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Investing in Vaccines to Mitigate Harm from COVID-19 and Future Pandemics

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ABSTRACT

This chapter 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. Governments and international organizations can implement strategic policies to enhance these incentives and improve equitable vaccine distribution. In preparation for future pandemics, governments should make advance investments in vaccine manufacturing capacity as well as in research and development for vaccine prototypes and platforms. Investment to accelerate the research and development for a diverse portfolio of vaccine candidates and at-risk vaccine manufacturing capacity is likely to generate high returns during a pandemic.

OVERVIEW

By December 2023, COVID-19 (coronavirus) had caused 27 million excess deaths[1] and trillions of dollars in economic output and human capital losses (Azevedo et al. 2021; Walmsley et al. 2023). 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. Since the 1970s, in addition to COVID-19, we have experienced global pandemics due to HIV (human immunodeficiency virus), SARS (severe acute respiratory syndrome), and H1N1 (swine flu) as well as regional Ebola and Zika 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 provided important lessons about the global ability to use vaccines as an effective pandemic countermeasure. COVID-19 vaccines were developed at an unprecedented speed thanks to decades of advances in vaccine science, coronavirus research, and mRNA technology development (Dolgin 2021). Supporting multiple vaccine candidates across a range of technologies provided valuable insurance against the risk that some failed. Supply shortages, however, slowed vaccine distribution and contributed to inequitable global access. Nine months after COVID-19 vaccines received regulatory approval, vaccination rates remained below 50 percent worldwide and 8 percent in Africa (Baker, Chaudhuri, and Kremer 2021), in no small part because of 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, Kipshidze, and Limaye 2022). Preparing for future pandemics with advance investments and policies to accelerate vaccine availability can generate substantial social value and be highly cost-effective.

This chapter summarizes recent research on the expected losses from pandemics and the social value of investing in pandemic preparedness and response that can accelerate vaccine availability. It focuses 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, including new vaccines for particular pathogens or research on vaccine platforms (for example, 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 investment can increase the slate of available vaccine technologies, deepen understanding of the pathogen, improve supply chain resiliency, and expand available flexible manufacturing capacity—all of which influence the probability of successful vaccine candidates and accelerate their development and rollout when a pandemic hits.

This chapter discusses the case for investing in pandemic vaccines, but one could make a similar case for investing in other pandemic products, including

therapeutics, diagnostics, masks, and health infrastructure. Therapeutics may offer broader efficacy than vaccines, making them potentially useful against a novel pathogen at the start of a pandemic (Karim, Lo, and Einav 2023). However, patients must know they are infected to ask for treatment, which limits the value of therapeutics against pathogens that can spread asymptomatically. Masks can reduce airborne disease transmission even with low compliance and quality. For instance, free surgical masks in Bangladeshi communities reduced symptomatic seroprevalence by over 11 percent (Abaluck et al. 2021). The chapter focuses on vaccines because a large literature supports their substantial benefits and because of the longer time required for development and scaling up manufacturing relative to other countermeasures, leaving more scope for acceleration.

Market and government "failures" have made firms' incentives to supply pandemic vaccines quite low compared to the vaccines' social value. Vaccination of one person 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 (refer to 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 that person 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 that limit governments' ability to pay a lucrative price for vaccines (Athey et al. 2022). In 2022, COVID-19 vaccines sold for less than US$60 per course, orders of magnitude less than the estimated social value of US$6,200 (Castillo et al. 2021). "Profiting during a pandemic" may be viewed with repugnance (Roth 2007).

Given these constraints, incentivizing socially valuable vaccine investments requires carefully designed policies. This chapter 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 prepandemic investments and then on in-pandemic investments.

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 (1) the arrival rate of pandemics of varying sizes and (2) the social harm caused by pandemics of varying sizes. The following subsections discuss each forecasting exercise in turn.

Pandemic Frequency

Forecasting the arrival of pandemics is difficult because they are driven by highly nonlinear epidemiological forces. Moreover, the rarity of severe global

pandemics means that data on such pandemics are sparse. The following 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.

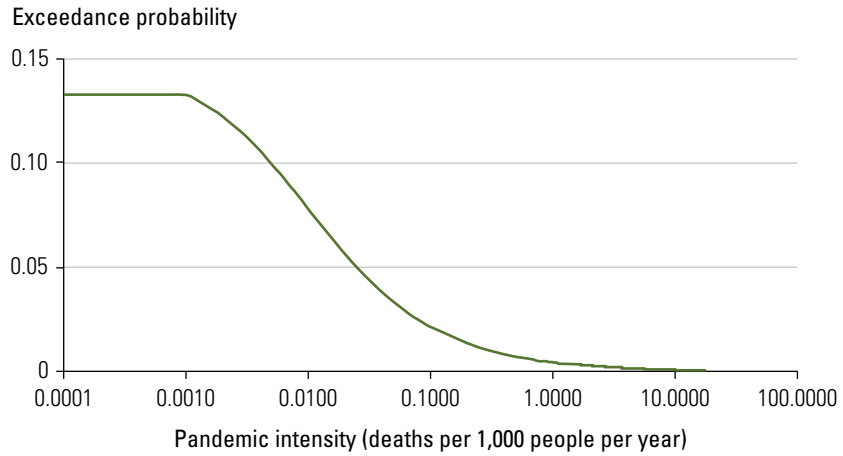
One approach used in the literature focuses on a single pathogen—influenza—the most likely pathogen to cause a severe pandemic (Madhav et al. 2023). Forecasting pandemics for influenza is facilitated by the recurrent pattern of outbreaks, which has remained fairly constant over the past 300 years for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

A drawback of focusing on influenza is that one pathogen provides only 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. 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. 2022).

Madhav et al. (2023) expand the set of pathogens included in their forecast of pandemics to include respiratory diseases (for example, pandemic influenza and coronaviruses) and viral hemorrhagic fevers (for example, Ebola and Marburg). Their model of regional disease spread captures the effect of variables, such as global travel, on pandemic frequency. They conclude that a pandemic that matches or exceeds the intensity of 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, 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 1,000 people) conditional on arrival. Those authors further estimate the probability of epidemic arrival using the recent 20 years of data. Glennerster, Snyder, and Tan (2023) take the combined estimates from Marani et al. (2023) and translate them into the exceedance probabilities shown in figure 10.1.

Figure 10.1 Estimated Annual Probability That a Pandemic Will Exceed Specified Intensity



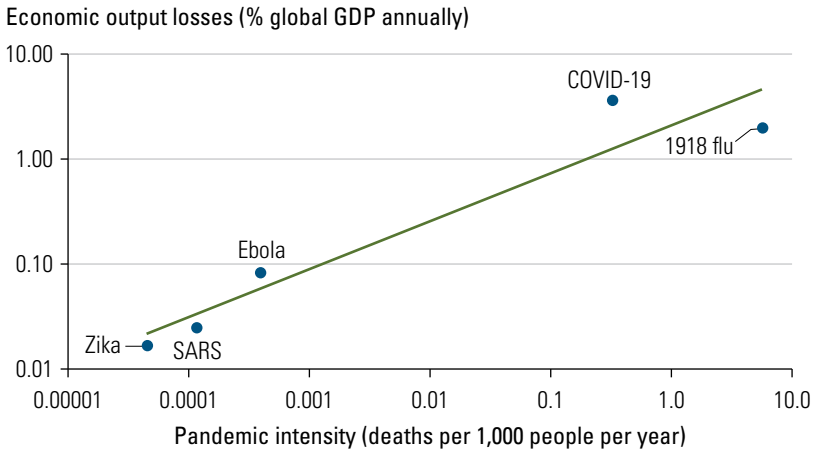
Source: Glennerster, Snyder, and Tan 2023, figure 1.

Social Harm from Pandemics

The next step is to translate forecasts of pandemic frequency into forecasts of total social harm from pandemics, converting losses from different channels (mortality, morbidity, gross domestic product [GDP] reductions, and learning losses) into a common money metric. Maintaining their focus on a single key pathogen, Fan, Jamison, and Summers (2018) estimate social losses from pandemic influenza at about US$500 billion (US$650 billion in 2023 dollars). Their estimate accounts for mortality losses by scaling forecasted deaths by the value of a statistical life, drawn from studies of consumers' willingness to pay for reductions in mortality risk (refer to Viscusi 2014 for a discussion of the value of a statistical life methodology). Mortality constitutes most of their total estimated pandemic losses. GDP losses constitute only about 15 percent, explaining why their estimates exceed earlier assessments focused solely on GDP losses (McKibbin and Sidorenko 2006).

Glennerster, Snyder, and Tan (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 10.2, covering the 1918 flu, SARS, Ebola, Zika, and COVID-19. Glennerster, Snyder, and Tan (2023) use the regression line shown in figure 10.2 to project GDP losses for epidemics of any intensity. They 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 affect future wages. Combining the estimate of the arrival rate of pandemics of varying intensities with estimates of mortality, economic damage, and learning losses, Glennerster, Snyder, and Tan (2023) forecast expected global social losses of about US$700 billion annually (table 10.1).

Figure 10.2 Relationship between Intensity and GDP Losses Estimated from Studies of Historical Pandemics



Source: Glennerster, Snyder, and Tan 2023, figure 2.

Note: GDP = gross domestic product; SARS = severe acute respiratory syndrome.

Table 10.1 Expected Annual Global Losses from Pandemics Caused by All Pathogens

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

Source: Glennerster, Snyder, and Tan 2023, table 2.

Note: Mortality losses are estimated using the US$1.3 million value of a statistical life estimate from Sweis (2022).

INVESTMENTS IN PANDEMIC PREPAREDNESS

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

Advance Investments in Vaccine R&D

Priorities. No one knows which pathogen will cause the next pandemic, but advance R&D can improve our ability to respond even without perfect foresight. COVID-19 vaccines were developed in record time thanks to decades of advances in vaccine science, coronavirus vaccine research, and mRNA technology (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, and US National Institute of Allergy and Infectious Disease—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 CEPI[2] and WHO (2018). Lassa fever, MERS (Middle East respiratory syndrome), Nipah, and Rift Valley fever appear on both lists as priorities.
- **Researching prototype vaccines for viral families.** 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 that 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 for evaluating immune response from a vaccine and can enable faster scientific evaluation (CEPI 2021; NIAID 2021).

Who should pay 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.

A cooperative global funding agreement might best solve this underinvestment problem. Countries could contribute to the fund in proportion to their GDP, but this requirement may prove overly burdensome to low- and middle-income countries (LMICs). More realistically, high-income countries (HICs) may fund most or all of the R&D for global pandemic threats, coordinated by the Group of Seven or other effective HIC conveners. The benefits to HICs from R&D are likely so much greater than the costs that they should be willing to provide all the funds themselves despite the benefits spillovers to LMICs. For example, the R&D into mRNA technology funded by the US National Institutes of Health was repaid many times by the huge returns for the US economy from accelerating COVID-19 vaccine development. Glennerster, Kelly, et al. (2024) suggest that the United States alone would obtain enough unilateral benefit from a universal COVID-19 vaccine to justify large R&D investments.

R&D for regional epidemic threats or for technologies specific to LMICs 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.

Funding advance vaccine R&D with push or pull funding. The general principles laid out in box 10.1 on push versus pull funding provide guidance on how advance vaccine R&D should 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 best be funded with push. R&D targeting the production of a tangible vaccine might best be funded with pull. For example, funders could offer a prize for the first firm that gains approval for a Lassa fever vaccine.

When pull funding is feasible, it offers some advantages, incentivizing firms to dynamically reduce their costs and 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 of developing a successful vaccine candidate (Athey et al. 2022).

Box 10.1

General Principles behind Push versus Pull Funding

Historically, funders have used different mechanisms to incentivize companies, academic researchers, and research institutions to undertake socially valuable research and development. These mechanisms include "push" funding, which pays directly for inputs (for example, grants that pay for developers' materials and labor), and "pull" funding, which links payments to successful achievement of an outcome. Both can play a role in supporting vaccine research and development.

Push funding is well suited to basic research aimed at expanding scientific understanding (Kremer and Glennerster 2004). With such research, many innovations are developed without a clear end-use case. Push funding is compatible with sharing knowledge and intermediate results, awarding grants 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 advance market commitments, advance purchase agreements, and prizes) commit to paying developers that successfully produce the specified target (Kremer, Levin, and Snyder 2020). By rewarding firms only if they are successful, pull funding leverages private expertise in identifying promising candidates and incentivizes firms to invest resources in such candidates to improve their probability of success. This mechanism aligns private incentives with public goals. Innovators bear the risk of development failure, whereas 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 held by each party (Kremer 2000).

Quantifying needed R&D spending. The next subsection presents estimates from Glennerster, Snyder, and Tan (2023) on determining the optimal amount to spend in advance on pandemic vaccine capacity and the cost-effectiveness of that spending. Those authors are working on using a similar approach to estimate the optimal amount and cost-effectiveness of advance 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.

Advance Investments in Capacity

Capacity priorities. Advance 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 or delivery capacity, was the major barrier to rapid COVID-19 vaccine deployment in most countries and will likely pose a challenge in future pandemics. Vaccine hesitancy was notably lower in LMICs than in 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 quickly and cost-effectively established mobile clinics and other distribution strategies with the help of international aid (Bloxham 2021; Mobarak et al. 2022).[3] Even countries with less developed health infrastructure had experience mobilizing mass immunization campaigns from previous epidemic threats, such as yellow fever, and from childhood vaccination campaigns (Mobarak et al. 2022; WHO 2016). Regulatory agencies achieved record approval times, while maintaining safety, using mechanisms such as the US Food and Drug Administration's Emergency Use Authorization and the World Health Organization's Emergency Use Listing (Kalinke et al. 2022), but manufacturing capacity became the rate-limiting step for vaccine access. This subsection focuses on advance investments in manufacturing capacity as a key limitation to vaccine access in LMICs and the hardest to scale quickly during the pandemic.

Prepandemic investment should create enough contract manufacturing capacity to avoid operating near full capacity during normal times, creating excess capacity available for use during a pandemic. Constructing new plants to sit idle until the next pandemic is not the only or best 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. For example, in 2022, Germany contracted with five manufacturers to maintain domestic vaccine production capabilities that could be rapidly activated for multiple vaccine technologies (Paul-Ehrlich-Institut 2022). 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 hard-to-scale egg-based production.

Manufacturing scale-up can also include intellectual property and technology transfer arrangements. A significant literature examines how different intellectual property frameworks—from patent pools to voluntary licensing—affect vaccine access and innovation incentives (refer to, for example, Adekola and Mercurio 2025; Gold 2022; Stevens and Schultz 2022). Successful production requires more than intellectual property rights alone: manufacturers need proper incentives to share technical expertise and coordinate production processes. During COVID-19, Merck and Johnson & Johnson demonstrated the feasibility of voluntary production partnerships when properly incentivized (Merck 2021). Government policies can support these arrangements by helping coordinate supply chains and stockpiling inputs, such as the United States achieved through actions taken under the Defense Production Act (Lupkin 2021).

Who should pay 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 used to supply the next countries in line (Athey et al. 2022).

Contracting for advance manufacturing capacity should use competitive and transparent processes to ensure value for money. Procurement officials should consider not only price but also the producer's ability to deliver on supply commitments during crisis. A firm's reputation and its host country's history of respecting the rule of law (for example, by honoring contracts) would bolster confidence in certain producers. Small countries may more credibly promise not to expropriate vaccines intended for export for domestic use because they need less supply to serve their populations. During the second wave of COVID-19, concerns over vaccine nationalism grew when, unable to keep up with domestic demand, India and certain European Union countries restricted vaccine exports (European Commission 2021; Koller et al. 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 the 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; it would be especially valuable for LMICs with low correlation in epidemic risks (say, countries in Latin America and the Caribbean and Sub-Saharan Africa). Further work is needed to more precisely estimate optimal advance procurement quantities for different regions and countries.

Cost-effectiveness. Glennerster, Snyder, and Tan (2023) analyze a program to install advance capacity capable of producing 24 billion annual doses beyond routine vaccination needs. They determine that this capacity level is necessary to vaccinate 70 percent 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 percent coverage in six months requires the world to install substantial additional capacity in-pandemic.

Glennerster, Snyder, and Tan (2023) estimate that the advance capacity program would cost US$60 billion up front and US$5 billion annually for maintenance thereafter. The program has two main benefits. It saves US$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 important, expanding capacity in advance relaxes the physical limit on rapid in-pandemic expansion. This additional available capacity can accelerate the global vaccination campaign, averting US$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 US$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 the 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 the rollout of vaccines can be as important as optimizing their capabilities. According to Castillo et al. (2021), a 70 percent effective COVID-19 vaccine would have the same social value as a 95 percent effective vaccine available two months later.

IN-PANDEMIC RESPONSE

This section turns to analyzing investments in R&D and capacity made during a pandemic rather than before.

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 supporting multiple vaccine candidates simultaneously to increase the probability that at least one is successful. Early in the COVID-19 pandemic, Baker, Chaudhuri, and Kremer (2021) estimated that obtaining an 80 percent chance of at least one success would

require supporting at least 15 vaccine candidates. Even if the marginal vaccine candidate contributes only 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 that Watson et al. (2022) estimated that COVID-19 vaccines averted in the first year of COVID-19 vaccine deployment translate into benefits of over US$18 trillion from reduced mortality alone (using the US$1.3 million value of a statistical life estimate from Sweis [2022]). Increasing the chance of averting such harm by even a percentage point is worth billions.

In-pandemic R&D investments should be complemented with capacity investments to 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"—that is, concurrently with clinical trials—is essential, even though some expenditures may be for candidates that fail. Ahuja et al. (2021) find that employing this strategy for COVID-19 capacity saved US$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. Although the quantitative results are specific to the COVID-19 pandemic, the qualitative principles are relevant for future pandemics.

Diversifying the Vaccine Portfolio

When choosing a portfolio of vaccine candidates for R&D and capacity investment during a pandemic, funders should consider the correlation in candidates' prospects to maximize the probability of at least one success. It may be worth passing over candidates that have higher individual probabilities of success to include candidates that have less correlated success with the rest of the portfolio. The point is illustrated in table 10.2, which lists 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 10.2 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: Original 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 percent success chance. Substituting an mRNA candidate for an inactivated virus candidate increases this chance to 66 percent, because candidates within the same platform share failure risks.

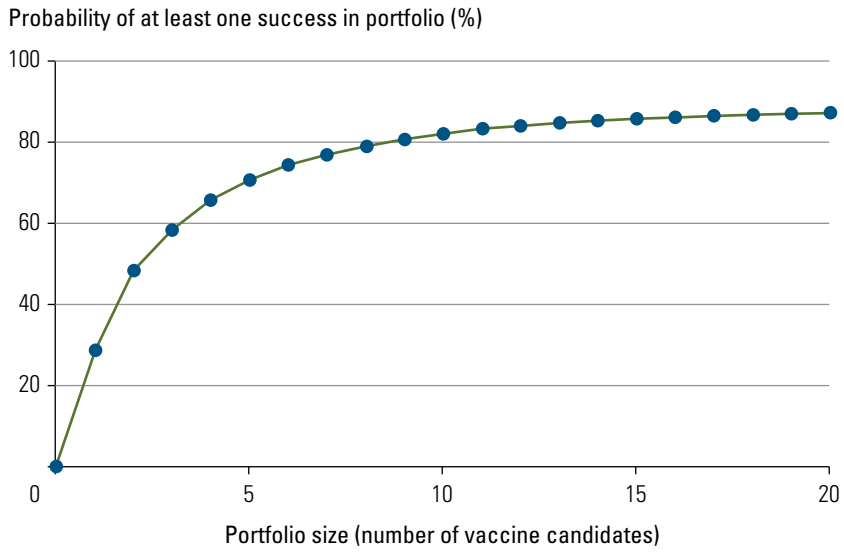
Although the thought experiment assumes equal social benefits for successful candidates, in practice candidates might differ in efficacy, duration of immunity, shelf stability, ease of administration, and so on. Considering these additional factors only strengthens the case for diversifying the candidate portfolio, helping ensure the emergence of a successful candidate that satisfies 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 formal analysis, Ahuja et al. (2021) construct optimal portfolios of various sizes from the COVID-19 candidates. Figure 10.3 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 contribute to the probability of overall success only if other candidates in the portfolio fail.

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 10.3 by the averted harm from early access to a successful vaccine and weigh the result against the cost of investing in more candidates.

Figure 10.3 Probability of Success in Optimal Vaccine Portfolio



Source: Ahuja et al. 2021, figure A6.

Table 10.3 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 (US$ per capita)	Cost of at-risk capacity (US$ 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 results in table 10.3 show that lower-income countries optimally procure fewer candidates and less capacity per candidate because of their tighter budget constraints. The results 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. By contrast, this analysis allocates the full cost to the investing country, assuming that waiting allows countries to free ride on others' at-risk capacity expenditures.

The recommended portfolio for the average HIC involves three times the number of candidates funded at risk under Operation Warp Speed, the US 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).

Contracting for At-Risk Capacity

Typically, vaccine manufacturers wait until regulatory approval to install substantial capacity, because the investment is wasted if the vaccine fails. As emphasized earlier, 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, and therefore requires 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, if the penalties are set anywhere close to the social cost of delay, they would bankrupt most firms.

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 10.1). 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 lead it to economize on investment costs. Operation Warp Speed involved hybrid contracts of this form (although some developers opted to participate solely 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.

Purchasers should contract for expanded capacity to fulfill procurement orders, not 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, HICs used advance purchase agreements to secure their place at the front of the vaccine queue. In contrast, LMICs did not have the financing tools to invest at risk, which led to inequitable access to vaccines (Thornton, Wilson, and Gandhi 2022). Agarwal and Reed (2022) attribute more than 60 percent of the delay in vaccine delivery to LMICs to those countries' signing of advance purchase agreements later than HICs.

COVAX (COVID-19 Vaccines Global Access) was established to ensure global equitable access to COVID-19 vaccines but faced several challenges. COVAX had two arms: a self-financing arm whereby HICs and middle-income countries (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 enter only 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 the ability of self-funding MICs to purchase vaccines at risk and delayed their contributions to COVAX (Hart, Prizzon, and Pudussery 2021). Consequently, most COVAX commitments occurred after HICs had already signed advance purchase agreements with vaccine developers separate from COVAX.

To address these issues, mechanisms enabling LMICs to borrow for at-risk investment during pandemics should be established through coordination with MDBs. Glennerster, Haria, et al. (2024) detail how MDBs can facilitate greater access to pandemic financing by relaxing restrictive lending criteria, establishing expert advisory panels, creating standardized loan templates and procurement contracts, and developing an optional guarantee mechanism backed by HICs. MDBs or other multilateral organizations such as regional health agencies; Gavi, the Vaccine Alliance; or the World Bank could also help coordinate purchase aggregation, enabling higher-volume capacity expansion contracts, and support a broader portfolio of candidates. This approach would unlock greater up-front financing

compared to donor-reliant schemes, enhancing the capabilities of LMICs to make at-risk investments.

Using Available Capacity Efficiently

During periods of vaccine scarcity, policy makers should optimize allocation strategies to maximize social benefits. Prioritizing high-risk populations, such as those with high mortality and morbidity risks and frontline workers, is essential. Bubar et al. (2021) estimate that vaccinating 20 percent of the population for COVID-19 could reduce mortality by 80 percent. 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; Więcek 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).

CONCLUSION

This chapter 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. Given the public good nature of many of these investments, public funding is important for bridging the gap between social and commercial incentives for pandemic preparedness and response. Mechanisms should pool resources from many public actors. The World Bank's Financial Intermediary Fund frameworks offer a proven model for this approach.[4] Examples of such funds include the Pandemic Emergency Financing Facility, which existed before COVID-19, and the Pandemic Fund, which was created in 2023 (Agarwal 2024; John Hopkins Center for Health Security 2020). Looking ahead, stakeholders can apply similar frameworks to implement the strategies outlined in this chapter.

For pandemic preparedness:

- Invest in advance vaccine R&D for priority pathogens and a broad range of vaccine platforms. Consider the use of both push and pull funding.
- Contract advance vaccine manufacturing capacity. Prioritize making this capacity flexible to different technologies.

For pandemic response:

- Invest in a diverse portfolio of vaccine candidates across many platforms. Account for the correlation of probabilities of success between different candidates.

- Directly incentivize vaccine manufacturing firms to build at-risk capacity.
- Use vaccine capacity efficiently. For example, use the "first doses first" strategy, fractional dosing, or cross-country vaccine exchanges. Target vaccines to populations that are more likely to experience high mortality and morbidity if infected.

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NOTES

1. Our World in Data, "Estimated Cumulative Excess Deaths During COVID-19," https://ourworldindata.org/grapher/excess-deaths-cumulative-economist.
2. Refer to CEPI's "Priority Diseases" web page, https://cepi.net/priority-pathogens.
3. Refer also to the World Bank's web page, "Eastern and Southern Africa's COVID-19 Vaccination Journey," https://www.worldbank.org/en/news/immersive-story/2022/06/30/unlocking-supply-and-overcoming-hesitancy-eastern-and-southern-africa-s-covid-19-vaccination-journey.
4. World Bank, "Financial Intermediary Funds (FIFs)," https://fiftrustee.worldbank.org/en/about/unit/dfi/fiftrustee/overview.

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