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FINANCING VACCINES FOR GLOBAL HEALTH SECURITY

Jonathan T. Vu[a,b], *Benjamin K. Kaplan*[c], *Shomesh Chaudhuri*[d], *Monique K. Mansoura*[e] *and Andrew W. Lo*[c,d,f–h*]

Recent outbreaks of infectious pathogens such as Zika, Ebola, and COVID-19 have underscored the need for the dependable availability of vaccines against emerging infectious diseases (EIDs). Prior to the COVID-19 pandemic, the cost and risk of R&D programs and uniquely unpredictable demand for EID vaccines discouraged many potential vaccine developers, and government and nonprofit agencies have struggled to provide timely or sufficient incentives for their development and sustained supply. However, the economic climate has changed significantly post-pandemic. To explore this contrast, we analyze the pre-pandemic economic returns of a portfolio of EID vaccine assets, and find that, under realistic financing assumptions, the expected returns are significantly negative, implying that the private sector is unlikely to address this need without public-sector intervention. However, in a post-pandemic policy landscape, the financing deficit for this portfolio can be closed, and we analyze several potential solutions, including enhanced public–private partnerships and subscription models in which governments would pay annual fees to obtain access to a portfolio of stockpiled vaccines in the event of an outbreak.

1 Introduction

The risks of emerging infectious diseases (EIDs) are inherently dynamic and largely unpredictable. New threats persist, including the recent outbreak

[a]Warren Alpert Medical School, Brown University, Providence, RI, USA
[b]Brown Center for Biomedical Informatics, Providence, RI, USA
[c]MIT Sloan School of Management, Cambridge, MA, USA
[d]QLS Advisors LLC, Cambridge, MA, USA
[e]The MITRE Corporation, McLean, VA, USA
[f]MIT Laboratory for Financial Engineering, Cambridge, MA, USA
[g]MIT Computer Science and Artificial Intelligence Laboratory, Cambridge, MA, USA
[h]Santa Fe Institute, Santa Fe, NM, USA
*Corresponding author: E-mail: alo-admin@mit.edu

of a novel coronavirus COVID-19 (CDC, nd), and government leaders face formidable decisions about the provision of health security measures against outbreaks of these threats. Given the range of potential biological threats, their randomness, and the limited resources available to address them, policymakers must necessarily prioritize their readiness efforts based on limited knowledge. All too often, they are forced to choose between priorities, and construct so-called limited lists of treatments, using testimony from teams of experts to inform these decisions. As recent history has shown, however, this approach leaves society vulnerable to unforeseen outbreaks. Therefore, a more rational approach is to develop a broad portfolio of vaccines in a coordinated manner and stockpile them *before* they are needed, mitigating the future risk posed by unpredictable outbreaks of these diseases.

However, prior to the COVID-19 pandemic, an increasing number of biotech and pharmaceutical companies had abandoned the vaccines business, citing declining and uncertain revenues due to the unwillingness of governments and investors to fund vaccine development in the absence of a clear and present need. Although seasonal flu vaccines are quite profitable because there is fairly steady demand from year to year, vaccines for less common but more deadly diseases such as Chikungunya, Ebola, SARS, and Zika are not nearly as financially rewarding. For example, in 2019 GlaxoSmithKline (GSK) transferred its Ebola and Marburg vaccine candidates to the non-profit Sabin Vaccine Institute at no cost, after acquiring them in 2013 as part of its $325 million purchase of Okairos, a for-profit Swiss biotech company. Sabin, in turn, entered into a collaboration with the Vaccine Research Center at the U.S. National Institute of Allergy and Infectious Diseases (NIAID)—a government agency—to complete the clinical trials for these promising candidates. The pre-pandemic exodus from the vaccine business by big pharma has been described as a crisis, and rightly so in retrospect as there were only four remaining major manufacturers that focused on vaccine development when the SARS-CoV2 virus emerged in 2019 (Plotkin *et al.*, 2015).

But the economics of the vaccines industry has changed completely since the COVID-19 pandemic and the successful development of vaccines by Moderna, Pfizer/BioNTech, Johnson & Johnson, and others. These changes include both scientific and medical innovations (e.g., mRNA vaccine technology), unprecedented coordination and collaboration among multiple stakeholder communities, and greater willingness of governments and investors to address the threat of EIDs in the wake of COVID-19's enormous toll on lives and livelihoods. To understand the full extent of this seismic shift in the vaccine business, and to develop the most effective policies to respond to this shift, it is necessary to explore the financial incentives involved in vaccine development prior to the pandemic. This is the goal of our article.

In this study, we examine the pre-pandemic economic feasibility of developing and supporting a portfolio of vaccines for the world's most threatening EIDs as determined by scientific experts, drawing from the list of targets made by the recently launched global initiative, the Coalition for Epidemic Preparedness Innovations (CEPI) (Brende *et al.*, 2016; WHO, 2017; Gouglas *et al.*, 2018) Our portfolio is composed of the 141 preclinical assets identified by Gouglas *et al.* (2018) to target the priority diseases. Previous research has demonstrated that a novel "mega-fund" financing strategy is capable of generating returns that could attract untapped financial resources to fund the development of a portfolio of drug development programs (Fernandez *et al.*, 2012; Fagnan *et al.*, 2014). We address this possibility by simulating the financial performance of a hypothetical megafund portfolio of 141 preclinical EID vaccine development programs across nine different EIDs for which there is currently no approved prophylactic vaccine.

Under pre-pandemic business conditions and pricing structures, we conclude that a private sector solution for the comprehensive development of EID vaccines is not yet feasible, and quantify the gap so as to inform current policy discussions regarding the need for public-sector intervention. Specifically, using industry-standard assumptions for vaccine development costs, pricing, and expected potential revenues, given outbreak estimates in the extant literature, a portfolio of CEPI vaccine candidates yielded a simulated expected return of −61% with a standard deviation of 4.0%. Combining this vaccine portfolio with an otherwise profitable small-cap pharma, mid-tier pharma, or top-10 pharma company yields similar results, turning expected profits into losses.

The only cases in which our simulations are able to produce positive expected returns are: (1) if we raise the prices of vaccines by two orders of magnitude, charging tens of thousands of dollars per dose rather than hundreds of dollars; or (2) creating a subscription model for vaccines in which governments around the world pay annual fees in proportion to their population to fund the development and stockpiling of vaccines in anticipation of outbreaks.

However, recall that these conclusions are based on pre-pandemic assumptions for the parameters of our simulations. Although it is too early to determine how to change those assumptions to reflect the innovations we have witnessed over the recent past, there is reason to be optimistic and we conclude with a discussion of how new policy can greatly increase the chances of avoiding future pandemics.

2 Literature Review

Uncontrolled outbreaks of EIDs, defined as infections that have "recently appeared within a population, or those whose incidence or geographic range is rapidly increasing or threatens to increase in the near future" (BCM, nd) have the potential to devastate populations globally, both in terms of lives lost and economic value destroyed. In addition to the COVID-19 pandemic, other notable recent outbreaks of EIDs include the 1998 Nipah outbreak in Malaysia, the 2003 SARS outbreak in China, and the 2014 Ebola outbreak. In addition to the thousands of lives lost, the economic costs of these outbreaks are estimated as $671 million, $40 billion, and $2.2 billion, respectively (BCM, nd; McKibbin, 2004; The World Bank, 2012, 2015), and the figure for COVID-19 will likely be in the trillions of dollars.

As the world becomes more globalized, urbanized, and exposed to the effects of climate change, the danger of infectious diseases has become an even greater concern (Hotez, 2017), as emerging and re-emerging strains become more diverse, and outbreaks become more frequent. While distinct from EIDs, influenza serves as a close example of the destruction that viruses with pandemic potential can inflict on the modern world. As a baseline, avian influenza outbreaks in the U.S. since late 2014 have caused economy-wide losses estimated at $3.3 billion domestically, and have significantly disrupted trade (Greene, 2015). The 1918 influenza pandemic is estimated to have infected 500 million people and killed 3–5% of the world's population. In 2006, Dr. Larry Brilliant stated that 90% of the epidemiologists in his confidence agreed that there would be a large influenza pandemic within two generations, in which 1 billion people would sicken, 165 million would die, and the global economy would lose

$1 to $3 trillion (Brilliant, 2006; see Supplementary Materials for further discussion). Controlling EIDs before they have the chance to reach comparable scale represents a significant opportunity to prevent similar loss.

Despite the threat that these diseases pose to global health and security, there were few economic incentives for manufacturers to develop preventative vaccines for EIDs in the pre-pandemic era, due to the high costs of R&D and the uncertain future demand. Even if protection against these emerging diseases were immediately achievable with existing technology, development costs are significant (Plotkin, 2005), as they are for any pharmaceutical development program. Pronker *et al.* (2013) estimate that it costs between $200 and $900 million for a new vaccine to be created. Failure to gain approval also poses a substantial risk, as successful passage through clinical trials only occurs 6–11% of the time (Davis *et al.*, 2011; Pronker *et al.*, 2013). Regulatory challenges are particularly prominent in EID vaccine development, as viable candidates are rarely available for distribution during outbreaks, making safety and efficacy testing difficult. As a result, vaccine development for EIDs has been reactive and technologically conservative (Bloom *et al.*, 2017a).

Moreover, vaccines sell for only a fraction of their economic value, in some cases for only a few dollars. They provide myriad benefits, like enabling would-be patients to live longer, healthier lives (Lieu *et al.*, 2005; Castro *et al.*, 2017), and bearing yet-undervalued gains in productivity and positive externalities to society at large (Bärnighausen *et al.*, 2014; Bloom *et al.*, 2017b; CEA, 2019). Although the low price of vaccines is meant to benefit individuals and regions with lower incomes, in the long run, it has had the opposite effect, causing them to be medically underserved due to a lack of vaccine investment. Pharmaceutical companies and investors are directing their resources to projects in which the estimated return on investment is more predictable and lucrative. Vaccine prices are currently set far below the prices of drugs that treat other serious conditions, such as cancer, despite the enormous societal value of vaccines in general, and those to ensure global health security in particular. The typical expected risk-adjusted net present value (NPV) of a vaccine in our hypothetical portfolio upon regulatory approval is on the order of only $7.6 million. This is two or three orders of magnitude lower than the comparable value of an approved cancer drug, yet the out-of-pocket costs to develop an EID vaccine are not dissimilar.

In addition to pricing, another challenge lies in assessing the future demand for EID vaccines. Due to the inherent unpredictability in the scale and timing of outbreaks, the future demand for a specific EID vaccine is typically unclear. An additional factor is geopolitical. Diseases that are traditionally found in only a few, lower-income countries may not attract as many R&D dollars because generating a return on investment is more difficult in those limited markets (Glennerster and Kremer, 2000; Plotkin *et al.*, 2015). While wealthier governments might issue purchase agreements to assure vaccine sponsors of returns (Glennerster and Kremer, 2000), these commitments are more difficult to secure for EIDs in lower-income countries or those undergoing economic hardship. However, an increasing number of stakeholders are realizing the danger of this dynamic for low- and high-income countries alike, as under epidemic outbreak conditions, diseases like Zika and Ebola have the potential to spread much further than their traditional locales. The Ebola outbreaks in West Africa in 2014 demonstrate how the absence of vaccine demand prior to an event may result in a tragic loss of life and a regional economic setback. It is a significant concern that years after those outbreaks, the demand for Ebola vaccines remains limited and uncertain, allowing gaps in preparedness to persist (Gavi, 2016; FedBizOpps, 2017; Wellcome Trust and CIDRAP, 2017).

Unless these market challenges are addressed, the global population will remain vulnerable to substantial human and economic losses when epidemics and pandemics arise.

We believe that this represents a significant missed opportunity. Aside from the nuclear threat and climate change, pandemics represent one of the most significant existential dangers facing humanity today (Gates, 2017). Nevertheless, investments in preparedness for biological threats remain underfunded, leaving the world vulnerable to catastrophic infectious disease events. With this in mind, we investigate several measures that might move the mission for EID vaccine readiness toward financial viability.

In spite of these substantial difficulties—or perhaps because of them—new global initiatives have drawn attention to the need for new approaches to encourage the development of vaccines against EIDs (NASEM, 2016a; Rappuoli *et al.*, 2019). International collaborations like CEPI have drawn extensive public, private, NGO, and academic attention to the perils of global epidemic unpreparedness (CEPI, 2016).

This crisis-driven expanded interest in vaccines to address epidemic threats is encouraging, but there is still much work to be done. There needs to be a viable, sustainable business model that will align the financial incentives of stakeholders to encourage the necessary investment in vaccine development (NASEM, 2016b; Sands *et al.*, 2016). While governments and international agencies have striven to create incentives to attract additional private sector investment in vaccine development, these efforts have so far failed in attracting sufficient capital to enhance preparedness against the world's most deadly emerging pathogens (CSIS, 2019).

Several mechanisms have recently been proposed or implemented to create incentives for industry to develop vaccines and other medical countermeasures for EIDs (IOM, 2010). Beyond the "push mechanism" of significant R&D support, these mechanisms provide some measure of a "pull incentive," recognizing that traditional market forces are insufficient to secure global health security aims. These strategies include the direct government acquisition of stockpiles of vaccines, the use of prizes, priority review vouchers, and the establishment of advance market commitments, each of which is described in more detail in Supplemental Materials. However, to date, none of these strategies have been deemed to be effective in addressing the growing threat of EIDs.

To create further incentives for investing in this space, we propose the creation of an EID megafund based on the model developed by Fernandez *et al.* (2012), which uses portfolio theory and securitization to reduce investment risk in these assets. In financial engineering, the practice of securitization requires the creation of a legal entity that issues debt and equity to investors, using the capital raised to acquire a portfolio of underlying assets—in this case, vaccine candidates targeting EIDs. These assets subsequently serve as collateral, and their future cash flows service the debt incurred to acquire them, paying the interest and principal of the issued bonds. Once the debt has been repaid, equity holders receive the residual value. If the portfolio's cash flows are insufficient to meet the obligations to the bondholders, the collateral will be transferred to bondholders through standard bankruptcy proceedings.

Given the characteristically high risk of default of candidates in the early stages of development, and the need for increased financial investment in vaccine research as a whole, securitization in the form of a vaccine megafund offers several key benefits. The securitization of vaccine research enables investors to reduce their risk of financial loss to a scale that is not readily achievable under current financing mechanisms, as they can invest in many vaccine projects at once, thus increasing the likelihood of at least one success. The normalization of returns created by the construction of an asset portfolio permits the issuance of debt, which allows fixed-income investors to gain exposure in a space that is traditionally too risky to represent a compelling opportunity for investment. The ability to issue debt is critical, because bond markets have much greater access to capital than venture capital or the private and public equity markets. This allows the megafund to raise enough funding to purchase an array of assets and reach its critical threshold of diversification.

One notable benefit of our megafund approach is that it hedges against the societal risk that the world will not have the "right" vaccine it needs for the next EID outbreak. To date, the U.S. government and CEPI programs have been forced to severely limit their portfolios, due to funding constraints. This approach allows us to assess the opportunity of addressing nine of the world's most threatening EIDs at once.

While the megafund approach is effective at reducing the development risk of EID vaccines, it should be emphasized that the success of this technique hinges upon securitizing assets that have the potential to be profitable individually if the development effort is successful. This flies in the face of conventional pharma wisdom that vaccines are commercially challenging, not only because of development risk but also because of the unpredictability of outbreaks and constraints on pricing when outbreaks occur. However, to quantify the gap between reality and commercial viability—and in light of global stakeholders' ongoing efforts to raise funding to combat these diseases—we suspended belief in this presumption so as to allow the financial analysis to determine the profitability of the EID portfolio in an unbiased fashion. Based on available pipeline data, an analysis by Gouglas *et al.* (2018) projects that the cost of progressing at least one vaccine candidate through the end of phase 2a against a comparable portfolio of 11 EIDs would cost between \$2.8 and \$3.7 billion. Our approach builds upon this analysis by quantifying the gap between the estimated costs of development and the sort of returns that would need to be generated by such an expenditure in order to justify investment.

3 Methods

To apply the megafund portfolio approach to EID vaccine development, we began by analyzing the hypothetical investment returns of a portfolio of 141 preclinical EID vaccine development programs across nine different emerging infections for which there is currently no approved prophylactic vaccine. Our analysis relies on several assumptions and parameters, including estimates of the cost of vaccine development, the length of time from preclinical testing to the filing of a new vaccine license application, the probability of success of each project, and pairwise correlations of success among the projects in the portfolio. It should be noted that, with the exception of the correlation assumptions, the rest of our assumed parameters have been calibrated to pre-COVID-19 values.[1]

The target diseases were selected from CEPI's Priority Pathogen list, which was based in part upon the WHO's R&D Blueprint focusing on epidemic prevention (Brende *et al.*, 2016; WHO, 2017). We drew our portfolio assets from CEPI pipeline research for each disease on its priority pathogen list (Brende *et al.*, 2016; Gouglas *et al.*, 2018). (See Supplementary Materials for more details.)

The model design is less complicated than that of Fernandez *et al.* (2012). Unlike oncology—a domain with many approved drugs and even more under development—there are currently few EID vaccines available on the market, indicating a paucity of data with which to calibrate our simulations. In setting our simulation parameters, we relied on generic information about the vaccine development process, specific estimates posited by CEPI (Brende *et al.*, 2016), and qualitative input from scientists with domain-specific expertise.

The present value of out-of-pocket development costs for each of the projects in the portfolio was set to $250 million, based on assumptions made by CEPI about the cost to develop a preclinical asset through phase 2 (Brende *et al.*, 2016). CEPI further estimates that it will take 5 years for this development to occur (Figure 1). CEPI proposes that assets at this level of development will justify stockpiling, further development, and conditional usage under emergency conditions, a plan that some experts believe may be feasible (Plotkin *et al.*, 2015; Brende *et al.*, 2016).

At $250 million per project, a megafund of 141 projects requires $35.25 billion. To determine the returns generated by such a portfolio, we assumed a 15-year period of exclusivity and a 10% cost of capital to calculate the NPV of future cash flows upon approval in year 5. This value must be weighed against the possibility of total loss if the vaccine project fails. An assessment of the megafund's returns therefore requires estimates of the probabilities of success of each of the 141 vaccine candidate projects as well as the pairwise correlation of success of all possible pairs of assets. The probabilities of success are based on estimates of the compounded probabilities of advancement from preclinical testing to vaccine approval. The probability of development through phase 2 of a vaccine at the start of preclinical testing is 32%, based on the transition probabilities provided by CEPI (Brende *et al.*, 2016). See Supplementary Materials for details on these estimates as well as on the method for assigning pairwise correlations.

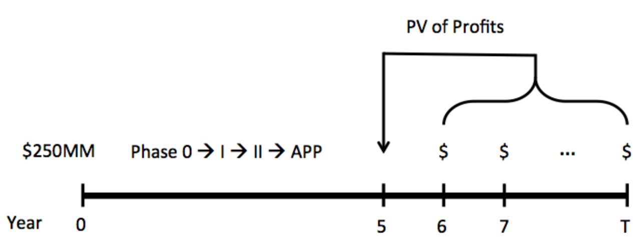

Figure 1 Timeline of a hypothetical EID vaccine development program.

Given the inherent unpredictability of a future EID outbreak, we necessarily made several practical assumptions to project revenue. In this model, we assumed that the prophylactic regimen would consist of a single dose of vaccine. The probability of disease outbreak was estimated based on historical outbreaks per disease, while regimen demand was projected using historical outbreak size, potential for pandemic spread, and an assessment of relative clinical severity. These demand parameters were determined respectively by case estimates from documented outbreaks, referencing the Woolhouse *et al.*'s (2013, 2016) assessment for pandemic potential, and comparing the clinical presentation and prognosis for each disease.

A perceived demand multiplier was assigned based on Woolhouse classification and clinical severity on a five-step scale ranging from mild to severe. The average number of cases and the perceived demand multiplier were used to calculate the number of regimens sold in an outbreak year for each disease. This product, the expected chance of outbreak in a given year based on historic outbreak data, and the expected selling price per vaccine regimen were used to subsequently calculate the annual expected revenue for each disease. The price per regimen was estimated based on whether the disease in question typically affected high-, medium-, or low-income countries. The expected price per regimen for each income level was informed by CDC, Gavi, and PAHO vaccine pricing data, respectively (CDC,

Table 1 EID vaccine sales. Annual expected revenues from direct sales of vaccines to susceptible populations for nine different EIDs. All values are annualized.

Disease	Outbreak Probability	Average Cases	Perceived Demand Multiplier	Average Regimens Sold	Average Price	Annual Expected Revenue
Chikungunya	11%	523,600	4×	2,094,400	$5.55	$1,278,600
MERS	40%	400	10×	4,000	$46.12	$73,800
SARS	7%	8,100	12×	97,200	$5.55	$37,800
Marburg	12%	100	10×	1, 000	$1.97	$200
RVF	11%	79,400	6×	476,400	$5.55	$290,800
Lassa	100%	300,000	8×	2,400,000	$1.97	$4,728,000
Nipah	16%	100	10×	1,000	$5.55	$900
CCHF	13%	300	10×	3,000	$5.55	$2,200
Zika	4%	500,000	12×	6,000,000	$5.55	$1,332,000

Table 2 EID megafund risks and returns to investors. Investment returns (%) of a portfolio of 141 preclinical EID vaccine candidates when projects are not independent (with correlation), and when projects are statistically independent (no correlation). The Sharpe ratio is estimated as the ratio of the expected return to the standard deviation. The bolded row indicates the results of the simulation with parameter values that are closest to industry averages. PV(Profits), present value of profits per successful vaccine in year 5; $E[R_{5y}]$, expected 5-year return on investment; $E[R_{1y}]$, expected annualized return; $SD[R_{1y}]$, annualized return standard deviation; CI, confidence interval; SR, Sharpe ratio.

PV (Profits)	With Correlation					No Correlation			
in $MM	$E[R_{5y}]$	$E[R_{1y}]$	$SD[R_{1y}]$	95% CI	SR	$E[R_{1y}]$	$SD[R_{1y}]$	95% CI	SR
0.1	−100.0	−83.6	1.7	(−87.4, −80.9)	—	−83.3	0.4	(−84.2, −82.6)	—
1.0	−99.9	−74.1	2.7	(−80.1, −69.7)	—	−73.6	0.7	(−74.9, −72.4)	—
7.6	**−99.0**	**−61.1**	**4.0**	**(−70.2, −54.6)**	—	**−60.4**	**1.0**	**(−62.4, −58.5)**	—
10	−98.7	−58.9	4.3	(−68.5, −51.9)	—	−58.1	1.0	(−60.3, −56.2)	—
100	−87.0	−34.8	6.8	(−50.0, −23.9)	—	−33.6	1.6	(−37.0, −30.5)	—
772	0.0	−1.9	10.2	(−24.8, 14.5)	—	0	2.5	(−5.2, 4.5)	—
1,000	29.7	3.3	10.7	(−20.8, 20.6)	0.3	5.2	2.6	(−0.1, 10.0)	2.01
10,000	1197.1	63.8	17.0	(25.6, 91.2)	3.8	66.8	4.1	(58.3, 74.5)	16.3

2017; UNICEF, 2015; PAHO, 2016). Please see Supplementary Materials for additional details.

4 Results

Table 1 provides estimates of the annual expected revenues from direct sales of vaccines to susceptible populations for the nine different EIDs considered in the megafund. (Please see Supplementary Materials for more details on how projected revenues were determined.)

The simulated investment performance of an EID vaccine portfolio as a function of the commercial potential of each individual vaccine project is provided in Table 2 and illustrated in Figure 2 (please see Supplementary Materials for more information on how returns were calculated). The commercialization potential of these vaccines is consistently very poor, orders of magnitude lower than what would be required to make them commercially viable. The parameter values that are

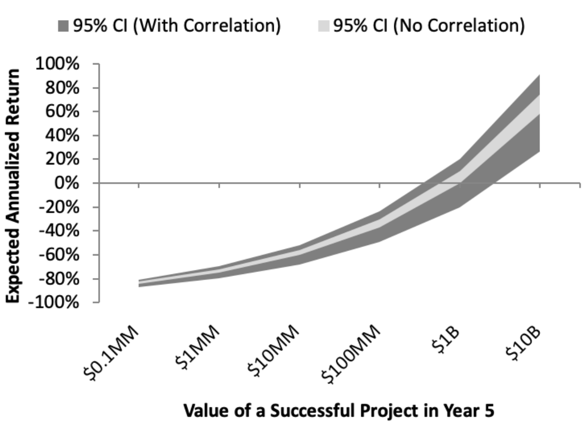

Figure 2 EID megafund risks and returns to investors. Investment returns and risks of a portfolio of 141 preclinical EID vaccine candidates when projects are not independent (with correlation), and when projects are statistically independent (no correlation). Expected returns break even when the annual expected profit per successful project is $772 million. CI, confidence interval.

closest to industry averages correspond to the highlighted row in Table 2, in which the expected annual profits upon FDA approval are $1 million, resulting in an NPV per successful EID vaccine of $7.6 million. For these values, the vaccine portfolio's expected return is −61.1%, with a standard deviation of 4.0%.

For completeness, Table 2 also reports megafund performance statistics for several other sets of parameters. The breakeven point, where the megafund's expected 5-year return is 0%, occurs as the NPV of a successful vaccine reaches $772 million, two orders of magnitude greater than our current estimates using past averages for costs, revenues, probabilities of success and outbreak, and other information. However, for an NPV of $1 billion, the vaccine portfolio becomes marginally profitable, and at $10 billion, it is highly profitable. These results suggest that many of the model parameters would have to change drastically for the portfolio to be profitable. In fact, holding all else equal, simply breaking even would require selling vaccines at approximately 100 times the price assumed in our simulations.

Megafunds are, of course, not the only business model through which vaccines can be developed. Traditionally, large pharmaceutical companies have incorporated vaccine programs into broader and highly diversified portfolios of therapeutics across many indications. To explore this possibility, we estimated the impact on risk and reward of incorporating the EID vaccines portfolio into a hypothetical pre-existing and profitable pharma company. Table 3 contains the estimated expected returns and volatilities of a representative top-10, mid-tier, and small-capitalization pharmaceutical company with and without the base case version of the EID vaccine portfolio. The best-case scenario—in which big pharma adds this portfolio to its existing products—turns an otherwise profitable business into an unprofitable one,

Table 3 Simulated performance of a hypothetical representative top-10, mid-tier, and small-cap pharmaceutical company with and without the EID vaccine portfolio. Pharmaceutical companies are classified according to their North American Industry Classification System (NAICS) code and their market capitalization each year from 2005 to 2016. Return statistics are averaged within each sub-group to form the expected return and standard deviation estimates. The performance of these representative companies combined with the EID vaccine portfolio is estimated by assuming no correlation with vaccine revenues. Market Cap, average market capitalization in billions of dollars; $E[R_{1y}]$, expected annualized return; $SD[R_{1y}]$, annualized return standard deviation; SR, Sharpe ratio.

	Without EID Vaccine Portfolio				With EID Vaccine Portfolio	
Company Type	Market Cap ($B)	$E[R_{1y}]$	$SD[R_{1y}]$	SR	$E[R_{1y}]$	$SD[R_{1y}]$
Top-10 Pharma	94.1	11.1%	23.8%	0.47	−8.6%	17.4%
Mid-Tier Pharma	12.9	14.3%	32.9%	0.43	−40.9%	9.3%
Small-Cap Pharma	1.6	19.6%	53.2%	0.37	−57.6%	4.5%

losing 8.6% per year on average in shareholder value. The results for mid- and small-cap pharma companies are even worse.

These results are consistent with the biopharma industry's trend toward fewer companies willing to engage in vaccine R&D, underscoring the infeasibility of a private-sector EID vaccine portfolio, given current cost and revenue estimates, and the need for some form of public-sector intervention. A sensitivity analysis of these results to perturbations in our model's key parameters is provided in the Supplementary Materials. We find that the EID vaccine megafund remains financially unattractive even under relatively optimistic cost and revenue assumptions, implying the necessity for some form of public-sector intervention. These findings may explain the dearth of EID vaccines developed over the past decade.

One intervention is the use of government-backed guarantees to mitigate the downside risk of the EID portfolio. In a guarantee structure, a government agency promises to absorb the initial losses on the portfolio to a predetermined amount, shielding private-sector investors from substantial negative returns. For example, a guarantee on 50% of the portfolio's principal improves the expected annualized return in the base case scenario from −61.1% to −12.6% (see Table S11 in the Supplementary Materials). While this negative-expected-return scenario is still unlikely to attract investors, expected returns can be further increased using mechanisms such as advance market commitments and priority review vouchers. The guarantee structure—in combination with other existing revenue-boosting mechanisms—has the potential to transform a financially unattractive portfolio of EID vaccine candidates into one that could realistically attract private-sector capital.

Finally, we consider a subscription model under which the largest governments around the world would purchase subscriptions to EID vaccines on behalf of their constituents. To fund the cost of pursuing 141 vaccine targets at $250 million per target (for a total of $35.25 billion), suppose that the governments of the G7 countries agreed to pay a fixed subscription fee per capita over a fixed amortization period to cover this cost. How much

Table 4 Annual total cost and per capita cost of subscription model for funding a $35.25 billion vaccines development fund by G7 countries where the per capita subscription fee is $12.08 per person per year over a 5-year period or $7.45 per person per year over a 10-year period.

			5-Year Amortization Period		10-Year Amortization Period	
Country	Population	Current Per Capita Healthcare Spending	Per Capita Fee as % of Current Per Capita Healthcare Spend (5-year)	Annual Total Cost	Per Capita Fee as % of Current Per Capita Healthcare Spend (10-year)	Annual Total Cost
Canada	37,411,047	$3,274	0.37%	$451,755,252	0.23%	$278,702,763
France	65,129,728	$3,534	0.34%	$786,470,817	0.21%	$485,199,871
Germany	83,517,045	$3,992	0.30%	$1,008,505,956	0.19%	$622,180,695
Italy	60,550,075	$2,039	0.59%	$731,169,443	0.37%	$451,082,623
Japan	126,860,301	$3,538	0.34%	$1,531,895,305	0.21%	$945,076,903
United Kingdom	67,530,172	$3,175	0.38%	$815,457,260	0.23%	$503,082,567
United States	329,064,917	$8,078	0.15%	$3,973,607,167	0.09%	$2,451,449,747

Source: Authors' computations based on population and healthcare expenditure data from the World Bank (https://databank.worldbank.org/source/world-development-indicators).

would this subscription fee be? For an amortization period of 5 years, and an estimated total G7 population of 770,063,285 (as of 2016, according to the World Bank[2]), and a cost of capital of 10%, the per capita annual payment to cover the total cost of $35.25 billion is $12.08 per person per year. If we extend the amortization period to 10 years, the subscription fee declines to $7.45 per person per year. Table 4 contains the per capital subscription fees as a percentage of the annual per capita healthcare expenditure of each G7 country and as expected, the cost is trivial for all countries, ranging from a high of 0.59% for Italy to a low of 0.15% for the U.S. using a 5-year amortization period.

Of course, this subscription model considers only the development cost of vaccines. Once developed, the production and stockpiling of these vaccines would require further funding, but the subscription model can be applied on an ongoing basis, and at a much lower annual cost. Access to these vaccines by non-G7 countries must also be considered, but such access involves political and ethical issues that are beyond the scope of this economic analysis.

These results suggest that a government-led subscription model is financially feasible and would likely yield significant economic and political benefits to all participating governments. While the usual challenges of broad multi-national cooperation must be overcome, early traction from organizations such as Civica Rx suggests that focused, inclusive collaboration can ensure sustained supplies of life-saving drugs (Lyford, 2019).

5 Discussion

Our analysis shows that relying solely on private-sector investment in EID vaccines is insufficient, given the negative returns achieved by an EID-focused megafund, and the negative impact such a pool of assets would have on an otherwise profitable pharmaceutical company. As a result, if EID vaccine candidates are to be developed, continued private–public cooperation will be imperative, and novel approaches to engage and attract capital will be needed. While bond markets are capable of providing access to substantial amounts of capital to help vaccine development efforts, the resources available to the public-sector have great potential as well (Hale *et al.*, 2011). In 2015, the U.S. spent $9,990 per person on healthcare (CMS, 2017). If we assume that there are 300 million Americans, just 1.25% of this amount of spending would yield $37.46 billion dollars, greater than the projected $35.25 billion it would take to fund the entire portfolio of EID vaccine candidates. While achieving such an allocation of funding would hardly be as simple as this calculation suggests, this thought experiment illustrates that encouraging the development of vaccines that protect against EIDs with pandemic potential is well within the means of the global public and private sector stakeholders, if there is public support and political will. In fact, there is evidence to indicate that people expect and would support further protection from these threats (Alliance for Biosecurity, 2016).

The U.S. government's Medical Countermeasures (MCM) program has demonstrated a capability to create incentives for the development of vaccines that would otherwise not be developed, once sufficient market demand is guaranteed ahead of time.[3] This has been true for anthrax and smallpox as well as for various strains of pre-pandemic influenza, for which the government provides market commitments on the order of $100–200 million per year for successful vaccine development programs (Johnson, 2009; HHS, 2014). While challenges exist (e.g., sustained funding commitments), new initiatives such as CEPI can learn important lessons from these examples (Russell and Gronvall, 2012; Hoyt and Hatchett, 2016).

Perhaps key to the problem of EID vaccine funding is a deficiency in the pricing of the risk of infection by EIDs. Although the prevention of epidemics and pandemics saves countless lives and billions of dollars of economic value, the revenue realized by vaccine manufacturers is only a very small fraction of this value. With this in mind, an examination of a capitated fee structure—a subscription model—applied to vaccine development and acquisition is promising. Under the current model, vaccines are purchased *a la carte* after outbreaks begin.

However, if stakeholders were to pay in advance to develop and stockpile vaccines, viewing their payment as a form of insurance that would maintain epidemic response capabilities and provide protection from EID outbreaks, much like a society-wide immune system, the amount of capital needed to fund these programs might be easier to raise and keep the price per regimen lower. Vaccine developers under this model would most likely sell subscriptions to governments, building upon existing infrastructure, such as the U.S. government's biodefense and pandemic preparedness programs. To balance the concern that non-subscribers may require vaccine regimens with the objective of encouraging subscription ahead of outbreaks, a tiered pricing scheme rewarding early adoption could be implemented. A private subscription model should also be explored, however, as it would enable individuals, communities, and corporations to take greater ownership in preparedness. Determining precisely who should pay the insurance premium, and who is willing to pay, is essential to this arrangement.

Although this model is a departure from the *status quo*, promising innovation in vaccine financing is becoming more commonplace. The World Bank issue of pandemic bonds and swaps for a Pandemic Emergency Financing Facility (PEF) in 2017 suggests that when structured appropriately, assets geared toward preparedness can be attractive to investors (Reuters, 2017). We believe that our model may shed some light on what will encourage more comprehensive pandemic preparedness by addressing shortcomings in the EID vaccine pipeline.

As demonstrated in our simulations, the investment required to reduce the global risk from EIDs is within reach. Securing these resources, however, will require governments to strengthen their commitments to supporting EID vaccine markets, in order to allow private sector stakeholders and untapped capital to engage with these markets substantively. The recent developments around Sanofi Pasteur's Zika collaboration highlight the risks of a variable commitment to preparedness. Due to changing epidemiology and internal disputes over potential product pricing, BARDA and Sanofi have chosen to halt further development of their Zika asset, leaving society vulnerable to future outbreaks (Sagonowsky, 2017).

As cases like these suggest, government buy-in is integral for long-term pipeline sustainability. Governments can catalyze outside investments through a range of strategies, including guaranteed commitments. Fifteen years of guaranteed revenue via purchase commitments, similar to the U.S. government's purchase of smallpox and anthrax vaccines, would do well to encourage development efforts. For example, an annual purchase commitment of $150 million per successful vaccine candidate would represent an NPV of $1.14 billion, exceeding our modeled breakeven NPV of $772 million. Our results suggest that investment in this space is highly unattractive to the private sector, requiring commitments of the aforementioned magnitude for development viability; as highlighted above, either the price per regimen or the demand from outbreaks would have to increase by orders of magnitude to have the same effect. We encourage readers to engage with these assumption parameters critically using our open source software.[4]

Finally, in the wake of COVID-19, a host of changes have occurred in the vaccine ecosystem. The unprecedented speed with which the SARS-CoV2 vaccine was developed, tested, and approved, provided a proof-of-concept demonstration that mRNA technology has forever changed the vaccine business. In particular, the duration, cost, and probabilities of success of developing and testing a vaccine, the pricing policies acceptable to governments and insurers, and the manufacturing and supply chain for delivering and administering vaccines have all changed in the last 2 years. The incalculable loss of lives and the economic devastation of the pandemic have now catalyzed policymakers around the world to allocate the resources needed to address future pandemics, and to explore more novel pricing models that address the incentive problems highlighted above. And the coordination of multiple stakeholder groups around the world has permanently changed the way we communicate and collaborate in the midst of crisis.

These changes suggest the possibility of another simulation exercise in which experts are empaneled to update the parameter values to reflect the new state of the vaccine business so as to inform policy proposals for addressing future pandemics. We hope to explore this direction in ongoing research.

6 Conclusion

While the main focus of this paper is the challenge of financing EID vaccine development, we realize that there are other concerns that must be considered in parallel before a portfolio of novel EID vaccine regimens is made available to the public. These issues include, but are not limited to, preclinical discovery, regulatory approval strategy, and post-approval procurement and distribution.

These are matters of great importance and warrant further investigation.

It is indisputable, however, that better business models for global health security are urgently needed. We expect that there may be benefits to extending the scope of the megafund approach beyond the particular EID vaccine assets considered in this study, perhaps to antibiotics or MCMs for intentional biological threats, an additional global health security concern. While this would do little to improve the desirability of EID vaccine candidates as assets, broadening the scope of a fund to address additional threats may create greater financial viability to global health security more broadly.

As past efforts demonstrate, the key to generating interest in developing vaccine assets is to offer sufficient financial incentives for would-be developers, such as direct market commitments or priority review vouchers. Closing the gap between the economic value of epidemic prevention and the financial returns of vaccine assets, whether by encouraging the market to compensate developers through a capitated vaccine "subscription" model, or by combining vaccine assets into a large portfolio to normalize investment risk as described here, will better enable the global health security community to address the dangers of EIDs. Enacting these changes may be the most positive way humankind can honor the memory of the hundreds of thousands of people who succumbed to COVID-19 over the last 2 years.

Endnotes

[1] The pairwise correlations among non-SARS EIDs are unlikely to be affected by the recent pandemic, given that the underlying biological properties of those EIDs remain unchanged post-pandemic.

[2] See https://databank.worldbank.org/source/world-development-indicators.

[3] https://www.medicalcountermeasures.gov/.

[4] See https://projectalpha.mit.edu/resources.

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S.C. is a co-founder and chief technology officer of QLS Advisors, a healthcare analytics and consulting company.

M.K.M. is Executive Director for Global Health Security and Biotechnology at The MITRE Corporation, a not-for-profit organization working in

the public interest as an operator of multiple federally funded research and development centers (FFRDCs). She is focused on the sustainability of the biodefense industrial base and the public–private partnerships that are vital to national and global health security.

A.W.L. reports personal investments in private biotech companies, biotech venture capital funds, and mutual funds. He is a co-founder and partner of QLS Advisors, a healthcare analytics company; an advisor to Apricity Health, Aracari Bio, BrightEdge Impact Fund, Enable Medicine, FINRA, Lazard, NIH/NCATS, Quantile Health, SalioGen Therapeutics, the Swiss Finance Institute, Thalēs, and Think Therapeutics; a director of AbCellera, Atomwise, BridgeBio Pharma, Roivant Sciences Ltd., and Annual Reviews; and a member of the NIH's National Center for Advancing Translational Sciences Advisory Council. During the most recent six-year period, A.L. has received speaking/consulting fees, honoraria, or other forms of compensation from: AlphaSimplex Group, Annual Reviews, Atomwise, the Bernstein Fabozzi Jacobs Levy Award, BIS, BridgeBio Pharma, Cambridge Associates, CME, Financial Times, Harvard Kennedy School, IMF, JOIM, National Bank of Belgium, New Frontiers Advisors (for the 2020 Harry M. Markowitz Prize), Q Group, Research Affiliates, Roivant Sciences, and the Swiss Finance Institute.

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