Accelerating vaccine innovation for emerging infectious diseases via parallel discovery

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Executive Summary

The COVID-19 pandemic has raised awareness about the global imperative to develop and stockpile vaccines against future outbreaks of emerging infectious diseases. Prior to the pandemic, vaccine development for emerging infectious diseases was stagnant, largely due to the lack of financial incentives for pharmaceutical firms to invest in vaccine research and development (R&D). This R&D requires significant capital investment, most notably in conducting clinical trials, but vaccines generate much less profit for pharmaceutical firms compared to other therapeutics in disease areas such as oncology.

The portfolio approach of financing drug development has been proposed as a financial innovation to improve the risk/return tradeoff of investment in drug development projects through the use of diversification and securitization. By investing in a sizable and well-diversified portfolio of novel drug candidates, and issuing equity and securitized debt based on this portfolio, the financial performance of such a biomedical "megafund" can attract a wider group of private-sector investors.

To analyze the viability of the portfolio approach in expediting vaccine development against emerging infectious diseases, we simulate the financial performance of a hypothetical vaccine megafund consisting of 120 mRNA vaccine candidates in the preclinical stage, which target 11 emerging infectious diseases, including a hypothetical "disease X" that may be responsible for the next pandemic. We calibrate the simulation parameters with input from domain experts in mRNA technology and an extensive literature review, and find that this vaccine portfolio will generate an average annualized return on investment of −6.0% per annum and a negative net present value of −$9.5 billion, despite the scientific advantages of mRNA technology and the financial benefits of diversification. We also show that clinical trial costs account for 94% of the total investment, while vaccine manufacturing costs account for only 6%. The most important factor of the megafund's financial performance is the price per vaccine dose, while other factors, such as the increased probability of success due to mRNA technology, the size of the megafund portfolio, and the possibility of conducting human challenge trials do not significantly improve its financial performance.

Our analysis indicates that continued collaboration between government agencies and the private sector will be necessary if the goal is to create a sustainable business model and robust vaccine ecosystem for addressing future pandemics.

I. Introduction

The extraordinary human, social, and economic losses caused by the COVID-19 pandemic has heightened the global imperative to prepare for the next pandemic by proactively developing novel vaccines against emergent infectious diseases (EIDs). EIDs are a broad class of infectious agents that have either recently appeared for the first time, or whose incidence has rapidly increased in terms of size of the affected population or geographic area (WHO 2014; NIAID 2018). A closely related threat is the reemergence of new variants of a previously identified EID, which may have become more transmissive or pathogenic through genetic mutation or shifting environmental conditions (Morens and Fauci 2020).

Given the dynamic and stochastic nature of EID outbreaks, the most effective strategy to prevent a future pandemic is to develop and stockpile vaccines before an outbreak occurs (Jarrett et al. 2021). A notable example of proactive vaccine development is the Coalition for Epidemic Preparedness Innovations (CEPI), which has a portfolio of 32 vaccine candidates, as of April 14, 2022 targeting COVID-19 and six other priority EIDs (CEPI 2022). Currently, the CEPI portfolio is diversified across 13 different therapeutic mechanisms (e.g., nucleic acid, recombinant protein, etc.) and five different stages of clinical development, from preclinical research to Emergency Use Listing by the World Health Organization (WHO). A similar example of proactive response was the International Coordinating Group (ICG) on Vaccine Provision's stockpiling of 2 million doses of yellow fever vaccines during a global shortage in 2000 (Nathan et al. 2001). In 2019, members of ICG renewed its pledge to maintain a stockpile of 6 million yellow fever vaccine doses (WHO 2020). Stockpiling vaccines well before an epidemic outbreak enables local governments and public health agencies to quickly address the sharp increase in vaccine demand following the outbreak, and facilitates more efficient vaccine allocation (Jarrett, Yang, and Pagliusi 2020).

These considerations—and the remarkable effectiveness of messenger RNA (mRNA) vaccine technology against COVID-19—naturally lead to the question of the financial feasibility of a portfolio of mRNA vaccine candidates diversified across target EIDs, including both local EIDs and pathogens that may cause the next global pandemic.

We address this question in this article by evaluating the financial performance of a hypothetical portfolio of 120 mRNA vaccine candidates targeting 11 EIDs, and determining whether the risk/return profile of such a portfolio might be attractive to private-sector investors. We do this by performing Monte Carlo simulations of the outcomes of hypothetical vaccine development programs that conform to a pre-specified set of parameters, and then examining the statistical distribution of these outcomes. We calibrate the parameters of these simulations using input from domain experts in mRNA technology and an extensive literature review.

We find that this vaccine portfolio yields an average annualized return on investment of −6.0% per annum, and a negative net present value of −$9.5 billion, despite the scientific advantages of mRNA technology and the financial benefits of diversification. We also show that the clinical trial costs of this vaccine portfolio account for 94% of the total investment, while vaccine manufacturing costs account for only 6%. The most important factor of the portfolio's financial performance is the price per vaccine dose, while other factors, such as the increased probability of success due to mRNA technology, the size of the portfolio, and the possibility of conducting human challenge trials—in which healthy subjects are vaccinated and then deliberately infected with the virus to test vaccine efficacy—do not significantly improve its financial performance.

If the goal is to create a sustainable business model for addressing EIDs effectively, our results suggest that a likely pre-requisite will be continued collaboration between the public and private sector.

II. Brief Overview of Vaccine Development

A. *The Past: A Decline in Vaccine R&D Prior to the COVID-19 Pandemic*

Before the COVID-19 pandemic, pharmaceutical firms had pivoted away from vaccine R&D for EIDs, especially for small-scale but highly lethal agents such as the Ebola and Marburg viruses (Kelland 2019). Several important factors were involved in this exodus, including high R&D costs (Gouglas et al. 2018), a low probability of success (PoS) in developing a vaccine candidate from preclinical studies to regulatory approval (estimated to be between 6% and 25% by Davis et al. 2011; Pronker et al. 2015; Project ALPHA 2021; Vu et al. 2022), the low list prices of vaccines (CDC 2022), the uncertainty in vaccine demand and revenues (Glennerster and Kremer 2000; Plotkin et al. 2015), and the lack of sustainable funding from public and private sectors in the absence of an imminent epidemic outbreak. Pharmaceutical firms have a greater financial incentive to develop and manufacture vaccines for common seasonal epidemics such as influenza compared to EIDs, since there is much less uncertainty in the estimated demand of these vaccines (Douglas and Samant 2018).

To illustrate the financial disincentives of vaccine R&D for EIDs more concretely, consider the following simplified model. Assume that the cost of developing a single vaccine candidate, from preclinical studies to regulatory approval or emergency use authorization (EUA), is $200 million, the probability of receiving regulatory approval is 25%, and the target EID occurs with probability 10% in any given year. If an outbreak does occur, we assume 10 million doses are manufactured, with a list price $20 per dose. Under these assumptions, the total expected revenues over the next 20 years (which is the duration of a vaccine patent):

$$25\% \times \$20 \times 10 \text{ million} \times 10\% \times 20 = \$100 \text{ million}$$

is only half of the R&D costs, despite rather optimistic assumptions about these costs and the PoS compared to more realistic estimates found in the literature (Pronker et al. 2013; Project ALPHA 2021; Vu et al. 2022). This simple example also shows that the financial returns of vaccine R&D can be increased if the PoS can be improved due to scientific innovation (e.g., mRNA technology) or financial innovation (e.g., a portfolio approach to parallel vaccine development), or a combination of both.

B. *The Present: A Revolution in mRNA Vaccines*

Vaccine R&D has gone through a scientific revolution during the pandemic, exemplified by mRNA technology, which has demonstrated robust levels of safety, high efficacy, and unprecedented speed in clinical vaccine development (Chaudhary, Weissman, and Whitehead 2021). Once the genetic sequence of a pathogen is known, mRNA vaccine candidates can be designed more quickly than traditional vaccines. In addition, since mRNA vaccines do not require the production of inactivated or attenuated pathogens, they can be manufactured at large scale at higher efficiency, lower cost, and with more robust safety guarantees (Pardi et al. 2018). This technology has the potential to significantly reduce both the cost and the duration of vaccine R&D, enabling a much more rapid response to future EIDs. It is also particularly suited for the development of multiple mRNA vaccines in parallel, as in the portfolio approach taken by CEPI, since different mRNA vaccines may be able to share the same resources and facilities for preclinical studies, clinical testing, and post-approval manufacturing and delivery (Szabó, Mahiny and Vlatkovic 2021).

As an illustration of the success of mRNA vaccine development, consider the mRNA-1273 vaccine developed by Moderna for COVID-19, which was designed in 2 days, tested on the first human volunteer in 63 days, and received an EUA from the US Food and Drug Administration (FDA) in a little over 11 months after the genetic sequence of the original viral strain was first released (Nielson, Dunn and Bendix 2020; Harbert 2020). The R&D period of mRNA vaccines is significantly shorter than the usual 5 to 10 years for traditional vaccine development that were required before the COVID-19 pandemic.

We should note that the stunning successes of mRNA vaccine R&D against the COVID-19 virus was a result not only of technological advances, but also due to the close partnership between the public and private sectors in developing a mature mRNA technology well over a decade before the pandemic (Dolgin 2021), as well as a product of the unprecedented collaboration between the government, regulatory agencies, scientists and clinicians around the world, and the pharmaceutical industry to expedite vaccine development in the midst of the COVID-19 outbreak. As we illustrate in subsequent sections, the continued collaboration and funding support from the public sector is critical to ensuring that vaccine R&D for EIDs can be financially sustainable.

C. *The Future: Parallel R&D for mRNA Vaccines*

mRNA technology brings a novel perspective to vaccine R&D in the portfolio approach used by CEPI by lowering the R&D and manufacturing costs through sharing resources on a common R&D platform, which improves the PoS of vaccine development by the "multiple-shots-on-goal" parallel strategy of discovery. However, a serious challenge to vaccine R&D remains in the lack of sufficient and sustainable funding to support the vaccine R&D pipeline over an extended period, typically multiple years from preclinical research to the regulatory approval of a vaccine, an issue known as the "valley of death" in translational medicine (Butler 2008).

Governments, international agencies, and non-governmental organizations such as the Gates Foundation, Wellcome Trust, and CEPI have made significant contributions to the development of a portfolio of vaccine candidates, but these efforts are not sufficient due to the scale of the challenge (see Section 2 of Vu et al. 2022 for a detailed discussion). The private sector does have sufficient resources to bridge this funding gap but will do so only if the portfolio can generate sufficiently attractive financial returns for its investors.

To illustrate the benefits and challenges of applying the portfolio approach to vaccine R&D, we return to our earlier back-of-the-envelope calculation. Suppose we invest in a portfolio of 10 mRNA vaccines candidates targeting local epidemics. The total cost increases to $10 \times \$200 \text{ million} = \$2$ bilion, while the probability that at least one vaccine candidate receives regulatory approval (assuming statistically independent outcomes) increases substantially to $1 - (1 - 25\%)^{10} = 94.4\%$. The expected revenues over the next two decades becomes:

$$94.4\% \times \$20 \times 10 \text{ million} \times 10\% \times 20 = \$378 \text{ million},$$

a financial loss of $1.6 billion. However, if the vaccine targets an EID which causes a global pandemic with an annual probability 1%, and 1 billion vaccine doses are produced if a pandemic occurs, the expected revenues of the vaccine portfolio increases to:

$$94.4\% \times \$20 \times 1 \text{ billion} \times 1\% \times 20 = \$3.8 \text{ billion}$$

a profit of $1.8 billion, while the expected revenues of investing in one vaccine is only:

$$25\% \times \$20 \times 1 \text{ billion} \times 1\% \times 20 = \$1.0 \text{ billion}$$

which implies a deficit of $1 billion.

These numbers highlight both the advantages and the bottlenecks to applying a portfolio approach to funding vaccine R&D. First, the parallel discovery strategy improves the PoS of vaccine R&D. Even if vaccine development outcomes are correlated to each other, the probability of having an approved vaccine in a portfolio is still higher than the PoS of investing in a single vaccine program (assuming that the pairwise correlations are not equal to 1). An increased PoS can make vaccine R&D profitable for those EIDs capable of

causing global pandemics. However, it is insufficient to generate financial value for vaccines against local EIDs, since the revenues of local vaccine sales is limited. In addition, since the mRNA vaccines share the same therapeutic mechanism, it is reasonable to assume that there will be no significant difference in efficacy between different approved mRNA vaccines for the same EID (as in the case of COVID-19). As a result, there will be considerable cannibalization of demand for vaccines targeting the same EID, since the demand for vaccines will not increase with the number of approved vaccines. Finally, the stochastic nature of EID outbreaks induces large variance in the revenues of vaccine sales. For vaccine R&D aimed at preventing a global pandemic, even though the expected financial return is positive, there is still a significant probability in our illustrative model of $(1-1\%)^{20} = 81.8\%$ that a global pandemic will not occur in the next 20 years, leading to a financial loss of $2 billion.

III. Portfolio Approach to Financing Drug Development

A. *Challenges of the Drug Development Process*

To develop a novel therapeutic candidate from laboratory discovery to regulatory approval, a drug developer needs to conduct multiple clinical trials to test the safety and efficacy of the therapeutic candidate on the target patient population. These clinical trials are conducted in sequence through four stages (preclinical, phase 1, phase 2, and phase 3).[1] Trials in a more advanced phase typically require a larger patient enrollment and a longer time to complete, and are correspondingly more expensive. If the phase 3 clinical trial shows clear safety and efficacy, the drug developer files a new drug application (NDA) to the FDA for regulatory approval. If the FDA approves the NDA, the drug developer may manufacture the drug and collect revenues from drug sales. Sometimes, the FDA may require an additional phase 4 clinical trial after regulatory approval, in order to test the long-term benefits and side effects of the drug on a large patient population.

Despite the tremendous breakthroughs in biomedicine over the past decades, new drug development has become slower, more expensive, and less likely to succeed, causing a

[1] Phase 1 trials typical involve 10 to 50 patients, with the only goal of establishing the safety and the maximum tolerable dose of a given drug candidate. If no significant side effects are encountered in Phase 1, a Phase 2 trial is initiated in which 50 to 500 patients who suffer from the targeted disease are carefully selected to test the drug candidate's efficacy. If significant benefits are detected in that trial, a much larger Phase 3 trial involving thousands of patients is launched to test the drug candidate's efficacy in a broader and less carefully curated sample of patients, and if significant benefits are detected in Phase 3 with no serious side effects, the drug is approved for general use. Because vaccines are administered much more widely than other drugs, and given to healthy subjects rather than only those with a given disease, the regulatory hurdle for determining safety and efficacy is considerably higher—a typical Phase 3 trial for a vaccine involves 30,000 subjects (as in the case of the COVID-19 vaccines), hence the outsized costs of Phase 3 trials. See Lo and Chaudhuri (2022, Ch. 8) for further details.

significant funding gap for early-stage drug development programs. The lack of sufficient funding for translational biomedical R&D is due to several institutional features of drug development, including a low PoS, a long investment horizon, high clinical trial costs, and a high cost of capital, especially for small biotechnology companies which do not have marketed drugs that generate revenues and must rely on external financing to sustain its R&D pipeline.[2] The declining efficiency of translating scientific discoveries in research laboratories into novel products has also been observed in other industries in the US (Arora et al. 2020).

B. *Advantages of Financing Vaccine R&D via the "Vaccine Megafund"*

To address the challenge of funding translational medicine, Fernandez et al. (2012) proposed a novel financing vehicle, the biomedical "megafund", which invests in a sizable portfolio of drug candidates diversified across different clinical stages and therapeutic areas. Using financial engineering techniques such as securitization, the authors show that the risk/return profile of the megafund is attractive to a wide group of investors. Originally proposed to finance oncology drug development, the megafund model was subsequently applied to other disease areas, including orphan diseases (Fagnan et al. 2014), Alzheimer's disease (Lo et al. 2014), pediatric cancer (Das et al. 2018), ovarian cancer (Chaudhuri et al. 2019), glioblastoma (Siah et al. 2021) and vaccines against EIDs (Vu et al. 2022). It is currently being applied by the National Brain Tumor Society (NBTS) to finance novel drug candidates to treat glioblastoma (NBTS 2021).

The key idea behind the megafund is to reduce the financial risks of its assets and improve its expected returns by raising capital to acquire a portfolio of vaccine candidates, issuing equity and securitized debt with different risk/return profiles that appeal to a wide range of private-sector investors. The vaccine candidates are used as collateral, and the revenues generated by future vaccine sales are used to service its debt and interest payments. The residual equity is then distributed among its equity holders. If the future cash flows are insufficient to service the debt, the megafund declares bankruptcy and the collateral is transferred to its bondholders.

The main advantage of portfolio diversification is that by increasing the PoS of having at least one approved drug candidate, the megafund is able to lower the financial risks and attract large amounts of capital from the bond market, whose size is much larger than the venture capital, public equity, or private equity market (SIFMA 2021). In 2020, a total of $12.2 trillion worth of fixed income securities were issued in the US, compared to $390 billion of equity. In the same year, the total private placement was $330.1 billion in the US,

[2] See Lo and Thakor (2021) for a systematic review of financing issues in the biopharma industry.

of which $314.4 billion was in the form of debt and $15.8 billion in the form of equity (SIFMA 2021).

C. *Evaluating the Financial Performance of the Vaccine Megafund*

In the vaccine megafund simulation analysis of Vu et al. (2022), the financial performance of a vaccine-focused portfolio is extremely unattractive to for-profit investors, with an expected annualized return of −61% and a standard deviation (SD) of 4%. Multiple factors lead to this negative financial return, including a low PoS of vaccine trials, high clinical trial costs, and limited revenues from vaccine sales. Based on these findings, the authors propose several strategies to finance the vaccine megafund, including higher vaccine prices, public sector funding, and a novel subscription model in which subscribers would pay annual fees for priority access to the vaccines in case of future outbreaks.

In this paper, we extend the work of Vu et al. (2022) in several important ways. First, Vu et al. simulated vaccine trial outcomes stochastically, but used a single fixed expected value to estimate the annual profit for approved vaccines. We implement a more realistic simulation framework in which the entire value chain of vaccine development, manufacturing, and sales is simulated under the stochastic occurrence of EID outbreaks. The uncertainty in future EID outbreaks increases the variance of megafund cash flows, which directly impacts its risk/return profile. In addition, we use improved PoS estimates of mRNA vaccines to adjust the cash flows of the megafund, and calibrate the cost structure of mRNA vaccine manufacturing with input from domain experts and an extensive literature review. Finally, while Vu et al. (2022) mainly focused on the annualized return of the vaccine megafund, we systematically investigate a wide spectrum of metrics to gauge its financial and social impact, such as the net present value and the number of EID outbreaks prevented. We also provide a detailed breakdown of the cost structure for the vaccine megafund to identify the main drivers of its financial performance.

The risk/reward profile of the vaccine megafund hinges on the scientific and business expertise of fund managers to select promising drug candidates and diversify the portfolio (Siah et al. 2021). For a real-world vaccine portfolio such as CEPI's, active portfolio management is critical, given budget constraints, to select a limited number of vaccine candidates. Gouglas and Marsh (2019) apply multi-criteria decision analysis to select promising vaccine candidates for the CEPI portfolio in the context of multiple trade-offs and heterogeneous stakeholder preferences. In a subsequent study (Gouglas and Marsh 2021), the authors apply portfolio decision analysis to optimize the investment of CEPI in 16 vaccine technology platforms. Ahuja et al. (2021) analyzed the optimal investment strategy of vaccine manufacturing capacity for countries with different socioeconomic characteristics.

While we fully recognize the importance of active portfolio management in improving the financial performance of a vaccine megafund, we do not impose exogenous budget constraints or perform any portfolio optimization in our simulation analysis since our goal is to understand the relationships between the investment and revenues of the vaccine

megafund and its endogenous factors such as the improvement in the PoS of mRNA vaccine development, the cost structure of mRNA vaccine manufacturing, the size of the megafund portfolio, and the possibility of conducting human challenge trials to expedite vaccine clinical trials.

IV. Simulation Methods

A. Vaccine Megafund Portfolio

We simulate the financial performance of a large portfolio of mRNA vaccine candidates using an adaptation of Vu et al.'s (2022) portfolio structure and probability of outbreak P_a of each EID, as shown in **Table 1**. We also include 10 vaccine candidates which target "disease X", the unknown pathogen which may cause the next pandemic, in accordance with the updated CEPI portfolio (CEPI 2022). We assume that disease X has a low annual probability of outbreak $P_a = 1\%$, and the number of infected cases will be 400 million, close to that of COVID-19.

Table 1. Portfolio for simulated mRNA vaccine megafund (CEPI, 2022; Vu et al., 2022).

Targeted Emerging Infectious Disease (EID)	Number of Vaccine Candidates (N_{vac})	Annual Probability of Outbreak (P_a, in %)	Average Number of Infections (n_I)
Disease X	10	1.0	400,000,000
Chikungunya	16	10.8	523,600
Zika Virus	18	4.3	500,062
Lassa Fever	7	100.0	300,000
Rift Valley Fever	3	10.5	79,414
SARS-CoV-1	2	7.1	8,098
West Nile Virus	23	10.0	500
MERS-CoV	8	40.0	436
Crimean-Congo Haemorrhagic Fever	7	12.5	320
Nipah Virus	20	15.8	136
Marburg Virus	6	12.0	75

B. Vaccine Clinical Trials

We use the simulation framework in Siah et al. (2021) to model the correlated outcomes of vaccine clinical trials. The assumed values of the simulation parameters of a vaccine clinical trial are summarized in **Table 2**. The simulated trial outcomes depend on two critical sets of parameters. First, the PoS to reach each stage in the clinical development process is estimated using historical industry average values (Project ALPHA 2021; Vu et al. 2022). In addition, since the mRNA vaccine for COVID-19 is known to induce humoral immune protection by producing neutralizing antibodies (Jain et al. 2021), we assume that mRNA

vaccines will have a higher PoS for the six EIDs in the portfolio whose correlates of protection are also neutralizing antibodies (Chikungunya virus, SARS-CoV-1, Marburg virus, Rift Valley Fever, Nipah virus, and Zika virus). To reflect the increased PoS due to mRNA technology for these diseases, we multiply the historical PoS by a technology factor α_{tech}. We set α_{tech} to 1.2 in the baseline model, which reflects a 20% increase in the PoS over the industry average. We do not increase the PoS for the other five diseases with cellular or unknown immune responses, including disease X. We vary α_{tech} in the sensitivity analysis to gauge the effect of increased PoS on financial performance.

Table 2. Simulation parameters for vaccine clinical trials.

Parameter	PRE to P1	P1 to P2	P2 to P3	P3 to EUA	Source
Probability of Success (PoS, in %)	60.0	83.6	65.8	80.9	Vu et al. 2022 Project ALPHA 2022 Wong et al. 2019
Duration (months) Standard clinical trial	18.0	24.0	18.0	14.0	Vu et al. 2022 Berry et al. 2020
Development cost ($M) Standard clinical trial	26.0	14.0	28.0	150.0	Gouglas et al. 2018
Duration (months) Human challenge trial	/	/	/	8.0	Berry et al. 2020
Development cost ($M) Human challenge trial	/	/	/	12.5	

Abbreviations — PRE: preclinical phase, P1: Phase 1, P2: Phase 2, P3: Phase 3, EUA: Emergency Use Authorization.
Note — We assume that a vaccine receives EUA once it successfully completes phase 3 clinical trial. Furthermore, we assume human challenge trials are only applicable to phase 3.

In addition, the correlations between vaccine trial outcomes play a major role in the simulation outcomes. If two vaccine trial outcomes are highly correlated, e.g., due to the same target pathogen or therapeutic mechanism, they are more likely to simultaneously succeed or fail, which leads to lower diversification benefits from the portfolio, greater variance in the cash flows of the megafund, and thus greater overall financial risk. Using the input of domain experts in mRNA technology, we construct a biologically motivated metric to estimate these correlations.

Specifically, we propose a novel distance metric d_{ij} between pathogens i and j, defined as the average of similarity scores based on four biological factors: taxonomy, qualitative features (e.g., type of disease vector, strand direction, nucleic acid topology), quantitative features (e.g., number of strands, total genome size), and the edit distance of protein sequences. Simply put, the more similar two pathogens are to each other, the more correlated we assume their trial outcomes will be. This value of d_{ij} is normalized between 0 and 1, with d_{ij} closer to 0 if pathogens i and j are more biologically similar, and $d_{ij} = 0$ if

they are identical. Given the values of d_{ij}, a natural way to define the correlation ρ_{ij} between the outcomes of vaccine trials targeting pathogens i and j is $\rho_{ij} = 1 - d_{ij}$, i.e., the vaccine trial outcomes have a higher correlation if their target EIDs are more biologically similar, and vice versa.

Figure 1 shows the heatmap of ρ_{ij} between each pair of pathogens, excluding disease X (which we assume to be independent of the other pathogens, to reflect its a priori unknown biological properties). The correlation matrix ρ_{ij} defined this way is positive definite (PD) in our calibration, although it is not guaranteed to be PD in general and may need to be transformed into a PD matrix by an appropriate method (Qi and Sun 2006).[3] Since this metric does not specify the correlation between two vaccine trials targeting the same pathogen, we assume this correlation to be 0.8, which is higher than the maximum correlation of 0.64 across different pathogens (**Figure 1**). To gauge the impact of correlation on the financial performance, we vary the assumed values of correlation in the sensitivity analysis.

Fig. 1. Estimated correlations between vaccine candidates. We assume that vaccine candidates for disease X are uncorrelated with vaccines for the other diseases and that vaccine candidates targeting the same disease have a 0.8 correlation.

	Chikun.	SARS	MERS	Marburg	RVF	Lassa	Nipah	CCHF	WNV	Zika
Chikun.	1.00	0.30	0.30	0.37	0.27	0.39	0.38	0.29	0.38	0.33
SARS	0.30	1.00	0.58	0.32	0.21	0.25	0.28	0.26	0.29	0.28
MERS	0.30	0.58	1.00	0.33	0.20	0.25	0.28	0.26	0.29	0.28
Marburg	0.37	0.32	0.33	1.00	0.27	0.37	0.46	0.37	0.36	0.35
RVF	0.27	0.21	0.20	0.27	1.00	0.48	0.29	0.52	0.27	0.26
Lassa	0.39	0.25	0.25	0.37	0.48	1.00	0.36	0.35	0.40	0.40
Nipah	0.38	0.28	0.28	0.46	0.29	0.36	1.00	0.32	0.39	0.39
CCHF	0.29	0.26	0.26	0.37	0.52	0.35	0.32	1.00	0.29	0.28
WNV	0.38	0.29	0.29	0.36	0.27	0.40	0.39	0.29	1.00	0.64
Zika	0.33	0.28	0.28	0.35	0.26	0.40	0.39	0.28	0.64	1.00

[3] Positive definiteness is a mathematical property that guarantees the positivity of the variance of a weighted average of random variables. Given that the risk (as measured by variance) of a portfolio is never negative, it is important to impose this property on any correlation matrix otherwise, nonsensical numerical results like negative risk may occur.

C. Human Challenge Trials

Given the demonstrated safety and efficacy of mRNA vaccines for COVID-19, it is conceivable that human challenge trials (HCTs) may be ethically justified for mRNA vaccine candidates in our portfolio. The HCT is an efficient yet highly controversial clinical trial design, in which healthy participants with no previous exposure to a disease are deliberately infected with the live pathogen in a controlled clinical environment (e.g., an isolated ward in a hospital). The controlled setting of a HCT allows much more precise and rapid testing of the safety and efficacy of vaccines with a smaller number of trial participants than standard vaccine trials. As a result, an HCT may significantly reduce the cost and duration of clinical trials and lead to expedited regulatory approval of effective vaccines. In a simulation analysis, Berry et al. (2020) showed that conducting an HCT for COVID-19 vaccines may significantly reduce the number of infected and deceased patients in the US compared to other clinical trial designs, provided that the vaccine is effective and the HCT is initiated in a timely manner.

Although conducting an HCT is in principle more efficient in time and cost than traditional vaccine trials, in practice it still faces multiple challenges. First and foremost, the ethical justification of deliberatively injecting healthy participants with a live EID agent is highly controversial, due to the absence of well-established ethical guidelines to specify the conditions under which an HCT may be deemed ethical. In addition, HCTs require more time and resources during their initial preparation stage (e.g., identifying and manufacturing low-risk virus strains, identifying low-risk populations, and establishing an acceptable HCT protocol with regulators). As a result, the first HCTs for COVID-19 were initiated after the mRNA vaccine candidates had already received EUA from the FDA in US and Europe (Callaway 2020; Rapeport et al. 2021).

Although we recognize the ethical and practical challenges of HCTs, we model an idealized scenario when an HCT is authorized for mRNA vaccine R&D and may be conducted in an ethical and timely manner. We use the binary variable HCT_i to denote whether an HCT is authorized by the FDA during an outbreak of disease i (i.e., $HCT_i = 1$ with probability p_{HCT} if the HCT is authorized by the FDA, and $HCT_i = 0$ with probability $1 - p_{HCT}$ if otherwise). If $HCT_i = 1$, we use the reduced cost and duration of HCT (rows 4 and 5 of **Table 2**) instead of the corresponding values of standard trials. We assume $p_{HCT} = 0$ in the baseline model (i.e., no HCT is conducted) and gauge the effect of p_{HCT} in the sensitivity analysis.

D. Vaccine Manufacturing and Supply Chain

The cost structures of mRNA vaccine manufacturing and its supply chain are key to simulating the cash flows of the megafund. Since mRNA vaccine manufacturers do not disclose this information, we use publicly available estimates in the literature (Kis et al. 2021; Kis and Rizvi 2021) to calibrate these cost structures. The line-item budget of mRNA

vaccine manufacturing is summarized in **Table 3**. The main factor driving the manufacturing costs is the amount of mRNA raw material needed to produce the target number of vaccines. We assume that each production line consists of a bioreactor with a 30-liter working volume and mRNA titer 5g/L (Kis and Rizvi 2021). We also assume that each vaccine dose contains 65μg of mRNA, the average of the Pfizer/BioNTech and Moderna vaccines for COVID-19.

Table 3. Cost structure of mRNA vaccine production. (Kis et al. 2021; Kis and Rizvi 2021)

Category	Item	Unit Cost (USD)	Quantity
Fixed cost	Production line	58 million	1 bioreactor of 30L working volume
Variable costs	Raw materials	456.6 million per (year · production line)	29,162 grams of mRNA per production line per year
	Consumables	150 million per (year · production line)	
	Labor	20 per hour	113,186 labor hours per production line per year
	Quality control	10 per hour	
	Fill-and-finish	0.27 per dose	10-dose vials
	Lab, utility, waste management, etc.	<1% total cost	Not modeled here

Using the estimates in **Table 3**, the variable cost of producing each mRNA vaccine dose is $1.60. We assume that each local EID outbreak requires 10 million vaccine doses. It takes 8.1 days to produce the mRNA needed with one production line, and an additional 4 to 5 weeks to perform quality control for each batch produced. The total manufacturing cost is $16 million if one uses the existing production line, and $75 million if one builds a new production line. Similarly, we assume that a disease X pandemic requires 1 billion vaccine doses. It takes 81.4 days to produce the mRNA needed with 10 production lines. The total cost is $1.6 billion with existing production lines, and $2.2 billion with new ones. Furthermore, we assume that the variable cost of delivering each vaccine dose in the supply chain is $1.00 (of the same order of magnitude as the manufacturing cost). We make a conservative assumption about the supply chain cost due to the lack of publicly available estimates in the literature. Our simulation results show that the supply chain costs constitute only 2% of total costs (**Figure 4**), so the financial performance is not sensitive to the detailed structure of supply chain costs, as long as it does not exceed $1.00 per dose by an order of magnitude.

To estimate the revenues generated by vaccine sales, we use the list prices of mRNA vaccines for COVID-19. As of October 26, 2021, the Pfizer/BioNTech vaccine is priced at $24.00 per dose in the US, and the Moderna vaccine at $15.00 per dose (Jimenez 2021). We

assume that the price per vaccine dose is $20.00. This is likely to be an underestimate, since it is below the prices of all adult vaccines listed in the vaccine price list of Centers for Disease Control and Prevention except for influenza vaccines (CDC 2022). To gauge the impact of the list price of vaccines, we vary the price in the sensitivity analysis.

E. Simulating Correlated Clinical Trial Outcomes

The key to simulating the financial performance of the vaccine megafund is to simulate the correlated binary outcomes of vaccine clinical trials. Vaccine clinical trials have five development phases (preclinical, phase 1, phase 2, phase 3, and emergency use authorization, or EUA), and need to successfully complete the first four phases in sequence before receiving the EUA. As in previous biomedical megafund studies (e.g., Siah et al. 2021), we use the technique proposed by Emrich and Piedmonte (1991) to simulate the correlated outcomes of vaccine clinical trials in each phase. A detailed description of our method is provided in **Section A** of the **Supplementary Materials**.

F. Overview of the Simulation Framework

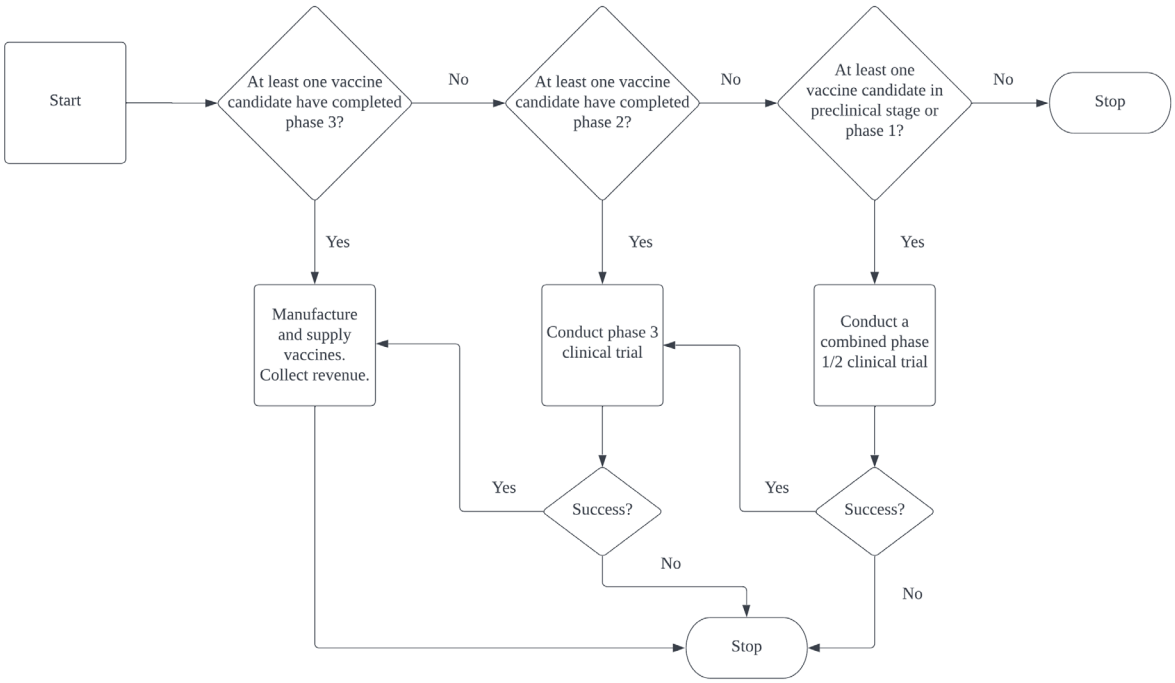
At the initial time $t = 0$, all vaccine candidates enter the preclinical stage. For simplicity, we assume that the development costs of each phase are incurred at the start of the phase. In each subsequent year from $t = 1$ to $t = T$, we simulate whether any EID outbreaks (including the disease X pandemic) occur in year t. In the absence of any outbreaks, we develop each vaccine candidate (except the ones for "disease X") from the preclinical stage to the completion of phase 2, assuming the cost and timeline of a standard clinical trial (rows 2 and 3 of **Table 2**). We do not initiate a large-scale phase 3 clinical trial unless an outbreak has occurred, since there will not be enough infected subjects with which to test vaccine efficacy until then. From a financial perspective, this also reduces the significant late-stage clinical trial costs compared to the simulation analysis of Vu et al. (2022).

If an EID outbreak occurs in year t, we assume that one of the four scenarios below will occur (**Figure 2**):

1. At least one vaccine candidate targeting the disease has successfully completed a phase 3 trial during a previous outbreak of the same disease and received approval or an EUA from the FDA. We manufacture the vaccines, supply them to the point of distribution, and collect the revenues from the vaccine sales.
2. At least one vaccine candidate targeting the disease has successfully completed a phase 2 trial. We initiate the phase 3 clinical trial. If the phase 3 trial is successful, the vaccine receives an EUA from the FDA. We manufacture and supply the vaccines, and collect the revenues from the vaccine sales.

3. At least one vaccine candidate for the epidemic is in the preclinical or phase 1 stage. We initiate an accelerated phase 1/2 trial, which costs $28 million (the same as a standard phase 2 trial) and completes in 3 months, followed by a standard phase 3 trial, which completes in 14 months. If the phase 3 trial is successful, the vaccine receives an EUA. We manufacture and supply the vaccines, and collect the revenues.
4. No vaccine candidates for the disease have previously completed a phase 3 trial or remain in the R&D pipeline. In this case, no cash flows are generated, since all vaccine candidates have failed in the clinical trial process.

Fig. 2. Overview of the simulation framework in the event of an epidemic outbreak.



We simulate an investment horizon of $T = 20$ years, which includes 5 years for standard clinical trial development from the preclinical phase to the completion of phase 2, and 15 years for the remaining duration of the vaccine patent. We compute the financial performance and social impact of the vaccine megafund at the end of the 20-year horizon.

V. Results

There are four key observations and insights from the results of the simulation analysis:

- Despite the improved PoS of mRNA vaccines, the vaccine megafund does not generate financial value for the investors, and is not a financially self-sustainable business model for the pharmaceutical industry.
- From the perspective of public policy, the vaccine megafund will require $9.5 billion funding from the public sector at its initiation to generate positive financial value for investors.
- The main bottlenecks of the financial performance are the limited and uncertain revenues generated by the vaccine sales and the significant costs of clinical trials, which account for 94% of the total investments in the megafund.
- The vaccine megafund generates significant social benefits by preventing, on average, 31 epidemic outbreaks out of 45 over the next two decades. In addition, there is a 66% probability that the next "disease X pandemic" will be prevented by vaccines developed from the megafund portfolio.

The performance of the baseline portfolio is summarized in **Table 4**. We find that this portfolio has a negative expected annualized return $E[R_a] = -6.0\%$ (standard deviation $SD[R_a] = 6.7\%$) and a negative expected net present value (NPV) of –$9.5 billion (standard error SE $13 million). The vaccine megafund does not generate positive financial value for its investors, since the revenues generated by the vaccine sales ($7.5 billion on average) is insufficient to recover the investment in clinical trial development and vaccine manufacturing ($17.7 billion on average). However, the financial value to private-sector investors does not capture the benefits generated by the megafund to society. On average, 45 infectious disease outbreaks will occur in the simulation period, 31 of which will be prevented or contained by vaccines developed from the portfolio. In addition, there is a 66% probability that vaccines in the portfolio will prevent the next "disease X pandemic," should one occur. Using even the most conservative "quality adjusted life year" estimate (e.g., Neumann, Cohen, and Weinstein, 2014), the lives saved and socioeconomic losses avoided by the vaccines far exceed the negative financial value of the megafund.

Table 4. Performance of the baseline portfolio computed with 100K Monte Carlo simulations.

Metric	Mean	Standard Error	Standard Deviation	Median	25% Qt.	75% Qt.
Annualized Return (R_a)	–6.0%	0.021%	6.7%	–5.7%	–7.4%	–4.4%
Net Present Value (NPV, USD, billion)	–9.5	0.013	4.1	–9.9	–12.1	–7.4

Investment (USD, billion)	17.7	0.017	5.3	17.8	14.0	21.4
Revenues (USD, billion)	7.5	0.024	7.7	5.8	3.4	7.0
Profit (USD, billion)	−10.0	0.023	7.4	−11.5	−14.9	−7.5
Number of Prevented Epidemics (N_{ep})	31	0.04	13	34	19	42

Note — NPV is computed with an annual discount rate r=10%. The standard deviation of preclinical trial cost is zero since the megafund invests in the preclinical trials of all 120 vaccine candidates at the initial time 0.

The distribution of key performance metrics of the megafund is displayed in the histograms of **Figure 3**. We find that, although R_a and NPV are negative in most simulations, there is a 9.8% probability that $R_a > 0$, and a 3.1% probability that $\text{NPV} > 0$. In addition, the distribution of megafund investments is smooth with a single peak (i.e., this is a unimodal distribution), while the distribution of revenues has two peaks (i.e., a bimodal distribution): although revenues are mostly likely to fall below $10 billion, there is a sizeable probability that revenues exceed $20 billion. The latter corresponds to the rare scenarios when a disease X pandemic occurs, generating revenues of $20 billion from vaccine sales. This bimodality of revenues leads to significant variance in the annualized return and NPV of the megafund.

To gain additional insight into the major costs that reduce the financial performance of the megafund, we present a breakdown of megafund investment in **Figure 4**, and find that the costs of clinical trials constitute 94% of the total cost, with phase 3 trials alone accounting for 59%. The net cost of vaccine manufacturing and its supply chain constitute only 6% of the total cost, and the higher efficiency of mRNA vaccine manufacturing is not sufficient to generate financial profits for the investors. Our finding is consistent with the "valley of death" in financing translational medicine (Butler 2008), in which the main bottleneck is the risk associated with the uncertainty of revenues at the early stages of drug discovery versus the enormous cost of clinical trials. Even with more efficient vaccine manufacturing technologies and supply chain designs, the significant cost of clinical trials still prevents the vaccine megafund from generating positive financial value to its investors.

Fig. 3. Histograms of key performance metrics of vaccine megafund. (A) Annualized return R_a. (B) Net present value (NPV). (C) Number of epidemics prevented N_{ep}. (D) Total investment. (E) Total revenue. (F) Net profit.

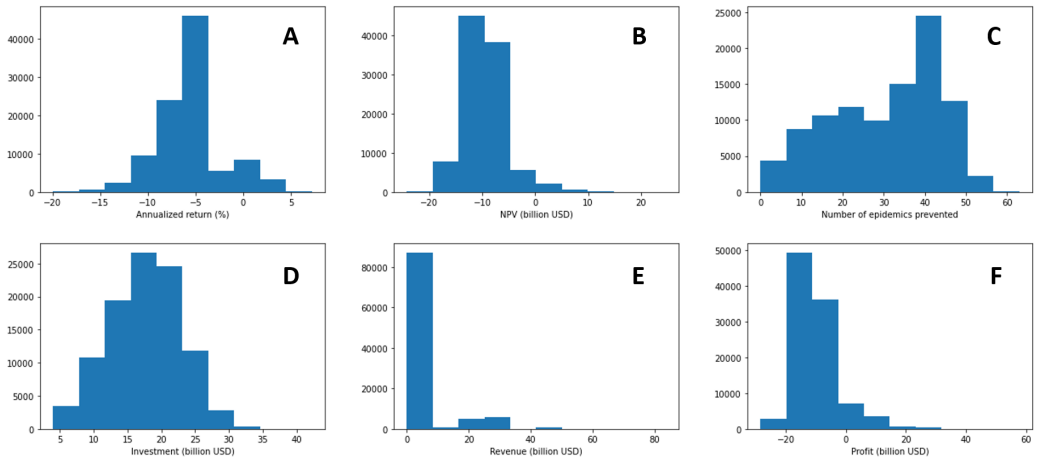
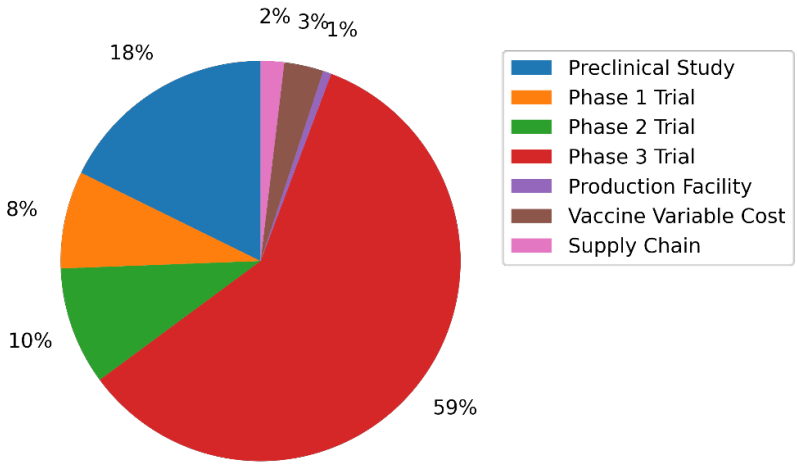


Fig. 4. Breakdown of cost structure of the vaccine megafund. Clinical trial costs constitute 94% of all costs, while manufacturing costs constitute only 6%.



VI. Sensitivity Analysis

The simulated financial performance of the vaccine megafund hinges on the assumed values of key simulation parameters calibrated using inputs from mRNA domain experts and estimates from the literature. We perform a sensitivity analysis to test the robustness of our simulation results against the assumed parameter values. The results are

summarized in **Table S1** and discussed in detail in **Section B** of the **Supplementary Materials**. We highlight the key findings for public policy consideration in this section.

A. Vaccine Price

The price per vaccine dose π is the most important driver of financial performance. To achieve a positive expected annualized return (or a positive NPV), the list price per vaccine dose needs to be set above \$69.00 (or in the case of positive NPV, \$78.00), much higher than the assumed price of \$20.00. While prices above \$100.00 for a vaccine dose are not uncommon in the US (CDC 2022), high vaccine prices are a major obstacle for low-to-middle income countries to conduct massive vaccine campaigns and may increase vaccine hesitancy.

B. Improved Probability of Success of mRNA Vaccines

Increasing the PoS of mRNA vaccine clinical trials leads to higher investment in clinical trials and a larger number of vaccines approved by the FDA. However, due to cannibalization between vaccines targeting the same EID and the stochastic nature of EID outbreaks, the ultimate revenues increase by a much smaller amount than the investment. The net effect is that the expected NPV decreases with the PoS while the expected annualized return becomes less negative (due to higher increase in investment than revenue).

C. Correlations between Clinical Trial Outcomes

Increasing the correlation between vaccine trial outcomes decreases both the expected return and expected NPV of the vaccine megafund, while significantly increasing the volatility of the annualized return, since the portfolio becomes less diversified.

D. Human Challenge Trials

Increasing the probability p_{HCT} of conducting an HCT for vaccine clinical trials during an EID outbreak reduces the cost and duration of clinical trials, since a smaller group of subjects is enrolled. While the expected annualized return and NPV both increase with p_{HCT}, they still remain negative. We conclude that the HCT design is insufficient to generate positive financial value.

E. Megafund Portfolio Size

Increasing the number of vaccine candidates for each EID by 50% increases both the investment in clinical trials and the likelihood that at least one vaccine candidate for the EID will be approved by the FDA. While the expected investment increases by almost 50%, the expected revenues only increases by about 5%, due to cannibalization and stochastic occurrence of EID outbreaks. Decreasing the number of vaccine candidates for each EID

improves the expected annualized return and NPV, but both remain negative. Furthermore, the number of EID outbreaks prevented decreases from 31 to 27, resulting in a greater loss to society that is not captured by our financial analysis.

VII. Discussion

Our analysis illustrates three major challenges to the portfolio approach of financing mRNA vaccines for EIDs. First, the portfolio approach reduces the supply side risk of vaccine R&D by increasing the probability of having at least one effective vaccine against an EID. However, it does not mitigate the *demand side risk* in the revenues generated by vaccine sales since vaccine demand is mainly determined by the natural occurrence of EID outbreaks. The stochastic nature of outbreaks limits the revenues generated by the approved vaccines, unless we increase the list price to $78.00 per dose. But with such a high list price, local governments and populations may not be able to afford the vaccines, which further reduces their demand and revenues. In addition, since mRNA vaccines share the same therapeutic mechanism, it is reasonable to expect that there will be no differentiated efficacy of different vaccines against the same disease. As a result, there will be significant market cannibalization between approved vaccines since the total revenues of vaccine sales will not increase if there is more than one approved vaccine. Finally, the significant costs of clinical trials constitute 94% of megafund investment and severely limit its financial performance. One potential solution is to use more cost-effective clinical trial designs such as adaptive trials (Berry 2011) and platform trials (Woodcock and LaVange 2017), which simultaneously test multiple vaccine candidates using a shared control arm. These innovative trial designs have been shown to significantly reduce clinical trial costs and expedite the R&D process for glioblastoma therapeutic candidates (Siah et al. 2021). In addition, they do not elicit the ethical controversies of human challenge trials.

We also note that the primary goal of the vaccine megafund is to prevent future EID outbreaks and minimize the overall burden of disease. In light of this goal, our simulation assumes that we invest in clinical trials for all vaccine candidates simultaneously without optimizing for financial performance using sophisticated investment strategies (Gouglas and Marsh 2021) or financial engineering techniques such as dynamic leverage (Montazerhodjat et al. 2016). For example, if three vaccine candidates for the same infectious disease successfully complete their phase 2 trials, we may instead first conduct phase 3 trials for two vaccine candidates, initiating the phase 3 trial for the third vaccine only if the first two have failed. This will reduce the costs of late-stage clinical trial development and improve its financial value. However, the increased financial value must be weighed against potential delays in FDA approvals of life-saving vaccines. A robust and multi-criteria optimization framework is needed to ensure that their value to society is not compromised by optimizing financial returns for the investors.

VIII. Conclusion

Despite an increased probability of success due to mRNA vaccine technology, diversification across a large number of vaccine candidates, and the potential benefits of conducting human challenge trials, the vaccine megafund model does not generate positive financial value for private-sector investors. The three bottlenecks of its financial performance are the limited revenues of vaccine sales, the cannibalization of approved vaccines for the same infectious disease, and the significant costs of late-stage clinical trials. Nonetheless, the vaccine megafund does generate tremendous social value by preventing future epidemic outbreaks; if endowed with public sector funding of $10 billion, it may also generate positive financial value for investors.

Our analysis indicates that continued collaboration between government agencies and the private sector will be necessary if the goal is to create a sustainable business model and robust vaccine ecosystem for addressing future pandemics. Strategies such as stockpiling vaccines for the most dangerous EIDs, putting in place advance market commitments or subscription fees to purchase/reserve mass quantities of vaccines in case of outbreaks, creating government-sponsored manufacturing and distribution facilities that can supplement private-sector resources, and providing limited government guarantees to investors funding vaccine programs for a pre-specified list of priority diseases may all play a role in helping us reduce the impact of, or even prevent, future pandemics.

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Accelerating vaccine innovation for emerging infectious diseases via parallel discovery: Supplementary Materials

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A. Simulating Correlated Clinical Trial Outcomes

The key to simulating the financial performance of the vaccine megafund is to simulate the correlated binary outcomes of vaccine clinical trials. As in the previous biomedical megafund simulations (e.g., Siah et al. 2021), we use the technique proposed by Emrich and Piedmonte (1991) to simulate correlated Bernoulli variables, e.g., variables that can only take the values 0 or 1, representing the failure or success of a clinical trial.

Vaccine clinical trials have five development phases (preclinical, phase 1, phase 2, phase 3, and emergency use authorization, or EUA), and need to go through four phase transitions before receiving the EUA. Let the Bernoulli variable $B_{ij} \in \{0,1\}$ denote whether vaccine candidate i has entered the development phase j, with $j \in \{0,1,2,3,4\}$. Initially all vaccines

are in preclinical stage, i.e., we set $B_{i0} = 1$. If the vaccine trial advances from phase $j-1$ to j where $j \in \{1,2,3\}$, we set $B_{ij} = 1$. If the vaccine receives EUA from the FDA, we set $B_{i4} = 1$.

To simulate the correlated phase transitions of clinical trials from phase j to $j+1$, we first draw a vector of multivariate standard normal variables $\varepsilon_j = [\varepsilon_{1j}, \ldots, \varepsilon_{nj}]$ with independent components ε_{ij}, where the length n is the number of vaccines in the portfolio. Next, we compute $z_j = \Sigma^{1/2}\varepsilon_j$ where $\Sigma^{1/2}$ is the Cholesky decomposition of the correlation matrix Σ (**Figure 1**). The resulting vector z_j then follows a multivariate normal distribution with zero mean and covariance matrix equal to Σ, key to our simulation. Given the probability of success p_j for phase transition from j to $j+1$ (**Table 2**), we can now simulate the binary clinical trial outcome as:

$$B_{i,j+1} = \begin{cases} 1, & z_{ij} > \alpha_j \\ 0, & z_{ij} \leq \alpha_j \end{cases} \#(1)$$

where z_{ij} is the i-th component of z_j, $\alpha_j = \Phi^{-1}(1-p_j)$, and Φ^{-1} is the inverse cumulative distribution function of the standard normal variable. The clinical trial outcomes B_{ij} generated this way are positively correlated in each phase transition and used in our financial calculations.

In each Monte Carlo simulation, if we observe that $B_{ij} = 0$, the clinical trial for vaccine i terminates in phase j and all subsequent B_{ik} (with $k > j$) are set to 0. If we observe $B_{ij} = 1$, the megafund incurs the clinical trial cost for phase j. If an epidemic outbreak occurs and there is at least one vaccine i with $B_{i4} = 1$ (i.e., it has received EUA), we manufacture the vaccine and collect the revenues from vaccine sales.

B. Sensitivity Analysis

We perform a sensitivity analysis to test the robustness of the simulation results against the assumed parameter values. The results are summarized in **Table S1**.

a. Vaccine Price

The price per vaccine dose π is the key driver of the financial performance. In the baseline model, we assume $\pi = \$20.00$, where both the annualized return and NPV are negative. Increasing π to \$69.00 (row 2 of **Table S1**) achieves the breakeven point for the annualized return. Increasing π further to \$78.00 (row 3 of **Table S1**) achieves the breakeven point for NPV. Assuming $\pi = \$100.00$ (row 4 of **Table S1**), the megafund generates a small but positive expected annualized return of 1.9%, with a volatility of 7.2% and an expected NPV of \$3.6 billion (SE \$55 million). Such a high list price of \$100.00 per vaccine dose is not unusual in the US. As of April 14, 2022, thirteen common adult vaccines have list prices above \$100.00 in the US (CDC 2022). However, these may be impossible to afford in low-to-

middle income countries, and may even increase vaccine hesitancy among the affected population.

b. Improved Probability of Success of mRNA Vaccines

To test whether the increased PoS of mRNA vaccines leads to improved financial performance, we multiply the PoS of vaccine trials for six diseases by the technology factor α_{tech} to reflect the higher efficacy of mRNA vaccines for diseases with humoral immune protection. In the baseline model, we set $\alpha_{tech} = 1.2$ (i.e., a 20% increase in PoS). Surprisingly, increasing α_{tech} from 1.0 to 1.3 (rows 5 to 7 of **Table S1**) achieves a mixed effect: the expected annualized return increased from −6.7% to −5.8%, while the expected NPV decreased from −$8.1 to −$9.9 billion. As we increase α_{tech} from 1.0 to 1.3, the average number of approved vaccine candidates increases from 28 to 49, and the expected investment also increases from $15.2 to $18.4 billion. However, the reason for the mixed effect is that the expected revenues undergo a much smaller increase, from $7.1 to $7.6 billion, since on average only 3 additional EID outbreaks are prevented by the approved vaccines (due to the stochastic occurrence of EID outbreaks). The smaller ratio of revenues to investment causes the annualized return to be less negative and increase, while the larger increase in investment causes the NPV to be more negative and decrease. We conclude that the higher PoS of mRNA technology alone does not generate positive financial value for the megafund unless we also reduce the clinical trial costs or raise the price of the vaccine.

c. Correlations between Clinical Trial Outcomes

The correlation between vaccine trial outcomes measures the tendency for multiple vaccine trials to simultaneously succeed or fail due to a common target disease or mechanism of action. In the baseline model, we estimate the correlation via the novel virus distance metric d_{ij}. However, we cannot simply rescale d_{ij} in the sensitivity analysis, since the resulting correlation matrix is not guaranteed to remain positive definite. Instead, we gauge the impact of correlation by assuming an equi-correlated correlation matrix, in which $\rho_{ij} = \rho$ is the same for all diseases, and vary the value of ρ from 0 (independent) to 80% (highly correlated), as shown in rows 8 to 12 in **Table S1**. As expected, we observe that higher values of ρ lead to worse financial performance, as the expected annualized return decreases from −3.5% to −11.7% and the expected NPV decreases from −$8.3 to −$9.5 billion. In addition, the volatility of the annualized return dramatically increases from 2.5% to 23.6%. This shows the importance of diversity in the megafund portfolio to generate positive financial value.

d. Human Challenge Trials

If deemed ethical, an HCT may be able to significantly reduce the cost and duration of the clinical development of vaccine candidates by testing a smaller group of participants than traditional vaccine trials. We investigate the effect of HCTs on the megafund performance by assigning the probability p_{HCT} that HCT is allowed for each EID. The baseline portfolio does not utilize HCT, i.e., $p_{HCT} = 0$. Increasing p_{HCT} from 0 to 30% (rows 13 to 14 of **Table S1**) reduces the expected investment and increases both the annualized return and NPV, although both remain negative. We find that utilizing HCT alone is also insufficient to generate positive financial value for the investors.

e. Megafund Portfolio Size

The parallel vaccine development strategy increases the probability that at least one vaccine candidate will be approved, but it also increases the investment in clinical trials. To investigate the effect of portfolio size, we multiply the number of vaccine candidates for each infectious disease by a factor γ. The baseline portfolio corresponds to $\gamma = 1$. Increasing the portfolio size by 50% ($\gamma = 1.5$, row 16 of **Table S1**) leads to worse financial performance, since the expected investment increases from \$17.7 to \$25.7 billion, while the expected revenues only increases by a much smaller amount, from \$7.5 to \$7.9 billion, as the natural occurrence of EID outbreaks remains the same. Decreasing the portfolio size by 50% ($\gamma = 0.5$, row 15 of **Table S1**) increases both expected return and NPV, though both remain negative. In addition, the average number of epidemics prevented decreases from 31 to 27, which reflects a higher loss to society not captured by our financial analysis.

Table S1. Sensitivity analysis of key simulation parameters computed with 100K Monte Carlo simulations.
R_a denotes annualized return (p.a.); NPV denotes net present value, Inv denotes net investment, Rev denotes net revenue, in billion USD; N_{ep} denotes the number of EID outbreaks contained by vaccines from the portfolio; π denotes the price per vaccine dose in USD; α_{tech} denotes the technology factor; p_{HCT} denotes the probability of HCT; ρ denotes the pairwise correlation between vaccine trial outcomes; γ denotes portfolio size factor. NPV is computed with an annual discount rate r=10%.

Portfolio	E[R_a]	SD[R_a]	E[NPV]	SD[NPV]	E[Inv]	SD[Inv]	E[Rev]	SD[Rev]	E[N_{ep}]	SD[N_{ep}]
Baseline	−6.0%	6.7%	−9.5	4.1	17.7	5.3	7.5	7.7	31	13
π = $69/dose	0.0%	7.1%	−1.4	11.9	17.7	5.3	25.8	26.7	31	13
π = $78/dose	0.7%	7.1%	0.0	13.5	17.7	5.3	29.2	30.2	31	13
π = $100/dose	1.9%	7.2%	3.6	17.4	17.7	5.3	37.4	38.7	31	13
α_{tech} = 1.0	−6.7%	11.9%	−8.1	4.1	15.2	5.3	7.1	7.8	28	14
α_{tech} = 1.1	−6.2%	9.1%	−8.8	4.1	16.4	5.4	7.3	7.8	29	14
α_{tech} = 1.3	−5.8%	4.8%	−9.9	4.1	18.4	5.1	7.6	7.7	31	13
ρ = 0%	−3.5%	2.5%	−8.3	3.7	18.1	2.5	10.7	8.9	43	7
ρ = 20%	−3.8%	2.7%	−8.5	4.0	18.0	3.9	10.2	8.7	41	9
ρ = 40%	−4.2%	4.2%	−8.7	4.3	17.9	5.0	9.6	8.6	38	11
ρ = 60%	−5.9%	11.1%	−9.0	4.6	17.8	6.0	8.7	8.3	35	14
ρ = 80%	−11.7%	23.6%	−9.5	4.8	17.7	7.1	7.5	7.9	31	17
p_{HCT} = 10%	−5.7%	6.7%	−8.8	4.1	16.7	5.1	7.5	7.7	31	13
p_{HCT} = 30%	−5.1%	6.7%	−7.6	3.9	14.7	4.6	7.5	7.7	31	13
γ = 0.5	−4.1%	8.9%	−3.7	3.0	9.3	2.9	6.5	7.3	27	14
γ = 1.5	−7.3%	5.7%	−15.3	5.4	25.7	7.6	7.9	7.9	32	13