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ABSTRACT

This paper evaluates the social value of investing in vaccine research, development, and manufacturing capacity for pandemic preparedness and response. Rapid vaccination during pandemics can significantly reduce mortality, economic losses, and societal disruptions. However, vaccine manufacturers often lack sufficient incentives for speed and capacity expansion. Strategic policies by governments and international organizations could enhance these incentives and improve equitable vaccine distribution.

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1. INTRODUCTION

By December 2023, COVID-19 had caused 27 million excess deaths (Our World in Data, no date) and trillions of dollars in economic output and human capital losses (Walmsley et al. 2023; Azevedo et al. 2021). Madhav et al. (2023) estimate that the world can expect three pandemics at least as severe as COVID-19 each century going forward, with less severe pandemics and regional epidemics occurring more frequently. In the last 50 years, in addition to COVID-19, the world has experienced pandemics due to HIV (human immunodeficiency virus), SARS (severe acute respiratory syndrome), and H1N1 (swine flu) and regional Zika and Ebola epidemics.

Vaccines are among the most effective medical countermeasures against pandemic harm. Vaccines protect against severe disease and, for some diseases, can block infection and transmission. Effective vaccines benefit society by reducing mortality and allowing economic activity to resume.

COVID-19 vaccines were developed at an unprecedented speed, but supply shortages slowed their distribution and contributed to inequitable global access. Nine months after COVID-19 vaccines received regulatory approval, vaccination rates were still below 50% worldwide and 8% in Africa (Baker et al. 2021), due in no small part to insufficient vaccine supply (Mobarak 2023). Such delays in vaccine rollout were responsible for substantial social harm in the form of continued high case counts, excess mortality, and economic losses (Duroseau et al. 2022). Preparing for future pandemics with advance investments and policies to accelerate vaccine availability can generate substantial social value and be highly cost-effective.

In this paper, we summarize recent research on the expected losses from pandemics and the social value of investing in pandemic preparedness and response that can accelerate vaccine

availability. We focus specifically on vaccine research and development (R&D) and manufacturing capacity.

- *Vaccine R&D* encompasses any investments aimed at advancing scientific knowledge and technological capabilities to produce new vaccines. This could include new vaccines for particular pathogens or research on vaccine platforms (e.g., mRNA vaccines). R&D investments can increase the probability of developing a successful vaccine and reduce the time from pathogen identification to authorization.
- *Vaccine capacity* refers to the infrastructure, resources, and processes required to produce and deliver vaccines at scale. Investments in capacity can increase the supply of vaccines, allowing for faster widespread deployment.

Within both domains, preparedness and response are linked. Prepandemic work determines the slate of vaccine technologies available, knowledge of the pathogen, resiliency of supply chains, and amount of flexible manufacturing capacity available at the start of the next pandemic. This influences the probability of a successful vaccine, speed of development/approval, and rapidity of supply scale-up when a pandemic hits.

This paper discusses the case for investing in pandemic vaccines, but a similar case could also be made for investing in other pandemic products, including therapeutics, diagnostics, masks, and health infrastructure. Therapeutics have the potential to offer broader efficacy than vaccines, which could enable them to be used against a novel pathogen at the start of a pandemic (Karim et al. 2023). However, patients need to know they have been infected to ask for treatment, limiting their value against pathogens that can be spread asymptotically, like COVID-19. Masks can reduce

airborne disease transmission even with low compliance and quality. Free surgical masks in Bangladeshi communities reduced symptomatic seroprevalence by over 11% (Abaluck et al. 2022). We focus on vaccines because a large literature supports their substantial benefits and because developing and scaling up manufacturing for vaccines takes longer than many other countermeasures, leaving more scope for acceleration.

Firms' incentives to supply pandemic vaccines are quite low compared to the vaccines' social value due to market and government "failures." One person's vaccination benefits others by reducing transmission and helping keep their corner of the economy going, but that person is unlikely to be willing to pay for these broader benefits (see Goodkin-Gold et al. 2024 for a full analysis of vaccine externalities). Moreover, selling a treatment to a patient who has contracted a disease can be more lucrative than selling them a preventive beforehand (Kremer and Snyder 2015). In these various ways, the market "fails" to reflect vaccines' full social value in suppliers' incentives. A pandemic may lead to government "failure," exerting political and social pressures limiting governments' ability to pay a lucrative price for vaccines (Athey et al. 2022). In 2022, COVID-19 vaccines were selling for less than $60 per course, orders of magnitude less than the estimated social value of $6,200 (Castillo et al. 2021). "Profiting during a pandemic" may be viewed with repugnance (Roth 2007).

Designing policies to better align vaccine investment incentives with their social value could address existing constraints. This paper analyzes a suite of such investments and funding options. The next section provides estimates of the enormous expected harm from future pandemics. Subsequent sections analyze the cost-effectiveness of investments in vaccine R&D and capacity, first focusing on pre-pandemic investments and then on in-pandemic investments.

2. FUTURE HARM FROM PANDEMICS

The value of pandemic preparedness hinges on the expected harm from future pandemics to be mitigated. Estimating the expected harm from future pandemics requires forecasting (i) the arrival rate of pandemics of varying sizes and (ii) the social harm caused by pandemics of varying sizes. We discuss each forecasting exercise in turn.

2.1. Pandemic Frequency

Forecasting the arrival of pandemics is difficult because they are driven by highly nonlinear epidemiological forces and severe global pandemics are rare, so the data on such pandemics are sparse.

One approach used in the literature focuses on a single pathogen—influenza—the most likely pathogen to cause a severe pandemic (Madhav et al. 2023). Forecasting pandemics for influenza is facilitated by the recurrent pattern of outbreaks, which has remained fairly constant over the past 300 years for this pathogen (Potter 2001). Unlike bacterial pandemics, which the invention of antibiotics curtailed, no similar medical advance has as sharply reduced the risk of future influenza outbreaks. Using historical data on global influenza epidemics since 1700, Fan et al. (2018) estimate that epidemic influenza will cause 720,000 annual deaths.

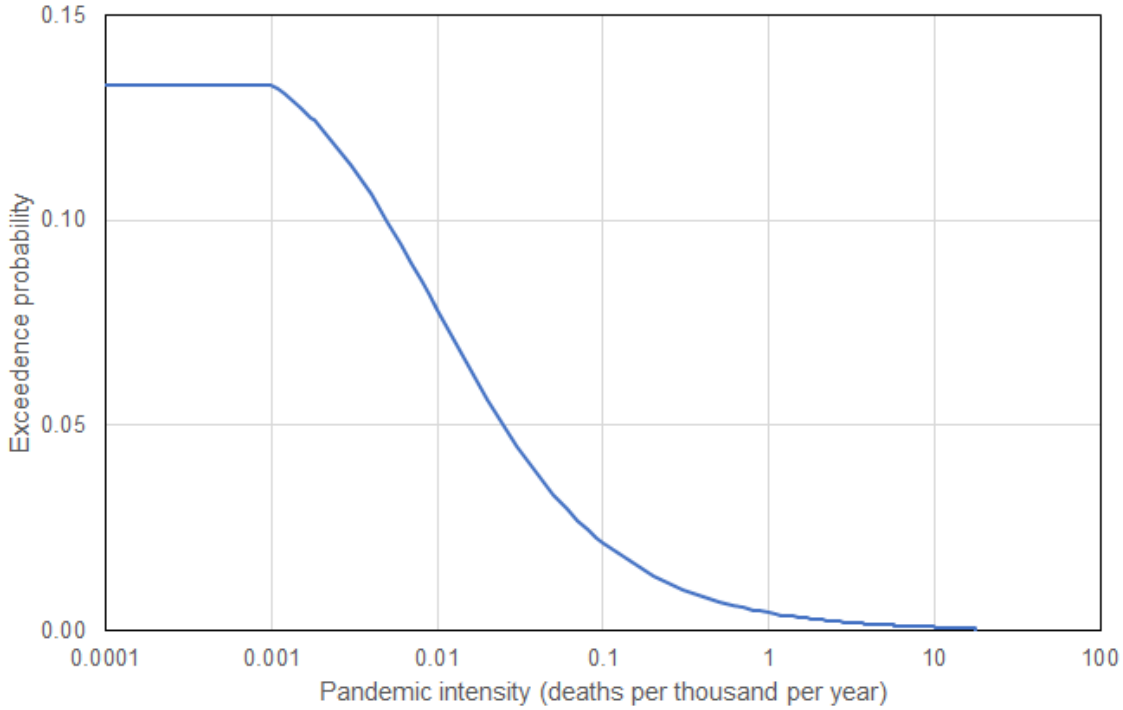
A drawback of focusing on influenza is that one pathogen only provides a lower bound on "all-cause" pandemic risk. In addition, advances in treatments and control measures (such as personal protective equipment) have reduced the frequency of influenza pandemics somewhat and may continue to do so in the future. Working in the opposite direction, climate change, habitat fragmentation, population density, and global travel may increase the frequency of pandemics (Madhav et al. 2023). Climate change, for example, may increase viral sharing and thereby the

emergence of novel pathogens by bringing mammals into greater contact with each other and with humans (Carlson et al. 2021).

Madhav et al. (2023) expand the set of pathogens included in their forecast of pandemics to include respiratory diseases (e.g., pandemic influenza and coronaviruses) and viral hemorrhagic fevers (e.g., Ebola and Marburg). Their model of regional disease spread captures the effect of variables such as global travel on pandemic frequency. Madhav et al. (2023) conclude that a pandemic as or more intense than COVID-19 can be expected to come along at least once every 50 years and that respiratory diseases will lead to a global annual average of 2.5 million deaths and viral hemorrhagic fevers to a global annual average of 26,000 deaths.

Marani et al. (2021, revised 2023) further expand the set of pathogens to cover pandemics from any cause. They analyze intensity data on nearly 500 significant epidemics since 1600, more than half of which include detailed information on duration and deaths. Their data contain enough episodes to accurately estimate a power-law distribution for pandemic intensity (deaths per 1000) conditional on arrival. The authors further estimate the probability of epidemic arrival based on the recent 20 years of data. Glennerster et al. (2023) take the combined estimates from Marani et al. (2023) and translate them into the exceedance probabilities shown in Figure 1.

Figure 1 Estimated Annual Probability of a Pandemic Exceeding Specified Intensity



Source: Glennerster et al. (2023), Figure 1.

The surveyed approaches to forecasting expected global pandemic deaths provide a range of estimates, but even the low end is in the hundreds of thousands of lives annually.

2.2. Social Harm from Pandemics

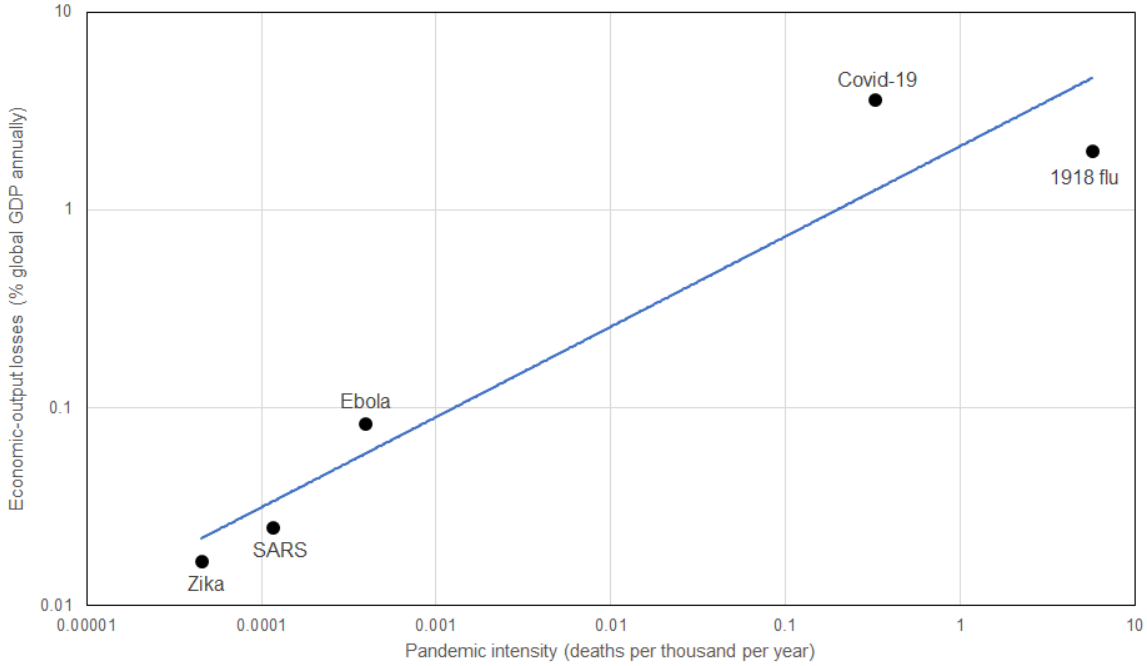
The next step is to fold forecasts of pandemic frequency into forecasts of total social harm from pandemics converting losses from different channels (mortality, morbidity, GDP reductions, and learning losses) into a common money metric.

Maintaining their focus on a single key pathogen, Fan et al. (2018) estimate social losses from pandemic influenza to be about $500 billion ($650 billion in 2023 dollars). Their estimate accounts for mortality losses by scaling forecasted deaths by the value of a statistical life (VSL), drawn from studies of consumers' willingness to pay for reductions in mortality risk (see Viscusi

2014 for a discussion of the VSL methodology). Mortality constitutes most of their total estimated pandemic losses. GDP losses constitute only about 15%, explaining why their estimates exceed earlier assessments focused solely on GDP losses (McKibbin and Sidrenko 2006).

Glennerster et al. (2023) expand the analysis to pathogens beyond influenza. A search for academic studies providing joint estimates of mortality and GDP losses from historical epidemics and pandemics yielded the five data points graphed in Figure 2, covering the 1918 flu, SARS, Ebola, Zika, and COVID-19. The authors use the regression line shown to project GDP losses for epidemics of any intensity. The authors project learning losses for pandemics of any intensity using results from Azevedo et al. (2021) on school closures experienced during COVID-19 combined with estimates of how years of schooling impact future wages.

Figure 2 Relationship between Intensity and GDP Losses Estimated from Studies of Historical Pandemics



Source: Glennerster et al. (2023), Figure 2.

Combining the estimate of the arrival rate of pandemics of varying intensities with estimates of mortality, economic damage, and learning losses, Glennerster et al. (2023) forecast expected global social losses of about $700 billion annually, as detailed in Table 1.

Table 1 Expected Annual Global Losses from Pandemics Caused by All Pathogens

Loss category	Expected losses (billion $)	Percent of total losses
Mortality	519	73%
Economic output	112	16%
Learning losses	81	11%
Total	**712**	**100%**

Source: Glennerster et al. (2023), Table 2.
Note: Mortality losses are estimated using Sweis' (2022) $1.3 million VSL estimate.

3. PANDEMIC-PREPAREDNESS INVESTMENTS

The forecasted harm from pandemics creates a case for investments to accelerate vaccine availability to mitigate this harm. This and the next section analyze two categories of cost-effective investment: vaccine R&D and vaccine capacity. This section focuses on preparedness investments undertaken in *advance* of future pandemics, while the subsequent section focuses on response investments undertaken *during* a pandemic.

3.1. Advance Investments in Vaccine R&D

3.1.1. Priorities

No one knows which pathogen will cause the next pandemic, but advance R&D can improve our ability to respond to it even without perfect foresight. COVID-19 vaccines were developed in

record time due to decades of advances in vaccine science, coronavirus vaccine research, and mRNA technology development (Dolgin 2021). Advance R&D is called for on specific virus families identified as pandemic threats and on technological platforms that apply generally across pathogens (Jain et al. 2021).

Institutions in charge of infectious disease control—including the Coalition for Epidemic Preparedness Innovations (CEPI), World Health Organization (WHO), and U.S. National Institute of Allergy and Infectious Disease (NIAID)—have outlined strategic plans prioritizing advance R&D that would enhance our readiness for the next pandemic. The plans include the following priorities.

- *Developing vaccines for pathogens with high epidemic risk.* Notable lists of priority diseases include World Health Organization (2018) and CEPI (2023). Lassa fever, MERS, Nipah, and Rift Valley fever appear on both lists as priorities.
- *Researching prototype vaccines generating knowledge spillovers to the broader viral family.* This approach focuses on basic, preclinical, and translational research of the shared characteristics within a viral family to develop generalizable countermeasure strategies. It can accelerate the discovery, development, and evaluation of vaccines against novel pathogens (Cassetti et al. 2022).
- *Advancing technologies that transform vaccine capabilities.* Transformative technologies include universal vaccines against the most likely pandemic threats (influenza and coronavirus), novel routes of administration, and enhancements in immune response. For example, intranasal vaccination could improve the immune response in the respiratory tract at the same time it reduces hesitancy by eliminating the painful shot (Jabbal-Gill 2010).

- *Innovation in enabling technologies.* Vaccine research, clinical trials, and manufacturing rely on many supporting technologies that could be advanced to accelerate vaccine development. For example, comprehensive antigen-specific and serological assays are critical to evaluating immune response from a vaccine and can enable faster scientific evaluation (CEPI 2021; National Institute of Allergy and Infectious Disease 2021).

3.1.2. Allocating Financing Responsibility for Advance R&D

Vaccine R&D that generates broad spillovers across pathogens and advances general-purpose technologies is a global public good. The scientific and technological advancements benefit all countries without diminishing the benefit to any single nation. Countries can "free ride" on others' R&D without paying for it themselves, leading to global underinvestment.

The underinvestment problem might most efficiently be solved by negotiating a cooperative global funding agreement. Countries could contribute to the fund in proportion to their GDP, but this may prove overly burdensome to low- and middle-income countries (LMICs). Alternatively, high-income countries (HICs) may fund most or all of the R&D for global pandemic threats, coordinated by the G7 or other effective HIC convener. The benefits to HICs from R&D investments are likely so much greater than costs that they could find it economically justifiable to fund such efforts themselves, despite the benefits spillovers to LMICs. For example, the R&D into mRNA technology funded by U.S. National Institutes of Health was repaid many times by the huge returns for the U.S. economy from accelerating COVID-19 vaccine development. Glennerster et al. (2024) suggest the U.S. would obtain enough unilateral benefit from a universal COVID-19 vaccine to justify large R&D investments alone.

R&D for regional epidemic threats or LMIC-specific technologies may be underfunded if left to HICs' self-interest. LMICs may need to coordinate R&D investments, supplemented by aid (for example, through CEPI), that address regional threats. Multilateral development banks could be well suited to coordinate investments in regional public goods, but new funding facilities may be needed with the flexibility to allow for group lending.

Box 1

General Principles Behind Push Versus Pull Funding

Historically, R&D has typically been paid for through "push" funding which pays directly for inputs (e.g., grants to developers for the cost of their materials, labor, and trials). An alternative is "pull" funding that links payments to successful achievement of an outcome. Both can play a role in supporting vaccine R&D.

Push funding is well suited to basic research aimed at expanding scientific understanding (Kremer and Glennerster 2005). Many innovations are developed without a clear end-use case, push funding is compatible with sharing knowledge and intermediate results, with grants awarded through competitive research calls.

Pull funding is useful when the funder can specify the needed innovation but does not know who is best placed to develop it or how. Pull-funding mechanisms (such as advanced market commitments, advance purchase agreements, and prizes) commit to paying developers who successfully produce the specified target. By only rewarding firms if they are successful, firms are incentivized to invest resources to identify candidates with the highest probability of success and to take measures to improve that probability. Innovators bear the risk of

development failure, while funders bear the market risk by committing to pay for an innovation meeting their specifications, even if its value changes over time. This division of risk appropriately accounts for private information each party holds (Kremer 2000).

3.1.3. Funding Advance Vaccine R&D with Pull

The general principles laid out in Box 1 on push versus pull funding provide guidance on how advance vaccine R&D could efficiently be funded. General-purpose technologies that spill over across products and pathogens or that are difficult to predict or embody in a technical product profile may be best suited for push funding. R&D targeting the production of a tangible vaccine might best be funded with pull. For example, a prize could be given for the first firm to gain approval for a Lassa fever vaccine.

Where pull funding is feasible, it offers some advantages, incentivizing firms to dynamically reduce their costs and to improve their probability of success. It can also help reduce the likelihood that funders pay for innovation approaches with little prospect of succeeding. These advantages can reduce overall program expense and improve the likelihood a successful vaccine candidate is developed (Athey et al. 2022).

3.1.4. Quantifying Needed R&D Spending

The next section presents estimates from Glennerster et al. (2023) on determining the optimal amount to spend in advance on pandemic vaccine capacity and the cost-effectiveness of that spending. The authors are working on using a similar approach to estimate the optimal amount and cost-effectiveness of advanced R&D investments. It is reasonable to suppose that the large benefits

estimated for accelerating the completion of a pandemic-vaccine campaign with more advance capacity will carry over for accelerating the rollout of the first vaccine with more advance R&D.

3.2. Advance Investments in Capacity

3.2.1. Capacity Priorities

Advanced vaccine capacity investments can refer to anything that is needed to produce and deliver vaccines including manufacturing facilities, workforce readiness, supply-chain resiliency, vaccine distribution infrastructure, and updating regulatory framework.

Supply, rather than lack of demand, was the major barrier to rapid deployment in most countries. Vaccine hesitancy was notably lower in LMICs compared to HICs (Mobarak et al. 2022; Solís Arse et al. 2021). Despite initial challenges with vaccine distribution channels and concerns about cold-supply chains, many LMICs were able to set up mobile clinics and other distribution strategies quickly and cost-effectively with the help of international aid (World Bank, no date; Mobarak et al. 2022; Bloxham 2021). Even countries with less developed health infrastructure had experience mobilizing mass immunization campaigns from previous epidemic threats, such as yellow fever and childhood vaccination campaigns (World Health Organization 2016; Mobarak et al. 2022). Investments in last-mile delivery are an essential capacity investment to ensure equitable access to vaccines but can be scaled up quickly. In this section, we focus on advance investment on the upstream problem that led to slower access to vaccines in LMICs: manufacturing capacity.

In order to have excess capacity available for use during a pandemic, pre-pandemic investment would need to create enough contract-manufacturing capacity to avoid operating near full capacity during normal times. Constructing new plants to sit idle until the next pandemic is not the only or more effective way to expand pandemic-vaccine capacity. Existing facilities can

be modified to add production lines quickly, with some of the necessary capital equipment stored on-site. Manufacturers could be paid a retainer or premium on current products to maintain this expansion option. Routine vaccines could be sourced from rotating facilities to keep excess capacity up-to-date. The platforms used to produce current vaccines can be switched over to more scalable and repurposable alternatives. For example, funders could subsidize mRNA-based seasonal flu vaccines to encourage manufacturers to switch from egg-based production, which is notoriously hard to scale. Additionally, including technology transfer agreements in advanced capacity investments can help ensure capacity can be leveraged effectively with the necessary expertise and technology to produce successful pandemic vaccines rapidly. Other investments such as stockpiling critical inputs could help relieve bottlenecks in other parts of the supply chain during a pandemic.

3.2.2. Allocating Financing Responsibility for Advance Capacity

Unlike R&D, manufacturing capacity is a rivalrous private good: capacity tied up in fulfilling one order cannot fulfill another simultaneously. A contract that reserves some capacity for one country without expanding the global total exerts a negative pecuniary externality on other countries, raising the bid needed to secure their place in the vaccine queue. Contracts that expand global capacity, by contrast, exert a positive externality on other countries. Once the contracting country has received the vaccine it needs, the capacity can be utilized to supply the next countries in line (Athey et al. 2022).

Competitive and transparent processes for advance manufacturing capacity contracts help ensure value for money. Procurement decisions could take into account both the price and the producer's ability to deliver on supply commitments during a crisis. Confidence would be bolstered by a firm's reputation for solid performance and its host country's history of honoring

contracts and respecting the rule of law. Small countries may more credibly promise not to expropriate vaccines intended for export for domestic use since less supply is needed to serve their population.

During the second wave of COVID-19, concerns over vaccine nationalism grew when, unable to keep up with domestic demand, India and certain E.U. countries restricted vaccine exports (Koller et al. 2021; European Commission 2021). Increased global vaccine manufacturing capacity would have mitigated these disruptions.

Pooling capacity investments via a global compact could help coordinate contracting, reduce supply-chain disruptions, and distribute vaccines to hardest-hit areas. HICs might be nervous about ceding control in a crisis to a multinational compact, but a world-class compact might still encourage their participation, even if supplemented by unilateral investments.

Pooled capacity would have the greatest insurance value in regional epidemics when competition for capacity is less intense, allowing all the capacity to be devoted to serving the countries experiencing outbreaks. Pooling resources would be especially valuable for LMICs, which have less available financing and higher epidemic risk, and especially valuable for LMICs with low correlation in epidemic risks (say countries in South America and Sub-Saharan Africa). Further work is needed to more precisely estimate optimal advance procurement quantities for different regions and countries.

3.2.3. Cost Effectiveness

Glennerster et al. (2023) analyzed a program to install advance capacity capable of producing 24 billion annual doses beyond routine vaccination needs. The authors determined this capacity level was necessary to vaccinate 70% of the global population in six months with a two-dose course, accounting for some wastage of capacity that is not a good match for the ultimately successful

vaccines. As ambitious as the size of the advance capacity is, reaching 70% coverage in six months requires the world to install substantial additional capacity in-pandemic.

Glennerster et al. (2023) estimate the advance-capacity program would cost $60 billion upfront and $5 billion annually for maintenance thereafter. The program has two main benefits. It saves $32 billion of in-pandemic expenditures by reducing the amount of capacity that the world needs to install in the heat of the pandemic. More importantly, expanding capacity in advance relaxes the physical limit on rapid in-pandemic expansion. This additional available capacity can accelerate the global vaccination campaign, averting $539 billion in social losses relative to the status quo of waiting until a pandemic to scale capacity.

Based on mortality reductions alone, the advance-capacity program would cost $4,000 per year of life saved. At a third of current global GDP per capita, the program would be judged highly cost-effective according to standard metrics (Marseille et al. 2015).

The precise public health benefits of accelerating vaccinations depend on the nature of the pathogen and vaccine. A vaccine capable of reducing transmission and maintaining durable protection might push the population over the threshold for herd immunity and end the pandemic sooner. Less capable vaccines can nonetheless generate large benefits. COVID-19 vaccines did not provide the durable protection and transmission prevention that health officials hoped for, leading aspirations for achieving herd immunity to be dropped. Still, these vaccines prevented over 14 million deaths within the first year of their deployment (Watson et al. 2022), and economies were able to reopen. Accelerating vaccine rollout can be as important as optimizing their capabilities. According to Castillio et al. (2021), a 70% effective COVID-19 vaccine would have the same social value as a 95% effective vaccine available two months later.

4. IN-PANDEMIC RESPONSE

In this section, we turn to analyzing investments in R&D and capacity made during a pandemic rather than before.

4.1. Investing in Multiple Vaccines and Investing "At Risk"

Vaccine development is technologically challenging, with low success rates (MacPherson et al. 2020). The high risk of failure calls for multiple vaccine candidates to be supported simultaneously to increase the probability that at least one is successful. Early in the COVID-19 pandemic, Baker et al. (2021) estimated that at least 15 vaccine candidates would need to be supported to obtain an 80% chance of at least one success. Even if the marginal vaccine candidate only contributes a few percentage points to the probability of success of the portfolio, the investment to support this candidate may be worthwhile. The over 14 million deaths Watson et al. (2022) estimated that COVID-19 vaccines were averted in the first year of COVID-19 vaccine deployment translates into over $18 trillion benefit from reduced mortality alone (using the $1.3 million VSL estimate from Sweis 2022). Increasing the chance of averting such harm by even a percentage point is worth billions.

In-pandemic R&D investments would generate greater benefits when complemented with capacity investments, which can help enable rapid vaccine distribution. Waiting until regulatory approval before expanding capacity can result in months of delay during which social harms from the pandemic mount. Expanding capacity “at-risk”—concurrently with clinical trials—is essential, even though some expenditures may be for candidates that end up failing. Ahuja et al. (2021) found that employing this strategy for COVID-19 capacity saved $1.6 trillion in global harm by accelerating availability by three months. More capacity would have saved more harm: increasing

at-risk capacity from the observed level (6 billion annual doses) to the optimal level (14 billion) more than doubles the harm saved in the Ahuja et al. (2021) model. While the quantitative results are specific to the COVID-19 pandemic, the qualitative principles are relevant for future pandemics.

4.2. Diversifying the Vaccine Portfolio

When choosing a portfolio of vaccine candidates for R&D and capacity investment during a pandemic, considering the correlation in candidates' prospects can maximize the probability of at least one success. It may be worth passing over candidates with higher individual probabilities of success to include candidates with less correlated success with the rest of the portfolio.

The point is illustrated in Table 2, listing the six COVID-19 vaccine candidates in phase-3 clinical trials by August 2020. Their probabilities of success are derived from the model of Ahuja et al. (2021), reflecting their best estimates of correlated failure risk within technology platforms and declining failure risk for candidates further along in clinical trials.

Table 2 Constructing an Optimal Vaccine Portfolio

Vaccine candidate	Clinical platform	Candidate's stand-alone probability of success (%)	Probability of at least one success in portfolio (%)
A	Inactivated virus	29	29
B	Viral vector	29	48
C	Inactivated virus	29	58
D	Inactivated virus	29	63
E	mRNA	22	70
F	mRNA	22	73

Source: Author's calculations using input from Ahuja et al. (2021) model.

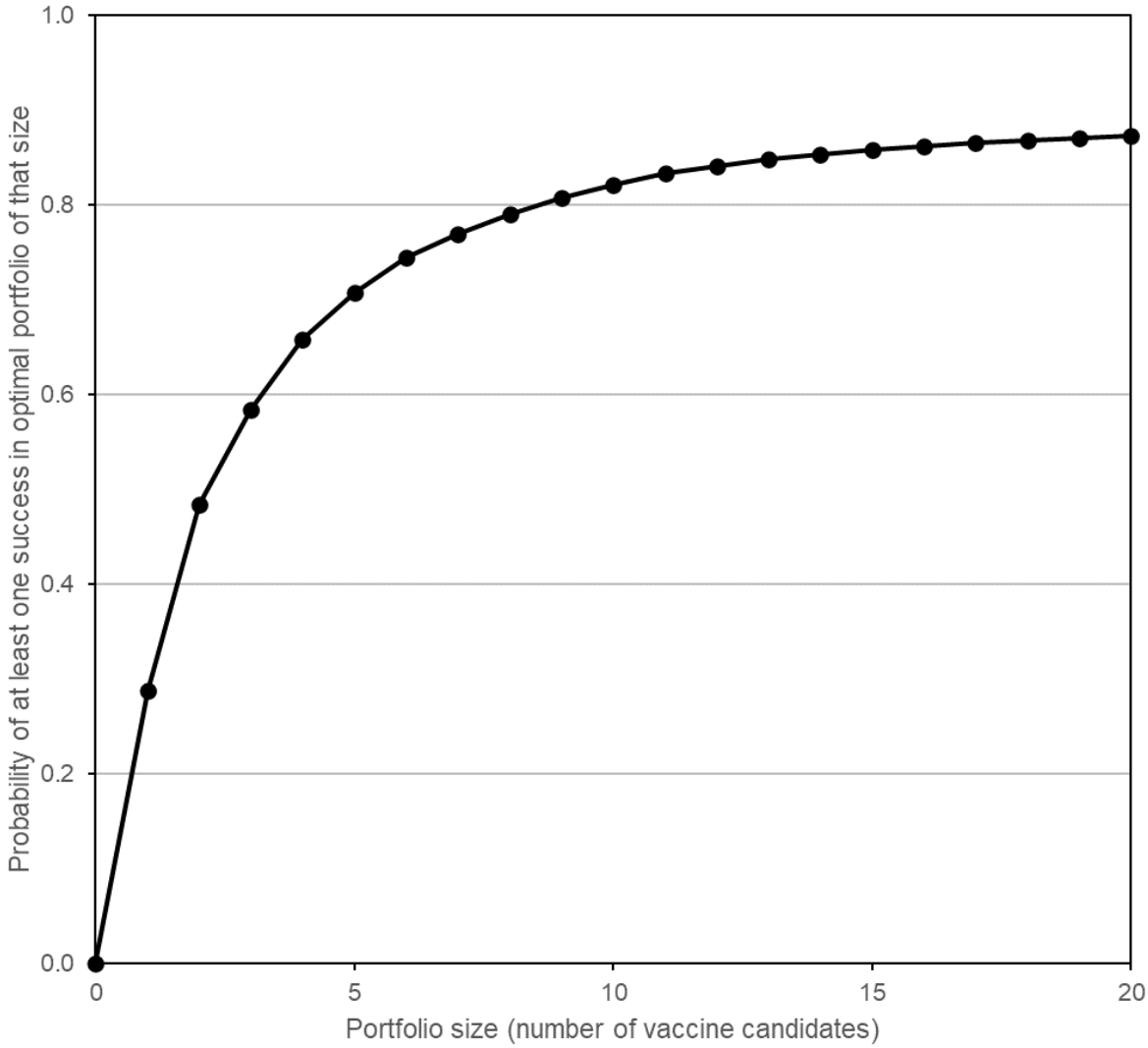
As a thought experiment, consider forming a portfolio of four candidates from the six listed. A portfolio of the four highest-probability candidates (A–D) has a 63% success chance.

Substituting an mRNA candidate for an inactivated virus candidate increases this to 66%, as candidates within the same platform share failure risks.

While the thought experiment assumes equal social benefits for successful candidates, in practice, they might differ in efficacy, duration of immunity, shelf stability, ease of administration, etc. Considering these additional factors only strengthens the case for diversifying the candidate portfolio, helping ensure a successful candidate emerges satisfying a variety of criteria. The modeled probabilities come with significant uncertainty, but even a rough understanding of correlations between candidates based on platforms, adjuvants, and antigens can help vaccine buyers make better-calibrated investment decisions.

Moving from thought experiment to the formal analysis in Ahuja et al. (2021), the authors construct optimal portfolios of various sizes from the COVID-19 candidates. Figure 3 graphs the probability of success generated by those portfolios. The diminishing returns to portfolio size exhibited by the graph arise because incremental candidates are less promising and only contribute to the probability of overall success if other candidates in the portfolio fail.

Figure 3 Probability of at Success in Optimal Vaccine Portfolio



Source: Ahuja et al. (2021), Figure A6.

4.3. Sizing the Optimal Portfolio

How large should a country's at-risk investment portfolio be? To answer that question, Ahuja et al. (2021) scale the probability of a success shown in Figure 3 by the averted harm from early access to a successful vaccine and weigh the result against the cost of investing in more candidates.

The results are shown in Table 3. Lower-income countries optimally procure fewer candidates and less capacity per candidate because of their tighter budget constraints. The table may present an overly conservative benefit/cost ratio for at-risk capacity investment by reporting the incremental benefit of accelerating capacity availability by three months, not the benefit of that capacity relative to no capacity. On the other hand, it allocates the full cost to the investing country, assuming that waiting allows countries to free ride on others' at-risk capacity expenditures.

Table 3 Optimal At-risk Vaccine Capacity by Country Group

Country category	Vaccine candidates (per-country mean)	At-risk capacity (annual doses per capita)	Benefit from at-risk investment vs. 3 month delay ($ per capita)	Cost of at-risk capacity ($ per capita)
High income	18.3	23.5	699.3	143.6
Middle income	6.7	4.1	40.7	20.4
Low income	1.3	0.1	0.6	0.3
All in world	8.8	7.3	137.4	36.5

Source: Ahuja et al. (2021), Table A2.

The recommended portfolio for the average HIC involves three times the number of candidates funded at risk under Operation Warp Speed, the U.S. program for procuring COVID-19 vaccines, reputedly an aggressive investment program. Mango (2022) suggests that administrative bandwidth was a key constraint on the number of candidates the program could support. Another constraint is the number of large-scale clinical trials that can be conducted simultaneously. Relaxing the constraint on clinical trials by coordinating them more effectively has been suggested as an important investment in pandemic preparation (CEPI 2021).

4.4. Contracting for At-risk Capacity

Typically, vaccine manufacturers wait until regulatory approval to install substantial capacity, as the investment is wasted if the vaccine fails. As emphasized in a previous subsection, the social value of investing in vaccine capacity at risk in a pandemic to reduce the lag in availability can easily justify the "wasted" investment. Bridging the gap between social and commercial incentives to install capacity at risk undoubtedly involves public funding.

Inducing manufacturers to invest at risk can be challenging even in a pandemic, requiring careful contract design. A fixed price per dose, even if the price is high, provides little incentive to rush production. Penalties for missing delivery deadlines may not work because they would bankrupt most firms if anything close to the social cost of delay.

A cost-effective approach to get firms to install at-risk capacity is through direct contracts with firms using a combination of push and pull funding (Box 1). Purchasers can agree to directly fund most of the firm's at-risk capacity costs along with a commitment to buy output at a price that incentivizes the firm to complete the at-risk investment. This scheme transfers most of the risk of failure to the funder but leaves the firm with enough "skin in the game" to ensure it is a serious entrant and to lead it to economize on investment costs. Operation Warp Speed involved hybrid contracts of this form (although some developers opted to solely participate through supply commitments, forgoing push funding) (Congressional Research Service 2021). In contrast, firm-agnostic pull funding may not efficiently incentivize marginal firms with low probabilities of success to scale capacity because a standardized price high enough to attract these developers would overcompensate firms with more promising candidates.

To ensure supply is scaled appropriately, purchasers can contract specifically for expanded capacity to fulfill procurement orders rather than just for delivery of doses at an unspecified date, which might place the purchaser in the middle of a long queue. Such a contract allows the purchaser to secure access to vaccines as soon as they become available and has the external benefit of increasing the global supply of manufacturing capacity.

During COVID-19, high-income countries used advanced purchase agreements to secure their place at the front of the line for vaccines. In contrast, LMICs did not have the financing tools to be able to invest at risk, which led to inequitable access to vaccines (Thornton et al. 2023). Agarwal and Reed (2022) attribute more than 60% of the delay in the delivery of vaccines to LMICs to the fact that they signed advance purchase agreements later than HICs.

COVAX was established to ensure global equitable access to COVID-19 vaccines but faced a number of challenges. COVAX had two arms, a self-financing arm where HICs and MICs could pay for access to a pooled vaccine portfolio and a donation-funded arm providing vaccines to 92 eligible lower-income countries. Unlike sovereign HICs, COVAX lacked the flexibility to act swiftly to contract at risk. COVAX could only enter into contracts equivalent to the cash it had on hand (whether from self-funders or donations), which took months to receive, and it needed to develop novel risk-sharing and mitigation agreements (COVAX 2022). Restrictive lending criteria from multilateral development banks (MDBs) limited self-funding middle-income countries' ability to purchase vaccines at risk and delayed their contributions to COVAX (Hart et al. 2021). Consequently, most COVAX commitments occurred after HICs had already signed APAs with vaccine developers separate from COVAX. Establishing mechanisms that would enable LMICs to borrow for at-risk purchases during pandemics could address these issues. This will require coordination between COVAX and MDBs and the establishment of mechanisms by which HICs

can de-risk these loans. MDBs can also coordinate with stakeholders to create model procurement contracts and establish indemnity and liability frameworks to streamline processes and minimize delays.

4.5. Using Available Capacity Efficiently

During periods of vaccine scarcity, policymakers can optimize allocation strategies to maximize social benefits. Prioritizing high-risk populations, such as those with high mortality and morbidity risks and front-line workers, is essential. Bubar et al. (2021) estimated that vaccinating 20% of the population for COVID-19 could reduce mortality by 80%. Stretching available supplies through a "first doses first" policy, which involves delaying the second dose of a two-dose sequence to allow more individuals to receive vaccines early, or "fractional dosing," which reduces the active ingredient in each dose, can improve outcomes (Moghadas et al. 2021; Wiecek et al. 2022). Cross-country vaccine exchanges can further improve allocation, allowing countries to adjust to their needs and capacities. For example, countries may want to trade vaccines that require substantial cold storage, or trade current orders for more vaccines later if they are facing absorption constraints (Budish et al. 2022).

5. CONCLUSION

This paper emphasizes the enormous social value of investing in vaccine R&D and manufacturing capacity to prepare for and respond to pandemics. Such investments could dramatically reduce the time required to develop and distribute vaccines, mitigating substantial pandemic harm.

Pre-pandemic investments in vaccine R&D and flexible capacity can ensure readiness and rapid response capabilities and are more cost-effective than reactive measures. Both push and pull funding can be effectively used to invest in vaccine R&D. Additionally, investments to expand

global vaccine manufacturing capacity can accelerate vaccine rollouts and lead to more equitable vaccine distribution.

Once a pandemic arrives, investing in a diverse portfolio of vaccine candidates increases the likelihood of successful outcomes, enhancing global vaccine availability. At-risk investments in capacity can reduce the lag between vaccine approval and wide-scale deployment. To enable more equitable vaccine access worldwide, LMICs need access to financial tools to support at-risk investments.

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