demonstrate:* New antimicrobials are an insurance policy for the future, when existing antimicrobials fail. But to receive regulatory approval, they must demonstrate that they are non-inferior to the best available existing antimicrobials *now*. This is a very high standard given the very high current effectiveness of existing antimicrobials.
- *Traditional Reimbursement Approaches Undervalue New Antimicrobials:* Many benefits from new antibiotics lie outside of benefit to the individual patient and are therefore difficult to measure and compensate. These broader benefits are termed STEDI principles (Spectrum, Transmission, Enablement, Diversity, and Insurance) by Outterson and Rex (2020):[25]

22 A useful survey of the state of product development pipelines is set out in a blog by Rex and Outterson (2020): John Rex and Kevin Outterson, "FDA Analysis of 40-Years of Antibacterial Development: Dheman et Al.," *AMR.Solutions* (blog), June 30, 2020, https://amr.solutions/2020/06/30/fda-analysis-of-40-years-of-antibacterial-development-dheman-et-al/., drawing on recent papers, (Darrow et al. 2020; Dheman et al. 2020; and Kinch et al. 2014). In addition, WHO conducts regular reviews of the pipeline—see Butler et al. (2022) for the most recent WHO analysis.

23 The Pew Charitable Trusts (2019). "Antibiotics Currently in Global Clinical Development". Available at https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development.

24 See for example the modelling in Towse et al., 2017.

25 The STEDI term is usually attributed to Rothery et al., 2018. A comprehensive outline is set out in Karlsberg Schaffer et al., 2017 and Neri et al., 2019. As Rex states in: John Rex and Kevin Outterson, "Pull Incentives For Antibiotics: How Much And Why?—A Literature Survey," *AMR.Solutions* (blog), April 14, 2020, https://amr.solutions/2020/04/14/pull-incentives-for-antibiotics-how-much-and-why/., STEDI "was proposed by Outterson and Rex, *Translat Res* 2020, based on a list of attributes first proposed by Karlsberg 2017."

- Spectrum value from antibiotics that cover a narrower spectrum of pathogens, preventing 'collateral damage' to the microbiome and reducing the build-up of AMR;
- Transmission value, preventing the spread of the infection among the wider population by treating individual patients;
- Enablement value, from protecting the safety of surgical procedures or immunosuppressive drugs;
- Diversity value, from attenuating the 'selection pressure' on existing antibiotics and preserving the efficacy of these existing treatments against resistant pathogens;
- Insurance value, from the availability of an effective treatment in case of a catastrophic event, such as an outbreak of highly transmissible multi-drug resistant pathogen with a high case fatality rate.

As a result, even antimicrobial developers successfully achieving a licence for a new antibiotic generally fail to recoup their investments. Several small biotech companies have gone bankrupt even after market entry of new antimicrobial products—a cautionary tale for investors and entrepreneurs who might otherwise be interested in tackling a globally relevant challenge.[26]

A proposed subscription model for new antibiotic

One creative solution to the market failures described above is known as a "subscription model." Under this approach, the US government would seek to ensure that antibiotic developers receive a significant and predictable return on their investment if they successfully bring new antimicrobials to market—and without needing to generate sales volumes beyond the prudent level. The US government would do so by committing to reward new antibiotics with a fixed annual payment *that is not dependent on the volume of antibiotics used*. The payment would be made each year for a decade and would entitle the US government to procure an unlimited quantity of the drug on behalf of its citizens.

Based on the literature,[27] the following program parameters are modelled:

- The program should seek to generate a total of 18 new antibiotics—three drugs to treat each of the six priority pathogens. That translates to an expected value of .6 new antibiotic launches each year.

26 See Achaogen: John Rex, "Scary, Scarier, Scariest: Achaogen / FT Editorial / CBS '60 Minutes' on AMR," *AMR.Solutions* (blog), April 22, 2019, https://amr.solutions/2019/04/22/scary-scarier-scariest-achaogen-ft-editorial-cbs-60-minutes-on-amr/. and Melinta: John Rex, "Melinta, Part 2 / Bankruptcy Is Not The End / Post-Approval Costs For An Antibiotic," *AMR.Solutions* (blog), January 7, 2020, https://amr.solutions/2020/01/07/melinta-part-2-bankruptcy-is-not-the-end-post-approval-costs-for-an-antibiotic/.; other developers have been sold for a pittance, as in the case of Tetraphase (John Rex, "Tetraphase Sold for $14m … and $600m Goes up in Smoke!," *AMR.Solutions* (blog), March 23, 2020, https://amr.solutions/2020/03/23/tetraphase-sold-for-14m-and-600m-goes-up-in-smoke/.).

27 Please see detailed companion paper for underlying literature, assumptions, and discussion.

- Pulling one new antimicrobial to market (with full delinkage) would require a 10-year subscription model with total value of $4.5 billion. This is an upward adjustment for inflation of the central "best" estimate of $4.2bn in the range modelled by Outterson (2021) of $3.3 to $8.9 billion.[28] The US share of this total is proportionate to its share of GDP among the G7 + European Union, or 46%. This means that the US should pay $2.1 billion total per new drug, amortized over the ten-year subscription duration.
- Patent protection expires at the end of the subscription period, allowing for generic competition to push prices toward marginal cost.
- The US should commit to this program for the next 30 years to enable long-term investments in R&D. The ten-year cost of the program (without discounting) is $6.8 billion; the 30-year cost is $32 billion. Annual costs would peak and stabilize at a recurrent $1.24 billion per year, starting in year 10. This annual payment would account for 0.8% of US government spending on pharmaceuticals in 2019, and 0.3% of total US expenditure (public and private) on pharmaceuticals.[29]

As these parameters are selected for illustrative purposes only, they are constructed with some important simplifications and design choices that may not be optimal within a real-world program:

- In this simplified model, the US government offers a fixed, consistent payment for all antimicrobials without consideration of their relative efficacy and value. In practice, a subscription model should vary remuneration under the program based on a novel drug's specific characteristics and utility.
- The model is based on a US share of the total pull incentive that is equivalent to its share of GDP within the G7 + EU (46%).[30] Alternative cost-sharing approaches might be desirable; these could include, for example the US share of the on-patent antibiotic market (84%),[31] the US share of OECD GDP (40%), or the US share of global GDP (24%).

These parameters suggest a program that is broadly similar to the proposed PASTEUR Act, which is legislation introduced by lawmakers in the US House of Representatives and Senate, initially within

28 Outterson (2021) also models an "acquisition scenario," which calculates the pull incentive required for an acquired Phase II-ready asset; this can be thought of as accounting for complementary push funding that supports the candidate through preclinical development and Phase I trials. For this scenario, the Outterson calculates that a total subscription payment between $2.2 billion and $4.8 billion would be required, with a central "best" estimate of $3.1 billion. We opt to use the full delinkage numbers for the sake of producing a conservative ROI estimate, but we note there is some debate about whether this higher average payment would be required given early-stage push investments. See Outterson K. (2021a). Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines Health Affairs 2021 40:11, 1758–1765.

29 Office of the Inspector General reports U.S. prescription drug expenditures totalled $370 billion in 2019. Spending through Department of Health and Human Services (HHS) programs accounted for 41 percent ($151 billion) of this total., available at https://oig.hhs.gov/reports-and-publications/featured-topics/drug-spending/#:~:text=According%20to%20data%20from%20the,151%20billion)%20of%20this%20total.

30 Using World Bank data for 2021.

31 Rahman, S., Lindahl, O., Morel, C.M. *et al.* Market concentration of new antibiotic sales. *J Antibiot* **74**, 421–423 (2021). https://doi.org/10.1038/s41429-021-00414-5.

the 2021 CURES 2.0 Bill[32]—and which would provide both the requisite financing and authority to implement the program we describe. (A very similar proposal is also included within President Biden's 2023 Budget Request for the Department of Health and Human Services.[33]) The PASTEUR Act, as revised in September 2022,[34] would allocate $6 billion over 10 years to subscription payments for new antibiotics. For each novel antimicrobial, the bill text would authorize a minimum total subscription value of $750 million and a maximum total subscription value of $3 billion, with payment varying based on the efficacy and degree of innovation for each new agent. The mean cost estimate for the US share of a subscription payment ($2.1 billion per drug, on average) is thus aligned with the payment parameters suggested under the proposed PASTEUR Act.

Return on investment

First, we consider the ROI from the perspective of the US government. Full ROI calculations are presented in a complementary policy paper[35] and summarized in brief below (Table 1).[36] The following key assumptions are used across our modelling, which are elaborated and justified in detail within the complementary policy paper:

- Each new drug is held in reserve for 4 years and then reduces deaths by 5% each year; starting from year 5 onwards, effectiveness falls by 2% year on year, due to the build-up of resistance;
- The US share of this financing will be proportionate to its current GDP share in the G7 plus EU (46%) with the remainder paid by other countries;
- Health effects are discounted at a 1.5% discount rate; costs are discounted at a 3.5% for discount rate; and
- The projected rate of growth of resistance is 2%. Absent new drugs, annual deaths increase by 2% each year.[37]

32 U.S. Congress (2022). *H.R.6000—Cures 2.0 Act*. Introduced 17 November 2021. Available at https://www.congress.gov/bill/117th-congress/house-bill/6000/text#toc-H1E36E2D2B8384411967B2C8E4A3B36B0.

33 U.S. Department of Health and Human Services (2022). *Fiscal Year 2023 Budget in Brief*. Available at https://www.hhs.gov/sites/default/files/fy-2023-budget-in-brief.pdf.

34 Senate Congressional Record (2022). "Part W—Developing Antimicrobial Innovations." Amendment 6052 to bill H.R. 7900. September 29, 2022. Available at: https://www.congress.gov/117/crec/2022/09/29/168/158/CREC-2022-09-29-pt1-PgS5572.pdf.

35 Towse and Silverman Bonnifield (2022). An Ambitious USG Advanced Commitment for Subscription-Based Purchasing of Novel Antimicrobials and Its Expected Return on Investment. CGD Policy Paper 277. Washington, DC: Center for Global Development. Available at: https://www.cgdev.org/publication/ambitious-usg-advanced-commitment-subscription-based-purchasing-novel-antimicrobials.

36 We are grateful to Rory Todd for excellent assistance in developing the underlying excel model.

37 As described in Appendix C, there are no reliable projections about the growth of AMR deaths, and indeed CDC data suggested a decrease in AMR-related mortality within the US between 2013 and 2019. Nevertheless, our expectation (modelled here) is that there will be an eventual increase in AMR-related deaths in the absence of new therapeutic options. In the sensitivity analysis we model an alternative scenario of no growth in AMR deaths; the benefits are smaller in this scenario, but the program still offers a positive return over 10- and 30-year time horizons.

For the U.S. specifically, the modelling relies on the following assumptions:

- The six priority pathogens account for 27,800 US AMR deaths per year (79% of 35,000 US AMR deaths in total);[38]
- The DALY value of each death is derived from data presented in the GRAM study,[39] which suggests an average 17 DALY loss associated with each HIC death from AMR; this implies that 27,800 AMR-related deaths are equivalent to a loss of 472,600 DALYs;
- Each DALY is worth $100,000,[40] giving an estimate of $1.7 million per death and implying that current AMR-attributable health losses for those six infections in the US can be valued at $47.3 bn per year;
- Patent protection expires at the end of the subscription period, allowing for generic competition to push prices toward marginal cost; and
- Health system costs are derived from Nelson et al. (2021),[41] who estimate total AMR-related healthcare costs of $4.6 billion in the US—or $131,000 associated with each of 35,000 annual deaths. We assume that a reduction in deaths and associated illnesses which result from new drugs will lead to a proportionate reduction in healthcare expenditure.

TABLE 1. Domestic US costs and benefits, over 10 years and over 30 years

	Total Cost (Discounted)	Lives Saved	DALYs Saved	DALY Value	Healthcare Savings (Discounted)	DALY + Healthcare Savings (Discounted)	Benefit: Cost Ratio
10-Year	$5.4 bn	20,000	340,000	$30.0 bn	$2.0 bn	$32.0 bn	6:1
30-Year	$17.9 bn	383,000	6,510,000	$470.7 bn	$24.0 bn	$494.8 bn	28:1

Costs for the program begin to accrue immediately, whereas benefits only begin in year 5 (following the reserve period) and grow over time. Nevertheless, even in the relative short-term (10 years), the program costs $5.4 billion but generates $32 billion in domestic US benefits—a roughly 6:1 benefit/cost ratio. The ROI grows substantially in the longer-term (30 years), at which point the program will have generated $17.9 billion in costs and $494.8 billion in benefits—a 28:1 benefit/cost ratio.

These are relatively narrow and conservative estimates, as they are US-specific and include only direct effects on healthcare expenditure and deaths averted. They exclude, for example, DALYs

38 CDC (2019). Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA, US. Department of Health and Human Services, CDC, 2019.

39 Antimicrobial Resistance Collaborators (ARC) (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet; published online Jan 20. https://doi.org/10.1016/S0140-6736(21)02724-0.

40 Demand-side estimates have been recently estimated at $100,000 per QALY (Phelps, 2019). An alternative supply-side opportunity cost approach (Vanness et al. 2021) estimated $104,000 per QALY. As these two measures give us similar numbers of $100,000 per QALY, we can ignore the question as to which basis is most relevant. We equate QALYs and DALYs for the purpose of this exercise.

41 Nelson et al. (2021a). Mortality, Length of Stay, and Healthcare Costs Associated With Multidrug-Resistant Bacterial Infections Among Elderly Hospitalized Patients in the United States. Clinical Infectious Diseases, 2021.

averted from reductions in morbidity; reductions in transmission; and enablement value for surgeries, chemotherapy, and so forth. They also exclude indirect economic/productivity benefits from all of the above. However, is important to note that these benefits primarily accrue to individual patients, who are more likely to survive drug-resistant infections. The program is not justifiable through healthcare savings alone in the short term and would have a modest ROI on healthcare savings in the long-term (1.3:1), at least in this simplified model that does not consider enablement value.

The already very large ROI calculations grow dramatically when considering a global perspective (Table 2). Here, we make the following adjustments to the model parameters:

- We assume that 25% of the deaths outside of "high income" countries could be tackled by improved access to the suite of existing antibiotics;
- We consider the entire global cost of the incentive program, including complementary incentives that would be implemented elsewhere in the world;
- At the global level, we assume the new drugs can impact the MDR infections and deaths of the 73% of infections caused by our six pathogens (ARC 2022);
- We use $18,000 as the cost per DALY (roughly global average GDP on PPP, in effect assuming 1 x GDP value);
- We derive the DALY value of each death from data presented in the GRAM study (ARC 2022), which suggests an average 37.7 DALY loss associated with each global death from AMR, reflecting the younger average age of death across LMICs; and
- We did not find reliable estimates of health costs at the global level. Therefore, we omit this from our analysis and consider only the value of direct health benefits.

TABLE 2. Program costs and benefits (Global)

	Total Cost (Discounted)	Lives Saved	DALYs Saved	Value of DALYs Saved	Benefit: Cost Ratio
10-Year	$11.7 bn	518,000	19.5 million	310.6 billion	27:1
30-Year	$38.9 bn	9,933,000	374.5 million	4,874.2 billion	125:1

Globally, the proposed program would cost $11.7 billion in its first 10 years while saving 518,000 lives—a benefit to cost ratio of about 27:1. Over the entire 30-year program duration, costs would rise to $38.9 billion, but 9.9 million lives would be saved, for an ROI of 125:1.

Case study 2: A strategic partnership to tackle tuberculosis in India[42]

Background

Behind COVID-19, tuberculosis (TB) remains the deadliest infectious disease in the world, claiming about 1.5 million lives every year.[43] 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.[44]

Of the estimated 10 million people who developed active TB infections in 2020, only 5.8 million received a diagnosis.[45] Without diagnosis—and thus without receiving adequate treatment—about 45% of HIV-negative patients and almost all HIV-positive patients will die.[46] 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.[47]

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.[48] 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,[49] and rapid LAM tests[50]) have helped around the edges, but have had only marginal impact in identifying missing cases and connecting patients to prompt, appropriate treatment.

42 This section draws from an Investment Case prepared by Triangulate Health Ltd. for CGD, with contributions from Christian Hauck, Stasha Mamotra, Jorge Mestre-Ferrandiz, Christine Leopold, and David Tordrup; however, final figures and calculations differ from their inputs. This section also includes some background facts and analysis separately reported in a forthcoming CGD paper with Cordelia Kenney and Rachel Silverman Bonnifield as part of the same work program. All errors and omissions are my own.

43 "Tuberculosis (TB)," World Health Organization, October 14, 2022, https://www.who.int/news-room/fact-sheets/detail/tuberculosis.

44 "GBD Results," Institute for Health Metrics and Evaluation (IHME), October 15, 2020, https://vizhub.healthdata.org/gbd-results/; *Global Tuberculosis Report 2021* (Geneva: World Health Organization, 2021), https://www.who.int/publications/i/item/9789240037021.

45 *Global Tuberculosis Report 2021*.

46 "Tuberculosis (TB)."

47 "Tuberculosis (TB)."

48 *Optimizing Active Case-Finding for Tuberculosis: Implementation Lessons from South-East Asia* (New Delhi: World Health Organization, Regional Office for South-East Asia, 2021), https://apps.who.int/iris/handle/10665/343105.

49 See: "Xpert MTB/XDR," Cepheid, 2022, https://www.cepheid.com/en/tests/Critical-Infectious-Diseases/Xpert-MTB-XDR.

50 See: "Fujifilm SILVAMP TB LAM—A Sensitive Point-of-Care Tuberculosis Test," GHIT Fund (Global Health Innovative Technology Fund), accessed September 2, 2022, https://www.ghitfund.org.

India is ground zero for the global TB pandemic, accounting for 26% of all global TB cases and 34% of TB deaths.[51] In a typical pre-COVID year (2019),[52] 2.16 million Indians were diagnosed with TB; there are also an unknown number of "missing" TB cases that do not receive a diagnosis or treatment. The WHO has previously estimated that total incidence is 2.64 million, implying 480,000 missing cases (2019).[53] However, a recent national prevalence survey found overall TB prevalence of 316/100,000.[54] This would imply a total of 4.36 million active TB cases at the time of the survey; assuming a pre-COVID notification rate for a given year (2.16 million), that suggests that there are roughly 2.2 million missing TB cases at any time.

The Government of India has elevated TB eradication by 2025 as a government priority, and recently reaffirmed its commitment; however, TB cases are currently *increasing*, and India remains off-track for this goal.[55] To achieve this aspiration, India will need to dramatically change its approach to TB control with an ambition to find and successfully treat the missing cases, thereby short-circuiting the cycle of transmission while saving hundreds of thousands of lives.

The United States government has large financial interests in the global fight against TB. The US government has pledged $6 billion over three years for the 2022 replenishment of the Global Fund to fight AIDS, Tuberculosis, and Malaria ["the Global Fund"];[56] if the Global Fund reaches its full replenishment target ($18 million), this would imply the US government is spending $407 million per year, just via the Global Fund, to counter the TB threat around the world.[57] Beyond the Global Fund contribution, there are several other important US investments in global TB control. US government spending on TB research totals $401 million per year via seven different government agencies; in addition, USAID spends $295 million per year bilaterally on global TB control each year (excluding

51 *Global Tuberculosis Report 2021*.

52 Case notifications fell dramatically during COVID, and estimated cases have also increased. A typical pre-COVID year is used to illustrate a more "typical" gap between case notifications and estimated incidence.

53 "WHO Global TB Report Country Profiles" (World Health Organization, 2020), https://www.who.int/docs/default-source/hq-tuberculosis/global-tuberculosis-report-2020/country-profile-2020-final-web-min.pdf?sfvrsn=b4137a1c_0.

54 "National TB Prevalence Survey in India (2019–2021)," Summary Report (New Delhi: Indian Council of Medical Research (ICMR), ICMR-National Institute for Research in Tuberculosis (NIRT), Ministry of Health and Family Welfare (MOHFW), Government of India, Central TB Division (CTD) and National Tuberculosis Elimination Programme (NTEP), World Health Organisation (WHO), India Office, State TB Cells of all States and Union Territories, India, July 2022), https://tbcindia.gov.in/showfile.php?lid=3659.

55 Bindu Shajan Perappadan, "India to Be TB-Free by 2025, Says Minister," *The Hindu*, March 24, 2022, sec. National, https://www.thehindu.com/news/national/19-increase-from-previous-year-in-tb-patients-notification-in-2021-report/article65255289.ece.

56 "President Biden Signals a $6 Billion U.S. Pledge for the Seventh Replenishment and Offers to Match $1 for Every $2 Contributed by Other Donors," The Global Fund, March 28, 2022, https://www.theglobalfund.org/en/news/2022-03-28-president-biden-signals-a-6-billion-pledge-for-the-seventh-replenishment/.

57 "Global Disease Split for the 2023–2025 Allocation Methodology," Board Decisions - Forty-Sixth Board Meeting, The Global Fund, November 10, 2021, https://www.theglobalfund.org/kb/board-decisions/b46/b46-dp04/.

research spending).[58,59] Together, these investments total about $1.1 billion per year. By implication, the US government also has an interest in any innovations or advances that would increase the effectiveness of its global TB spending.

Beyond the general US government interest in TB, the US government also has specific interests in the US-India relationship. India is a very large emerging economy, and an important strategic and economic partner for the United States—both bilaterally and through the "Quad" grouping that also includes Japan and Australia.[60] Overall bilateral trade between the India and the United States continues to grow quickly, almost tripling over roughly 10 years—from just $59 billion in 2009[61] to $157 billion in 2021.[62] The US recognizes substantial shared interests with India and formally "supports India's emergence as a leading global power and a vital partner in efforts to safeguard the Indo-Pacific."[63]

The market failure

Unlike some other diseases that primarily affect LMICs, there is already a very large market for TB-related health technologies. In 2020, one source estimates the TB diagnostics market alone was worth about $2 billion and growing at a rate of 5 percent per year.[64]

However, the diagnostics market has become entrenched in a high-price, low-usage equilibrium. Rapid molecular diagnostics comprise about half of the total TB market ($1 billion per year)[65]—with most of the market captured by a single company, Cepheid.[66] "Accessible" negotiated prices for the Cepheid GeneXpert system start at about $10,000 for the machine/system and between $10–20 per single use cartridge.[67] The high up-front costs of the machine and training promotes "lock-in" and reduces the potential scope for competition,[68] while the per-use run cost is cost-effective only as a confirmatory test for patients already suspected of having TB. At this price point, the tests

58 "Breaking Down the U.S. Global Health Budget by Program Area: Tuberculosis (TB)," Kaiser Family Foundation (KFF), December 20, 2021, https://www.kff.org/global-health-policy/fact-sheet/breaking-down-the-u-s-global-health-budget-by-program-area/.

59 "A Time for Urgent Action to End TB: Tuberculosis Report to Congress FY 2021" (Washington D.C.: USAID, 2021), https://www.usaid.gov/sites/default/files/documents/USAID_TB_REPORT_2021_FINAL_508c_reduced.pdf.

60 "A Time for Urgent Action to End TB: Tuberculosis Report to Congress FY 2021."

61 "India," United States Trade Representative, October 2, 2020, http://ustr.gov/countries-regions/south-central-asia/india.

62 "U.S. Relations With India," Bilateral Relations Fact Sheet, United States Department of State, July 18, 2022, https://www.state.gov/u-s-relations-with-india/.

63 "U.S. Relations With India."

64 "Tuberculosis (TB) Diagnostics Market Size, Share & COVID-19 Impact Analysis," Fortune Business Insights, 2022, https://www.fortunebusinessinsights.com/tuberculosis-tb-diagnostics-market-102009.

65 "Tuberculosis (TB) Diagnostics Market Size, Share & COVID-19 Impact Analysis."

66 Cepheid enjoyed a virtual monopoly until 2020, when a second platform, TrueNat, received WHO endorsement.

67 "GeneXpert," FIND, 2022, https://www.finddx.org/pricing/genexpert/.

68 "Notes to Global Health Agencies and Civil Society Organizations Diagnostics, Market Monopoly and Intellectual Property" (Medecins Sans Frontieres Access (MSF), May 2020), https://msfaccess.org/sites/default/files/2020-05/Diagnostics%20monopoly%20and%20IP%20-preliminary%20notes%20-%20MSF.pdf.

cannot by widely deployed as screening tests within the community to find the "missing" TB cases.[69] Nor can many front-line facilities afford the capital costs of the system or meet its power and storage requirements, meaning that many health facilities will not have POC diagnostic capacity for TB.

An alternative market structure would be low-price (and low-margin) but high-volume. For example, imagine a rapid lateral flow test sold at $1.50, with a per-unit margin of $0.50. At the GeneXpert sales volume (about 12 million cartridges per year), this would only yield about $6 million in annual net revenue, which would be insufficient to justify up-front R&D expenses. However, if this test were used at scale—for example, for annual screening of India's entire vulnerable population (410 million people)—the low-price, low-margin tool could generate $204 million in annual net revenue. Yet manufacturers would only invest in the R&D and manufacturing capacity to produce such a tool at an affordable price point if they were confident that the very large market would materialize—in practice, requiring advanced, pooled commitments from government purchasers or other large procurers.

A quad partnership for a transformative diagnostic

This case study considers a hypothetical, highly ambitious strategic partnership—a "moonshot"—to end TB in India, as promised by Prime Minister Modi and supported by the other Quad countries (Australia, Japan, and the United States) and the Global Fund to Fight AIDS, TB, and Malaria. The partnership's goal would be to find the missing TB cases in India and link them to care—thereby saving their lives and short-circuiting the persistent cycle of transmission and disease.

As the core of this strategic partnership would be an AMC for a low-cost, rapid, point-of-care (POC) screening test that could be deployed at scale for active TB case-finding within vulnerable communities. The basic parameters are drawn from the Target Product Profile (TPP) developed by the WHO for a "Community-based triage or referral test for identifying people suspected of having TB"[70]; however, the TPP described below increases the required specificity to account for its usage as a screening tool in a low-prevalence community setting (Table 3).

69 A cost-of-goods analysis commissioned by the MSF Access Campaign suggests it may be possible to manufacture TB cartridges for $3 each at scale, underpinning a civil society demand to reduce the cartridge price to $5. However, no price reductions have been forthcoming. See: Treatment Action Group (TAG), MSF Access Campaign, and Global Coalition of TB Activists, "Fair Pricing for CEPHEID Xpert Tests (COVID-19, HIV, TB, HCV)."

70 "High-Priority Target Product Profiles for New Tuberculosis Diagnostics: Report of a Consensus Meeting" (Geneva: World Health Organization, April 29, 2014), https://apps.who.int/iris/bitstream/handle/10665/135617/WHO_HTM_TB_2014.18_eng.pdf.

TABLE 3. TB rapid test Target Product Profile (TPP)

Characteristics	Optimal Requirements
Goal	Test to be used during a patient's first encounter with the health-care system; identify a patient with any symptoms for active TB (incl. people living with HIV & children)
Target Population	Adults and children with active TB in countries with medium to high prevalence of TB
Setting	Community/village level and higher health care facilities
Diagnostic Performance	Sensitivity: >95% compared to confirmatory test Specificity: >98% compared to confirmatory test
Sample Type	Sample would be non-sputum (i.e.: urine, saliva, exhaled air, or blood)
Time to Result	Time to result would be <5 minutes
Cost Per Test	Price per test would range from <1$–2$

To determine the necessary AMC size and renumeration level, there are two cost components to consider: (1) the unit production costs (at scale) of test manufacturing; and (2) a profit-margin on top of production costs that would duly incentivize the requisite R&D for a novel diagnostic.

The first cost component is (relatively) simple to determine. Without knowing in advance the format or technological basis for any individual test, unit cost projections are necessarily speculative. Nevertheless, at-scale pricing for analogous tests suggest that a $1 unit cost of production is likely to be sufficient and realistic. CHAI and MedAccess recently facilitated a volume guarantee for HIV self-tests at a $1 price point (including profit margin for the manufacturer).[71] According to the Global Fund, the per-test procurement price for provider-administered rapid tests is $0.30–$1.32 for HIV; $0.65 for syphilis; $0.30–$0.65 for malaria; and $0.95–$1.50 for Hepatitis C.[72] (Notably, however, existing TB LAM tests are priced at $3.70.)[73] In India, pregnancy tests in retail pharmacies are priced between $0.45–$0.96.[74] International reference prices for COVID-19 rapid antigen tests start as low as $0.78 (but go as high as $5.00 per test).[75]

The requisite R&D incentive is more difficult to estimate, and there is no consensus estimate in the literature. Diagnostic development costs are substantially lower than drug R&D because of dramatically reduced clinical trial costs and duration. In the (relatively expensive) US context, senior pharmaceutical executives have estimated the cost of full R&D and commercialization for a

71 "New US$ 1 Price for HIV Self-Tests," News, World Health Organization, July 27, 2022, https://www.who.int/news/item/27-07-2022-new-1-dollar-price-for-hiv-self-tests.

72 "Pooled Procurement Mechanism Reference Pricing: RDTs" (The Global Fund, June 20, 2022), https://www.theglobalfund.org/media/7564/psm_hivrdtreferencepricing_table_en.pdf.

73 "Pooled Procurement Mechanism Reference Pricing: RDTs."

74 "Assessment of the Pregnancy Test Market in India" (USAID, Center for Innovation and Impact (CII), SHOPS Plus, July 2017), https://www.rhsupplies.org/uploads/tx_rhscpublications/Assessment_of_the_Pregnancy_Test_Market_in_India.pdf.

75 "Pooled Procurement Mechanism Reference Pricing: COVID-19 Diagnostics" (The Global Fund, May 17, 2022), https://www.theglobalfund.org/media/10233/covid19_diagnosticsreferenceprices_table_en.pdf.

novel diagnostic at $20.1–$106 million[76] However, to be effective, the AMC must offer a substantial ROI beyond cost reimbursement. One study from the US suggests roughly $500 million in net-present-value at launch as the "development threshold" for a novel diagnostic POC device, though the estimates vary dramatically.[77] Costs might be higher or lower for a standalone self-test; it is also plausible that non-US industry, for example India's very large pharmaceutical sector, might be able to produce a novel diagnostic at lower cost and/or accept a lower ROI.

Given these inputs, the case study tentatively sets the "profit" portion of the AMC at $200 million. The corresponding AMC volume is set at a level that would allow India to screen the entire vulnerable population of India for active TB—410 million tests.[78] The amortized profit per test is $0.49, rounded up to $.50. This implies a proposed price point of $1.50 and total AMC cost of $615 million.

The distribution of the total AMC cost could be determined at a later point. As a starting suggestion, the three Quad partners could agree to 50% total cost-sharing with the government of India for the AMC itself, with the acknowledgement that India would need to bear additional costs for program administration (costs outlined below). Assuming that the 75% cost-sharing was split by relative GDP, this would imply a $308 million contribution to the AMC from India; $235 million from the United States; $57 million from Japan; and $15 million from Australia. The Global Fund would not directly participate in the AMC with its core funding, but would commit to supporting India in program roll-out and implementation if and when the desired diagnostic achieved regulatory approval and market entry.

It may also be desirable for the Global Fund to act as an intermediary for collecting and guaranteeing the AMC financing from participating parties (e.g. the US and other Quad partners). Most helpfully, this would enable US participation in the AMC without additional Congressional authorization. However, the contribution would "score" in its entirety during the year in which the contribution is made, so the US government would need to identify a sufficiently large budgetary source for the outlay. The Administration would also need to ensure that total US contributions do not exceed 33% of total Global Fund financing—the statutory limit under authorizing legislation.

The AMC agreement should require the manufacturer to continue offering the test at the $1.50 price point to all LMICs in perpetuity. Once the test is developed, it will be available in all countries to help TB programs affordably and sustainably find missing TB cases; the proof-of-concept of a high-volume, low-cost market can also encourage other developers to enter the market, as occurred with

76 Doug Dolginow et al., "Mystery Solved! What Is the Cost to Develop and Launch a Diagnostic?" (Diaceutics, 2013).

77 Aylin Sertkaya et al., "ECONOMIC INCENTIVES FOR THE DEVELOPMENT OF RAPID POINT-OF-CARE (POC) DIAGNOSTIC DEVICES FOR C. DIFFICILE, CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (CRE), AND NEISSERIA GONORRHOEAE," Final Report (Lexington, MA, USA: Eastern Research Group (ERG), October 25, 2018), https://aspe.hhs.gov/sites/default/files/migrated_legacy_files/185571/RapidPOCIncentives.pdf.

78 "India TB Report 2022: Coming Together to End TB Altogether" (New Delhi: Ministry of Health and Family Welfare Government of India, March 2022), https://tbcindia.gov.in/WriteReadData/IndiaTBReport2022/TBAnnaulReport2022.pdf.

COVID-19 rapid diagnostics. In this way, the proposed AMC will help break the current impasse in global TB control and move the world toward the ambition of ending TB for good.

Return on investment

We make the following assumptions in our calculations:

- There are 4.4 million total active TB cases and 2.2 million missing TB cases at any given time (derived from the recent prevalence survey). This means roughly half of all cases are detected.
- The vulnerable population (410 million) in India has TB incidence that is 1.5 times as high as the general population (1.38 billion).[79] This implies that 45% of the 4.4 million active total cases are in this population—1.98 million, and a .48% prevalence rate.
- We assume that these cases are 25% less likely to be detected than cases in the general population. This implies that just 38% of cases in this group are detected under the status quo (compared to half for the general population), and there are 1.23 million missing cases in this population—accounting for 56% of all missing cases in India.
- Each TB case that is notified and successfully treated yields 13.6 DALYs averted.[80] Notified cases have an 82% treatment success rate.[81]
- The screening test has 95% sensitivity and 98% specificity.
- Though the government will order enough tests to screen the entire vulnerable population, in practice the program will only reach 90%, as there may be refusal, wastage, diversion, or duplicate testing.
- 90% of people who test positive on the screening test receive a confirmatory test; the remainder are lost to follow-up.
- The price of a confirmatory test is $20 and the price of treatment is $40.
- The total cost of administering the screening test is $2 ($1.50 for the test itself, $0.50 for the cost of administration).

Results of the screening exercise are reflected in Table 4, and the full diagnostic and treatment cascade is described in Figure 1.

79 M. Muniyandi and Rajeswari Ramachandran, "Socioeconomic Inequalities of Tuberculosis in India," *Expert Opinion on Pharmacotherapy* 9, no. 10 (July 2008): 1623–28, https://doi.org/10.1517/14656566.9.10.1623.

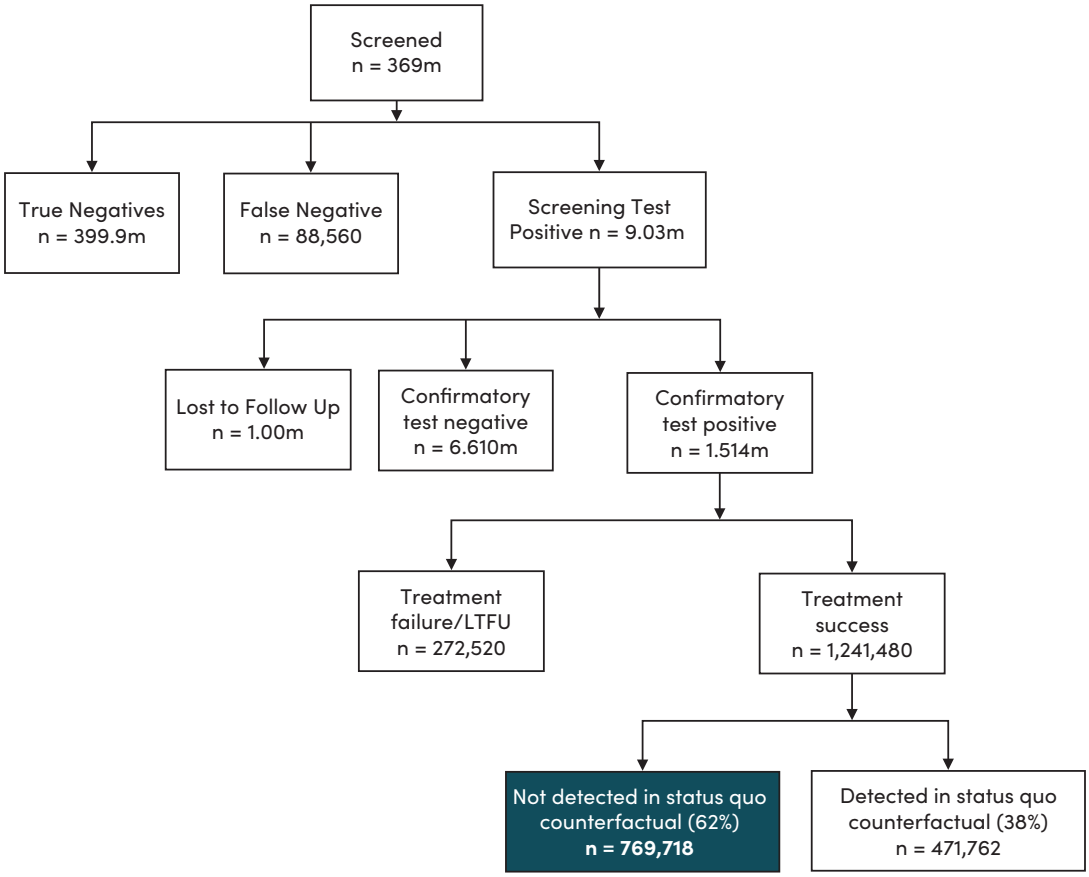
80 Nicolas A. Menzies et al., "Lifetime Burden of Disease Due to Incident Tuberculosis: A Global Reappraisal Including Post-Tuberculosis Sequelae," *The Lancet Global Health* 9, no. 12 (December 1, 2021): e1679–87, https://doi.org/10.1016/S2214-109X(21)00367-3.

81 "WHO Global TB Report Country Profiles."

TABLE 4. Results of screening exercise of India's vulnerable community (n = 369 million)

		Has Active TB? (n, Thousands)	
		Yes (n)	No (n)
Tests Positive? (n, Thousands)	Yes	1,682.6	7,344.6
	No	88.5	359,884.2

FIGURE 1. TB screening and treatment cascade



In total, this program would identify 939,000 missing TB cases that would not otherwise have been detected—about 43% of the estimated total. It would result in 769,718 additional people receiving a successful course of TB treatment, yielding 10.5 million incremental DALYs averted (Table 5).

TABLE 5. Incremental program costs and benefits

	Unit Cost	Number Needed	Total Cost
Screening Test	$2	410,000,000	$820,000,000
Additional Confirmatory Tests[82]	$20	7,548,680	$150,973,600
Additional Treatment Courses[83]	$40	938,680	$37,546,200
Total Incremental Cost			$1,008,519,800

	(N)	Incremental Cost Per DALY Averted
Incremental DALYs Averted	10,468,165	$96

Total program cost would just exceed $1 billion—a major investment to be sure, but one that would be highly cost-effective and contribute to India's strategic goal of controlling the TB epidemic. The program yields an incremental cost per DALY averted of $96, which compares favorably to the estimated cost per marginal DALY that could be generated with alternative health investments in the Indian context ($223-$351 US, as of 2015).[84] Returns would be substantially higher if transmission reduction and economic productivity were also considered.

Case study 3: A moonshot prize for POC rapid whole genome sequencing[85]

Background

In the last decades, emerging pathogens—infectious disease-causing bacteria, viruses, and fungi—have proliferated at an unprecedented rate.[86] Since the 1970s, around 40 emerging pathogens have developed into epidemics and sometimes pandemics, including SARS, MERS, HIV, Ebola, Zika, chikungunya, avian flu, swine flu, monkeypox, and COVID-19.[87]

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has led to many fatalities, major losses in overall population health, economic contraction, and political and social instability. And the budgetary toll has been high, with governments spending both to fund the pandemic

82 Against a status quo hypothetical in which 38% of people with TB received confirmatory testing and treatment.

83 Against a status quo hypothetical in which 38% of people with TB received confirmatory testing and treatment.

84 Jessica Ochalek, Miqdad Asaria, Pei Fen Chuar, et al. (2019). "Assessing Health Opportunity Costs for the Indian Health Care System." CHE Research Paper 161. Available online at http://eprints.lse.ac.uk/100109/1/Asaria_assessing_health_costs_indian_Published.pdf.

85 This section draws from an Investment Case prepared by Triangulate Health Ltd. for CGD, with contributions from Christian Hauck, Stasha Mamotra, Jorge Mestre-Ferrandiz, Christine Leopold, and David Tordrup; however, final figures and calculations differ from their inputs. This section also includes some background facts and analysis separately reported in a forthcoming CGD paper with Cordelia Kenney and Rachel Silverman Bonnifield as part of the same work program. All errors and omissions are my own.

86 Kate E. Jones et al., "Global Trends in Emerging Infectious Diseases," *Nature* 451, no. 7181 (February 2008): 990–93, https://doi.org/10.1038/nature06536.

87 Jones et al.; "Emerging Infectious Diseases," Baylor College of Medicine, accessed June 23, 2022, https://www.bcm.edu/departments/molecular-virology-and-microbiology/emerging-infections-and-biodefense/emerging-infectious-diseases.

response and mitigate its economic and social impacts. At the time of writing, the U.S. federal government alone has spent $3.70 trillion in its COVID-19 pandemic response,[88] equivalent to 41% of U.S. government total expenditure in 2021.

Despite a relatively low case fatality rate, COVID-19 resulted in a very large death toll due to its very high transmissibility, allowing it to spread rapidly within an immunologically naïve population. It is quite possible that the next emerging pathogen could pair a high fatality rate with high transmissibility, with a proportionately higher death toll. The experience with COVID-19—and, even more recently, the apparent failure to quickly contain Monkeypox in the United States and around the world[89]—suggests that the US government is still not ready to prevent or effectively mitigate the next pandemic.

One important dimension of pandemic preparedness is diagnostic and surveillance capacity. While the COVID-19 pandemic helped expand and fortify diagnostic infrastructure across much of the world, it has also revealed 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 are preventing case detection and very likely contributing to community spread.[90]

More specifically, genomic surveillance is a cornerstone of needed preparedness measures. Genomic surveillance involves sequencing the genetic material of pathogens to analyze and monitor changes between genetic sequences from different sources. In combination with clinical, epidemiological, and multi-source data, genomic surveillance contributes to:

- *Detecting the emergence of new pathogens,* by allowing researchers/public health departments to quickly determine that a specimen is genetically dissimilar from all previously known pathogens;
- *Monitoring the evolution of new variants of known pathogens,* by identifying mutations in the genetic sequences of a pathogen with relevance for transmissibility, severity, drug resistance, and/or immune evasion of a disease;
- *Tracking the source and spread of a pathogen,* by using the similarities and differences between genetic sequences to reveal transmission chains and rates/modes of spread within a population;

88 "Government Spending Open Data," USAspending, accessed September 2, 2022, https://usaspending.gov/.

89 Nick, "Former FDA Commissioner: U.S. Has Probably 'Failed To Contain' Monkeypox," HuffPost, July 18, 2022, https://www.huffpost.com/entry/scott-gottlieb-monkeypox_n_62d4d7b4e4b0f691303159eb.

90 Helen Branswell and Andrew Joseph, "'Testing Bottleneck' for Monkeypox Puts Hope of Containment at Risk, Experts Warn," *STAT* (blog), June 7, 2022, https://www.statnews.com/2022/06/07/testing-bottleneck-for-monkeypox-jeopardizes-containment-experts-warn/.

- *Developing vaccines, therapeutics, and diagnostics,* by providing scientists initial insight the pathogen they are aiming to prevent, detect, or counter; and
- *Tailoring effective treatment regimens and conserving antimicrobial efficacy,* by determining whether a given pathogen has genetic sequences associated with known drug resistance.

The market failure

Effective genomic surveillance is a global public good—it helps alert the entire global community to the emergence or evolution of pathogens; facilitates prompt development of medical countermeasures; and enables researchers to understand a pathogen's transmission dynamics. And given modern global connectedness, the COVID-19 pandemic has illustrated time and again that pathogens and even sub-variants do not stay regionally contained; new variants first detected in South Africa or India have reached the United States and spread rapidly with just a few weeks of lag. Accessible, affordable, and rapid pathogen surveillance tools—with findings shared promptly and transparently via networks and integrated databases—are thus critical for collective global health security.

But genomic surveillance capabilities are not equitably or uniformly distributed, leaving "blind spots" across major sections of the globe. Most existing technologies for genomic surveillance technologies are poorly suited to the needs of LMICs, at least outside of dense urban centers. HICs and some LMIC hospitals/cities have the financial means, infrastructure, and human resources required for effective genomic surveillance, including fully equipped diagnostic laboratories. But even POC genetic sequencing technologies can be out-of-reach for all but the richest residents of LMICs due to high costs (e.g. instrument acquisition costs, costs per run, and maintenance costs), power requirements, high technical requirements, and limited human resources. Many LMICs also lack sufficient funds to purchase novel diagnostics, leading to inadequate and inconsistent testing during outbreaks.

Various near-point-of-care (POC) and POC pathogen diagnosis and surveillance technologies currently exist within the sphere of genomic surveillance. These include molecular multiplex platforms, such as GeneXpert Systems from Cepheid, as well as portable whole genome sequencing (WGS) platforms, such as MinION from Oxford Nanopore Technologies. However, there are several prevailing limitations of these technologies, particularly for the scope of genomic surveillance. For example, GeneXpert Systems rely on a stable power supply and laboratory infrastructure for functioning,[91] while MinION requires additional sample preparation including extra time, reagents, and consumables, as well as cellular connectivity and up-to-date sequencing software and databases.[92] These limitations prevent effective utility in POC settings and in the field. Moreover,

91 "GeneXpert System," Cepheid, accessed June 24, 2022, https://www.cepheid.com/en_US/systems/GeneXpert-Family-of-Systems/GeneXpert-System.

92 "MinION," Oxford Nanopore Technologies, accessed June 24, 2022, http://nanoporetech.com/products/minion.

costs are quite high, with acquisition costs starting from $6,420 for GeneXpert and $1,000 for MinION, not including additional costs per run and regular maintenance costs.[93]

The United States has a strong rooting interest in boosting global visibility into the emergence and evolution of potentially dangerous pathogens. Genomic sequencing capabilities are evolving quickly, accompanied by falling price points—but innovators may still lack incentives to target technological development to low-resource settings, including countries and communities that lack the financial means, power requirements, and/or human resources to invest in cutting-edge diagnostic capabilities. To this end, the WHO's recent 10-year strategy for genomic surveillance emphasizes a need to "*stimulate innovation and research to address local to global needs*".[94]

A moonshot prize: Rapid whole genome sequencing for all

This case study considers a Moonshot Prize for the development of a transformative, all-inclusive detection, diagnosis, and surveillance platform that is based on whole genome sequencing and adapted for at-scale use across LMICs. The aspirational product—for now, beyond the scope of existing scientific capabilities—would be able to detect and diagnose:

1. A range of current (infectious) diseases and pathogens for which sequencing data are publicly available;
2. Emerging and re-emerging pathogens for which sequencing data are still unknown; and
3. Pathogen strain evolution and drug resistance for evolving infectious pathogens.

The aspirational device should have the following key characteristics:

1. Portable, i.e. a small device that can be transported by one person for use within POC health facilities and active case-finding in the field;
2. Adaptable to settings with minimal infrastructure and limited technical requirements, to eliminate the need for fully equipped diagnostic laboratories;
3. Robust to withstand harsh environmental and climactic conditions such as dust, heat, snow, ice, etc., extending the range of the product in the field;
4. Quick cellular connectivity to upload sequences while also accessing sequencing references and databases;
5. Low power requirements, e.g., battery-operated/rechargeable;
6. Scalable to test larger volumes of samples, for example during an emerging epidemic;
7. Rapid, with minimal sample preparation and quick data processing;

93 "GeneXpert"; "MinION."

94 World Health Organization, *Global Genomic Surveillance Strategy for Pathogens with Pandemic and Epidemic Potential, 2022–2032* (Geneva: World Health Organization, 2022), https://apps.who.int/iris/handle/10665/352580.

8. Low-cost, encompassing the initial acquisition cost of the instrument, cost per sample run, and any maintenance costs; and
9. Simple workflow from sample preparation to result, with the data easily interpretable, minimizing the need for highly qualified laboratory or healthcare workers.

Such a device would offer immense value both to the individual patient and to the broader global health security landscape. For the patient, the proposed device would enable an affordable and highly precise diagnosis, allowing for quick and appropriate treatment initiation; for many diseases, such an intervention could be life-saving. For the global community, the device would dramatically expand coverage of genomic surveillance, increasing the speed and efficacy of pathogen detection beyond the limits of current technology, with applications for emerging pathogens, AMR, neglected tropical diseases, and bioterrorism threats, among others. "Now, genomic epidemiologists are working to bring sequencing to the outbreak, rather than sending isolates to a reference laboratory. Such rapid results are crucial if the intention is to intervene in an outbreak rather than simply document it in retrospect." (Gardy, Loman, and Rambaut 2015).

The requisite incentive level to prompt this type of "moonshot" innovation is highly uncertain, as it is beyond the scope of existing technology/biomedical knowledge. To increase the likelihood of success, the incentive structure should also want to encourage non-traditional players (biotech start-ups, universities, LMIC-based biotech, and even individuals) to participate. As a starting point (but certainly not a final mechanism design), this case study considers a two-part commitment from the US government to incentivize the development and wide deployment of this potentially transformative technology—thereby separating the scientific innovation (proof of concept) from the manufacturing know-how required to scale and commercialized deployment:

1. A $1.5 billion prize for a proof-of-concept device prototype. The prize comes with the following conditions, in addition to meeting the minimum TPP standards:
    - Design must be openly shared (without patent protection), to be replicable by external manufacturers;
    - Cost of goods (COGs) for the device construction (capital cost) must be <$2,000; and
    - COGs for per-unit run cost must be <$10.
2. A $7.5 billion commitment to scale up manufacturing, procurement, and global distribution of these machines, including training and support, to low-income and lower-middle-income countries. At a price point of $3,000 for the capital equipment and $15 run cost (building in a 33% manufacturers' margin for other inputs and profit), this would cover 1 million devices, with 300 runs each—with each machine covering a population of about 4,100 people.[95] Countries that accept the devices would ideally commit to immediately share/upload all genomic pathogen data collected via the devices to a global database, which would in turn be accessible to both the WHO, as well as to Ministry of Health officials in all participating

95 Based on total population of LICs and lower MICs of 4.1 billion.

countries (including the US CDC). As a demonstration of goodwill and commitment to the global commons, the US government and other high-income countries should reciprocate with an open access/upload commitment of their own.[96]

Implementation of this proposal would be technically feasible to implement within the US context.[97] The America COMPETES Reauthorization Act of 2010 and American Innovation and Competitiveness Act of 2017 grants government-wide authority to conduct prize competitions. However, there are very significant practical challenges that must be overcome. Under the authorizing legislation, 30-day Congressional notification is required for any prize competition exceeding $50 million in total—and as late as FY2018, the annual total for prize money awarded through all federal competitions was $69 million. A $1.5 billion prize would be unprecedented in scale and likely to raise eyebrows within Congress, especially given the speculative nature of the desired innovation. Further, because of the large amount of funding required and the likely need to rely on discretionary appropriations, this funding would score up-front. No-year appropriations could be helpful in eliminating the risk of funding expiration without disbursement—but would not eliminate the requirement for up-front budgetary scoring.[98]

Return on investment

Development and wide deployment of the proposed product would have the following estimated effects on future pandemics:

- Reduce by 5% the probability that any emerging infectious disease outbreak expands into a global pandemic by enabling rapid countermeasures and containment; and
- Reduce by 10% the total health and economic impact of future pandemics by speeding the development of medical countermeasures and variant detection.

In the absence of additional investments in preparation, there is an estimated 25% chance of a similar pandemic occurring in the next 10 years.[99] This implies the following expected costs over the next decade, assuming similar levels of expenditure and loss of productivity experienced during Covid-19:

- $925 billion in US government expenditure

96 I note that managing the ethics and politics of such open data sharing is likely to be challenging. Any such database, realistically, could only be established through a collaborative, multi-stakeholder, international process, and hosted by international institutions with high perceived legitimacy. Establishment of such a database would be challenging even under the best of circumstances; it would be almost impossible, from a political and diplomatic perspective, if it were perceived as a unidirectional effort for HICs to surveil LMIC data without reciprocal open access.

97 Based on analysis and discussion in https://www.cgdev.org/sites/default/files/enabling-us-government-participation-pull-mechanisms-social-impact-innovation-survey.pdf.

98 Thanks to Steven Kosiak for his analysis to inform this section.

99 This is roughly in line with modelled estimates from Metabiota. https://www.cgdev.org/blog/the-next-pandemic-could-come-soon-and-be-deadlier.

- $5.5 trillion in lost global economic output
- 250,000 lives lost (US)
- 1.55 million lives lost (global)

We assume that each averted death is associated with 10 DALYs[100] averted, with a value of $100,000 per DALY averted. Applying the expected benefits of the product—a 5% reduction in the likelihood of a pandemic, and a 10% reduction in the total health and economic impact of each pandemic, implies the following expected costs averted:

TABLE 6. Expected 10-year ROI

	Averted US Government Expenditure	Averted Deaths (US)	Averted DALYs (US)	Health Value of Averted DALYS (US)	Averted Deaths (Global)	Averted Economic Losses (Global)
10% reduction in probability of a pandemic	$46.25b	12,500	125,000	12.5b	77,500	$275b
10% reduction in impact of a pandemic (that is 5% less likely to occur)	$88b	23,750	237,500	23.8b	147,250	$522.5b
Total	$134.25b	36,250	362,500	$36.3b	224,750	$797.5t

If the proposed device is not developed, the US government pays nothing and has no return on investment. However, if the program successfully generates the proposed device, the US government would realize a high return on investment. From the US government's perspective and combining the averted US government expenditure and health benefits, the investment would generate an expected ten-year ROI of $170.6 billion. Given the proposed program cost of $9 billion, this implies a 19:1 benefit-cost ratio. Benefits are of course much higher when considering lives saved and economic losses averted all over the world, but this investment appears highly cost-effective even when only considering benefits for Americans.

Discussion

These three illustrative case studies provide supportive evidence in favor of more robust and sustained US government engagement in driving targeted biomedical innovation, potentially using pull mechanisms.

The cases are primarily constructed for illustrative purposes; implementation of any actual program in practice would require far more due diligence and consultation. Nevertheless, one striking finding across all three is the sheer magnitude of the estimated returns on investment. Of course,

100 This is roughly in line with estimates of DALY losses due to COVID in HICs, for example Germany https://www.aerzteblatt.de/int/archive/article/218064/The-COVID-19-disease-burden-in-Germany-in-2020-years-of-life-lost-to-death-and-disease-over-the-course-of-the-pandemic.

the analytic and search criteria for case study selection steered toward health technologies with a high expected return, as they elevated critically underfunded health areas with high potential to save and improve lives. Nevertheless, the potential returns are unexpectedly large despite generally conservative assumptions for both cost and benefit; high returns are likewise robust to a range of variation in input parameters. (As a further caution, more sophisticated modelling would certainly be required to confirm preliminary findings before undertaking programs of this magnitude.)

The high projected returns on investment offer suggestive insight into biomedical R&D more broadly. They suggest that at least some market failures in R&D likely result in *very large* welfare losses—if lack of R&D investment does indeed proportionally reduce biomedical innovation for innovation without obvious commercial return, which is itself an unverifiable but reasonable assumption.

Perhaps the best illustration of this point is for the third case study, which considers a potential diagnostic device to improve pandemic preparedness through widely deployed genomic surveillance capability. The observed costs of an unmitigated pandemic—estimated through the observed health, economic, and fiscal costs associated with COVID-19—are so large that even *very small* reductions in the probability or anticipated severity of future pandemics would justify quite substantial ex ante investments. Specifically, just a 1% reduction in the likelihood of a COVID-19-scale pandemic over the next ten years would generate $9.25 billion in expected fiscal benefit to the US government over the same period—equivalent to a "blockbuster drug", more or less, if that return could be captured by a private, for-profit company. But such marginal reductions in pandemic likelihood or severity generate minimal private return to any individual or private entity, and thus funding to support such R&D can only be generated from public or philanthropic investment.

Notwithstanding the high projected returns, it is reasonable to challenge whether these are truly "good investments" on any number of bases. Probably the first case study, on development of new antimicrobials, is on the most solid ground; it targets a health problem that already causes substantial death and morbidity among Americans; the projected health effects are accrued through a relatively linear causal pathway; and most parameters are selected from the literature, with a bias toward more conservative estimates. However, most of the benefits accrue to individual patients—so there may be a net cost to the US government, at least in the short term. The second case study, on a rapid TB diagnostic in India, appears highly cost-effective by Indian standards; however, the expected returns all accrue within India, meaning the return on investment to the American taxpayer is indirect and dependent on the overall effectiveness of foreign aid/strategic partnership in boosting America's standing and long-term interests, as well as potential diffuse benefits of addressing the global TB pandemic and limiting the emergence and spread of drug resistance. The third case study is defensible from the perspective of American self-interest but relies on highly speculative and imprecise estimations for effect size in reducing pandemic risk; it is also most imprecise and speculative from a technological perspective, with returns estimated based on a desired (though perhaps unfeasible) feature set. The speculative nature of this final case study could also cut in the other direction; it is possible that private developers would bring such a product to

market even *without* an explicit US government commitment, in which case the prize payment may not induce any ROI, and would instead be captured as rents by the device developer. And in all cases, the expected returns are only realized if the desired innovations are actually developed and brought to market—though the same is also true for anticipated costs.

A related and quite valid question is whether these case studies are the "best" uses of scarce financial and political capital for pull mechanisms, even if they appear to generate high ROI when considered in a vacuum. This paper does not take a position on that specific question, and indeed is explicit that the selection criteria were not powered to select the "best" pull mechanisms. This paper intends to offer illustrative evidence of the ROI potential for US government investments to support pull mechanisms for biomedical innovation more broadly—not to narrowly advocate on behalf of these specific uses of funds. Other potential high-value applications of pull mechanisms, as highlighted in the companion horizon-scanning paper, could include improved treatment options for TB, sickle cell disease, leishmaniasis, kidney disease, lead poisoning, diabetes, and malaria; next-generation vaccines (e.g. HIV, malaria, pan-coronavirus, or pan-influenza); better diagnostics for pneumonia, leishmaniasis, cancer, sickle cell disease, and lead poisoning; and non-hormonal, male, and multipurpose contraceptives.[101]

It is also notable that all three case studies are relatively high cost, at least compared to "typical" global health investments in R&D. The least expensive case study—on TB in India—would still require over a billion US dollars in total expenditure. There is perhaps an important lesson here: to capture big opportunities and solve big problems, big investments are needed—an argument made by some observers in the aftermath of COVID-19.[102] Marginal allocations to R&D, whether push and pull, cannot reasonably be expected to drive transformative innovation. Global health advocates should be prepared to make big asks of funders, while demonstrating the potential for even larger returns on the far end; funders, likewise, should consider concentrated portfolios to attack "big problems" versus more diffuse, peppered grantmaking to many lower-cost, lower-potential endeavors. (As the ancient saying goes: you need to spend money to make money.)

This raises the "power of pull" specifically, versus a more general investment case for R&D investment. At least in theory, pull mechanisms ease the political economy challenge of R&D investments by conditioning payment on actual product delivery/health impact, such that outlays only occur in cases where anticipated/hypothesized returns will be realized. Pull mechanisms can also reduce the opportunities for patronage, inefficiency, and informational asymmetry in the allocation of R&D funding relative to status quo "push" funding mechanisms, in which very large monetary outlays are controlled largely at the discretion of individual policymakers or grant-makers. A pull approach to R&D financing reduces the burden on governments and philanthropies

101 Cordelia Kenney and Rachel Silverman Bonnifield. 2022. "The Next Game Changers: A Priority Innovation Agenda for Global Health." CGD Policy Paper 269. Washington, DC: Center for Global Development. https://www.cgdev.org/publication/next-game-changers-priority-innovation-agenda-global-health.

102 Pecetta et al., "The Trillion Dollar Vaccine Gap."

to "pick winners" from grant proposals—an exercise that is exceedingly difficult to do well even with maximal due diligence and the best of intentions. These benefits are magnified when needed R&D investments grow larger in magnitude and the stakes of funding decisions grow in turn.

The inverse also holds true. Critics of pull mechanisms often point to the high transaction costs required to effectively design a pull mechanism; generate and secure binding financial commitments; and develop a credible governance and evaluation structure for pay-out upon successful product development. These transaction costs, while substantial in any case, can be more easily justified when amortized across large (potential) health benefits versus in a relatively small pilot or trial. This can create a paradox of inaction: funders may be more willing to support experimental "pull" approaches in relatively small pilots, but shy away from making multi-billion-dollar commitments for an "untested" approach. While understandable, this can lead funders to concentrate their investments where they are least likely to succeed or generate large returns, and small-scale pilots of pull mechanisms may indeed appear ineffective or prohibitively complicated in part *as a result* of their small scale.

Conclusion

The case studies presented in this paper should serve as a rallying cry to the US government—and to philanthropies and governments more broadly—for ambitious investment in biomedical innovation to address today's causes of disease and tomorrow's emerging health threats. There are still enormous untapped opportunities on the table—and real, major threats that compromise Americans' health and welfare if not proactively addressed, alongside the rest of the world. Bipartisan support is needed to elevate strategic R&D investment and sustain America's status as the world's engine of innovation for a better, safer world.