NBER WORKING PAPER SERIES

QUANTIFYING THE SOCIAL VALUE OF A UNIVERSAL COVID-19 VACCINE AND INCENTIVIZING ITS DEVELOPMENT

Rachel Glennerster
Thomas Kelly
Claire T. McMahon
Christopher M. Snyder

Working Paper 32059
http://www.nber.org/papers/w32059

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
January 2024

The authors are grateful for helpful discussions with Willy Chertman, Jake Eberts, Josh Morrison, Stanley Plotkin, Alec Stapp, Nikki Teran, and Witold Więcek. This is a substantially revised and expanded version of our working paper: T. Kelly, R. Glennerster, C.M. Snyder (2023) "An advance market commitment to incentivize a universal coronavirus vaccine before the next variant," Washington, DC: 1Day Sooner. This working paper, in turn, built on initial work by Eric Mannes, to whom we are especially indebted. Snyder is grateful to the Institute for Progress for funding. The views expressed herein are those of the authors and do not necessarily reflect the views of the National Bureau of Economic Research.

Quantifying the Social Value of a Universal COVID-19 Vaccine and Incentivizing Its Development
Rachel Glennerster, Thomas Kelly, Claire T. McMahon, and Christopher M. Snyder
NBER Working Paper No. 32059
January 2024
JEL No. H51,I18,L65

ABSTRACT

A booster of the COVID-19 vaccine targeting the prevailing Omicron variant did not become available in the United States until a year after the variant was first detected. This pattern of developing, testing, and distributing a variant-specific booster may become the default response to further waves of COVID-19 caused by new variants. An innovation with realistic scientific potential—a universal COVID-19 vaccine, effective against existing and future variants—could provide much more value by preempting new variants. Averaged across Monte Carlo simulations, we estimate the incremental value to the U.S. population of a universal COVID-19 vaccine to be $1.5–$2.6 trillion greater than variant-specific boosters (depending on how the arrival rate of variants is modeled). This social value eclipses the cost of an advance market commitment to incentivize the universal vaccine by several orders of magnitude.

Rachel Glennerster
Saieh Hall for Economics, Office 432
University of Chicago
5757 S University Avenue
Chicago, IL 60637
and NBER
rglennerster@uchicago.edu

Thomas Kelly
1Day Sooner
thomas.kelly@1daysooner.org

Claire T. McMahon
University of Chicago
clairemcmahon@uchicago.edu

Christopher M. Snyder
Department of Economics
Dartmouth College
301 Rockefeller Hall
Hanover, NH 03755
and NBER
chris.snyder@dartmouth.edu

1. Introduction

In the nearly four years since the emergence of the COVID-19 pandemic, vaccines have been a key medical countermeasure. Against the original strain, vaccines proved highly effective in preventing infection, hospitalization, and death. Since then, continuous mutations of the virus have demanded an evolving approach to vaccine development.

The efficacy of the original COVID-19 vaccine waned over time as new variants emerged (Ferdinands et al. 2022). To address this waning efficacy, a bivalent booster targeting both the original strain and the circulating Omicron variant was developed. The short lag between the detection of Omicron in November 2021 (World Health Organization, no date) and its integration into a booster approved in the United Kingdom in August 2022 (Medicines and Healthcare Products Regulatory Agency 2022) and in the United States shortly after (Food and Drug Administration 2022) was a historic achievement. Still, Omicron circulated for nearly a year before distribution of the targeted booster began. For COVID-19 variants of concern before Omicron, including Alpha and Delta, there was no successful release of a variant-specific booster.

More recently, the United States has pivoted away from including the original strain in the booster. In September 2023, the U.S. Food and Drug Administration (FDA) authorized a newly formulated COVID-19 vaccine targeting the most prevalent subvariants of Omicron in circulation (Food and Drug Administration 2023). The director of the U.S. Centers for Disease Control and Prevention (CDC) has indicated that this will likely be the start of annualized COVID-19 vaccines (Jones and Talsolides 2023). This program is expected to mirror the long-standing approach to annual flu vaccines that are formulated to target the most prevalent mutations in circulation at the time of development.

The primary weakness of the strategy of variant-specific boosters is the reaction time needed to develop and distribute them in response to the emergence of a new variant. Even under the most favorable timetables, new variants can spread around the world and kill hundreds of thousands before the new vaccine can be distributed. A secondary concern is that the strategy relies on the general population's continual commitment to take vaccine after vaccine, an inauspicious approach in the light of vaccine hesitancy and the less-than-full uptake of even the original booster dose in the United States.

Vaccines designed to work against most or all coronaviruses, including all present and future COVID-19 variants, are in development in several labs across the globe. The history of the original COVID-19 vaccines shows that with financial backing that offsets risks involved in vaccine development, pharmaceutical companies are capable of rapid clinical testing and mass production of vaccines. Doses of the original COVID-19 vaccines were rolled out in high-income countries including the United States, United Kingdom, Israel, and the European Union within a year of the pandemic spreading there. Those countries demonstrated an ability to rapidly distribute vaccines once supply was secured. A universal COVID-19 vaccine has many advantages over a series of specific boosters developed to respond to specific variants. Most importantly, a universal COVID-19 vaccine can be produced and administered in arms before a new variant causes another wave.

The theoretical advantages of a universal coronavirus vaccine are easy to appreciate, but such vaccines are far from theoretical. Dozens of universal coronavirus vaccine candidates are already being developed (Dolgin 2022). Research teams are based at institutions such as Francis Crick Institute (Ng et al. 2022) and Pfizer and BioNTech (Burger 2022). Multiple universal

COVID-19 vaccines are in clinical trials, and multiple universal coronavirus vaccines are under preclinical study (Dolgin 2022).

We evaluate the incremental benefits of a successful universal COVID-19 vaccine over variant-specific boosters and consider the use of an advance market commitment (AMC) to incentivize its development. An AMC to vaccine manufacturers pledges the U.S. federal government or some other consortium of funders to buy courses of a universal COVID-19 vaccine at a pre-specified price provided that the vaccine meets pre-specified efficacy thresholds and receives regulatory approval. A guaranteed market for their vaccines would reduce manufacturers' uncertainty, bolstering their incentives to invest in research and development as well as manufacturing capacity. Absent dedicated funding, vaccine manufacturers may infer that funders do not prioritize having a universal COVID-19 vaccine over the status-quo booster program.

Funders have other ways to provide funds for a universal COVID-19 vaccine besides an AMC. A more standard funding channel is to provide grants to researchers working in the area, so-called "push funding." AMCs are a form of "pull funding," providing funding only if a product is successfully created and widely distributed. While push funding has advantages in certain contexts, for example for early research on basic principles, AMCs have other advantages. Funders need not pick winners: innovating firms—which have the best information about their own capabilities—decide whether and how to invest, and the most capable of them are naturally the most drawn to the program. In addition, the funder can avoid the political risk of funding a project that does not generate a tangible success: if no product is developed under an AMC, the funder pays nothing to firms.

The heart of our analysis is a model of continuing harm from the COVID-19 pandemic and the random arrival of various vaccine technologies that can mitigate some of this harm. We model

pandemic harm as coming from a background mortality rate punctuated by periodic arrivals of a new variant of concern causing a substantial mortality wave. In the status-quo program, the arrival of a variant of concern sparks the development of a variant-specific booster. In our competing-events framework, the booster may or may not arrive in time to mitigate much of the mortality from the wave. On the other hand, a universal COVID-19 vaccine is not specific to current or future variants, so research and development, production, and administration can begin immediately, increasing the chance that people can be effectively immunized before the wave peaks, mitigating more mortality harm. In addition, the universal vaccine can mitigate more of the background mortality from currently circulating strains that are not well covered by boosters.

Using this model, we conduct Monte Carlo simulations of the incremental benefits of a universal COVID-19 vaccine relative to variant-specific boosters. We use CDC data on the historical COVID-19 experience to calibrate the arrival rate of variants of concern and the amplitude and shape of the mortality wave conditional on their arrival. Parameters that cannot be estimated from data are calibrated according to conservative assumptions, complemented with sensitivity analyses that insert more and less conservative parameters to gauge robustness. Our Monte Carlo results suggest that an AMC for a universal COVID-19 vaccine could generate an expected social benefit of over a trillion dollars in the United States alone, eclipsing by several orders of magnitude estimates of the cost of a vaccine AMC discussed in Section 6.

Our paper is outlined as follows. Section 2 provides a literature review. Section 3 describes the data used to model benefits. Section 4 presents our model of the relative benefits of a universal COVID-19 vaccine. Section 5 presents the results from baseline Monte Carlo simulations and sensitivity analyses. Section 6 discusses the role of an AMC to fund the vaccine and its estimated cost. Section 7 concludes. An appendix provides details on the use of an international panel to

estimate of variant arrival rates as a robustness check on the main analysis in the paper, which uses U.S. data.

2. Literature Review

Our paper draws on and contributes to three existing strands of literature. Our paper is closest to the literature estimating the economic, health, and educational costs of COVID-19 (for example Glennerster et al. 2023; UNESCO et al. 2021; Msemburi et al. 2023) and other pandemics (Barro et al. 2020; Alfani 2022). Studies published before the COVID-19 pandemic that predicted enormous potential losses from pandemics and high returns to investment in pandemic prevention now appear prescient: for example, Fan et al. (2018), for example, estimated $490 billion annual global losses from influenza pandemics in expectation. Studies have also estimated the benefits of COVID-19 vaccines, suggesting they saved between 13.7 and 15.9 million lives globally in the first year of deployment (Watson et al. 2022). Analysis conducted during the height of the COVID-19 pandemic estimated very large benefits of even small accelerations in the timing of production and distribution of COVID-19 vaccines: advance investments in vaccine capacity to accelerate distribution by three months would have generated over a trillion dollars of global benefit (Castillo et al. 2021). Over 2020–2021, COVID-19 was estimated to cost the U.S. economy 26 billion dollars a day from lost GDP and health toll (Cutler and Summers 2020), thus accelerating the end of the pandemic by just 12 hours would cover the 13 billion Operation Warp Speed program budget (Baker et al. 2021).

A relevant literature in epidemiology has estimated the mutation rate and spread of COVID-19 variants. The SARS-CoV-2 genome has a high dynamic mutation rate across multiple regions (Abbasian et al. 2023). Analysis of emerging variants during the height of COVID-19

observed exponential growth rates of highly transmissible variants, which were able to become the predominant variant in circulation within a month (Korber et al. 2020; Ward et al. 2021). The same pattern of exponential growth occurred in populations in which a majority had received the full original COVID-19 vaccine regimens, demonstrating existing vaccines were not sufficient to prevent the spread of a novel variant (Ward et al. 2021).

We draw on the literature proposing AMCs to fund vaccine development in general (Kremer 2000a; Kremer 2000b; Kremer and Glennerster 2004; Levine et al. 2005; Berndt and Hurvitz 2005; Kremer and Williams 2010) and for COVID-19 specifically (Chalkidou et al. 2020). Previous studies have estimated AMC benefits and costs: Berndt et al. (2007) provide estimates for vaccines targeting various neglected diseases and Snyder et al. (2020) for a COVID-19 vaccine. Snyder et al. (2011) and Kremer et al. (2020) analyze the outcome of the pilot AMC program to accelerate the rollout of a second-generation pneumococcal vaccine in low-income and middle-income countries. Kremer et al. (2022) provides a general theoretical analysis of AMCs.

3. Data

3.1. COVID-19 Mortality

We forecast the pattern of future COVID-19 mortality using the time series of COVID-19 mortality in the United States compiled by the CDC's National Center for Health Statistics (NCHS) National Vital Statistics Surveillance (NVSS). In particular, we use the series on provisional deaths, which counts deaths during the week for which the death certificate indicates COVID-19 as an underlying or contributing cause. Our sample includes 196 weeks of data

spanning from the first detected COVID-19 death in the United States (the week of January 11, 2021) through the time of this writing (the week of October 7, 2023).[1]

3.2. COVID-19 Variants of Concern

Our model centers the possibility of future COVID-19 variants emerging that cause increased mortality. A variant of concern (VOC) is a technical designation, reflecting a new variant's "increase in transmissibility, more severe disease (for example, increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures" (Centers for Disease Control 2023a). To date, the CDC has identified six VOCs, listed in Table 1. Of the six identified VOCs, three spread quickly and became the dominant variant in circulation, accounting for over half of positive COVID-19 tests (GISAID 2023). Each of these variants, Alpha, Delta, and Omicron, coincided with an observable increase in deaths following its emergence, which we refer to as a "wave."

[1] Delays in completing and transmitting death certificates lead the most recent CDC data points to be undercounts, which are revised upwards as more data come in. According to the CDC, the data are 85% complete within four weeks and 95% complete within eight weeks. We use the week ending on October 7, 2023 (four weeks prior to when the data was downloaded) as our last data point. Even after this truncation, our last few included data points are likely to be slight undercounts of eventual totals, imparting a slight conservative bias in our forecasts of COVID-19 deaths.

Table 1 Variants of Concern designated by the CDC

Covid-19 variant	Date designated VOC	Week of peak mortality	Death toll during peak week
Alpha	Dec. 29, 2020	Apr. 24, 2021	4, 601
Beta	Dec. 29, 2020	Never predominate	-
Gamma	Dec. 29, 2020	Never predominate	-
Delta	Jun. 15, 2021	Sep. 4, 2021	15, 493
Epsilon	Mar. 19, 2021	Never predominate	-
Omicron	Nov. 26, 2021	Jan. 22, 2022	21, 332

Our analysis focuses on the emergence of future variants that fit the criteria of a VOC capable of inducing a mortality wave. We estimate the arrival probability of variants and model the size of future variant waves from the data available on Alpha, Delta, and Omicron. Less harmful variants and subvariants are included as part of the estimate of background mortality.

The emergence of a VOC can initiate certain public health responses including adapting vaccines to increase efficacy (Centers for Disease Control 2023a). We model the status-quo vaccine program as initiating the development of a new booster vaccine at that time a VOC is designated. In the absence of a new VOC, a portion of the population obtains periodic boosters to increase their immunity to circulating variants, as with the seasonal flu vaccine. We suppose that any mortality benefit from regular administration of existing boosters is already reflected in the background mortality estimate.

3.3. COVID-19 Vaccination Rate

We use uptake of the first booster approved in the United States as a benchmark for the uptake of future approved COVID-19 vaccines. Other potential benchmarks include the seasonal influenza vaccine, the original COVID-19 vaccine, and the bivalent booster vaccine.

The annual influenza vaccine deployment shares many of the important characteristics of a universal COVID-19 vaccine. Influenza vaccines are an important public health measure, broadly promoted especially to vulnerable populations, and widely available. Such vaccines have become a routine part of healthcare in the United States for many people and are not dependent upon a general sense of crisis nor extraordinary measures to encourage vaccination such as vaccine lotteries or vaccine mandates by employers. As it turns out, the popularity of the influenza vaccine for the most recent flu season (Centers for Disease Control and Prevention 2023c) was very similar to the popularity of the original COVID-19 booster vaccine (Centers for Disease Control and Prevention 2023d). Roughly half the population received each vaccine. This suggests that half of the U.S. population might seek out a high-value and effective vaccine promoted by the U.S. health system.

The most optimistic benchmark for vaccine uptake would be the original COVID-19 vaccines. Those early vaccines proved to be popular, leading to two-thirds of the population being fully vaccinated. We think this is too optimistic a benchmark: subsequent COVID-19 waves will likely not prompt the same sense of crisis as the original outbreak.

A final benchmark would be vaccination rates associated with the bivalent booster vaccine. A universal COVID-19 vaccine would offer much greater benefits than a new booster and should therefore be more valued by consumers. Further, a vaccine that is created and purchased through an AMC would by definition have met clear benchmarks of efficacy to qualify for the AMC, which should contribute to public trust and interest. In contrast, the bivalent vaccine drew controversy by skipping human subject trials before its release (Vogel 2022).

To be conservative, we assume that both a new universal vaccine and a new variant-specific booster would have the same uptake pattern. In reality, to the extent the universal vaccine provides

more protection, it would be more popular with consumers. Since it is difficult to predict how much more popular, we err on the side of conservatism by assuming no greater uptake of the universal vaccines. If we assumed more greater uptake of the universal vaccine, this would increase our estimate of its incremental value. We think it is reasonable to suppose that a universal vaccine providing durable protection against the background risk of COVID-19 mortality as against a deadly new wave would be at least as popular as the first round of COVID-19 boosters used to set our uptake benchmark.

We source our data from the CDC's COVID-19 vaccination tracker (Center for Disease Control and Prevention 2023d). Following the FDA approval of first COVID-19 booster on September 22, 2021 (Food and Drug Administration 2021), the cumulative percent of the population who have completed their primary series and received a booster dose is recorded daily through June 2022 and weekly thereafter. For consistency, we construct a weekly vaccination rate throughout the entire sample. Data is available for 86 weeks after initial deployment. The vaccination rate remains stable near 51% over the last four months of data available, such that we consider this rate full deployment. Within 36 weeks of approval, 90% of full deployment is reached.

4. Model

4.1. Setup

The benefit of a universal COVID-19 vaccine depends on several factors, including the subsequent path of the pandemic (mortality, emergence of new variants, and duration), the progress of vaccine development (timeline and likelihood of success of universal and variant-specific vaccines), the

rate of vaccine uptake, and the value of a statistical life. The following sequence of subsections explains how we specify each of these factors in the model.

Our analysis focuses solely on mortality losses from the pandemic, not additional harm from morbidity, loss of classroom time, losses of economic output, and so forth. The loss from mortality will prove to be substantial enough to make a strong case for funding a universal COVID-19 vaccine by itself. Focusing on mortality exempts us from having to take a stand on how these other losses trend as the population adapts to the pandemic and exempts us from forecasting how effective future vaccines will be against COVID-19 infection and illness. To date, COVID-19 vaccines have evidenced more consistent protection against the most severe harms (hospitalizations and death) than against moderate ones (infection or illness not requiring hospitalization) (Wu et al. 2023).

For concreteness, we analyze the benefits of a universal COVID-19 vaccine in the United States. This focus allows us to use CDC data on U.S. mortality, which is less noisy than the global mortality series. The estimated benefits are likely to be applicable to other countries (with appropriate scaling to reflect population, value of a statistical life, and background deaths in other countries) since other countries have experienced a similar pattern of mortality waves from emerging variants.

We model the course of the COVID-19 pandemic starting from the present by assuming a steady-state background death toll will continue until the random arrival of one of three competing events: the emergence of a new variant of concern, the successful development of a universal COVID-19 vaccine, or the end of the pandemic. We assume a constant background death toll to simplify the path of COVID-19 mortality in the United States since the passing of the peak of the Omicron wave. Although the COVID-19 death toll has fluctuated somewhat around its mean since

the passing of the Omicron peak, reflecting seasonality, the delivery of new booster vaccines, and the emergence of small mutations of variants in circulation, it has remained relatively constant and not evidenced an obvious trend. The background COVID-19 death toll may eventually wane due to a variety of factors such as therapeutic advancements, the dominance of less harmful mutations, or growing natural immunity to circulating variants. The model reflects the eventual waning of the COVID-19 pandemic by incorporating a probability each week that the pandemic ends. Until then, the population faces the risk that a new VOC emerges.

We model the emergence of a VOC as a random variable. The emergence of a VOC has two effects in the model. First, it generates a COVID-19 wave resulting in substantial mortality (at least in the absence of an effective vaccine). Second, it triggers an attempt to develop a booster specific to that VOC. By definition, existing boosters have limited efficacy against a VOC, or the variant would not be of concern. Based on the time it takes to develop and deploy, the variant-specific booster might come too late to have much impact on reducing the spike in deaths from the new variant, as was the case during the Omicron wave.

In the model, the universal vaccine is assumed to be effective against all existing and future COVID-19 variants. In practice, a next-generation vaccine may be more or less universal than this. A vaccine that is only marginally more effective than current boosters against future COVID-19 variants would not generate substantial benefits in our analysis and thus would be an inadequate candidate for an AMC. The model requires the next-generation vaccine to cover future COVID-19 strains to qualify as "universal." Scientists have made progress on vaccines covering a broader range of pathogens than just COVID-19. A pan-sarbecovirus vaccine, protective not just against COVID-19 (also known as SARS-CoV2) but also against SARS-CoV1 and future variants of SARS, has shown promise in animal models (Yuen et al. 2023). One can imagine yet more

universal vaccines, say a universal Betacoronavirus vaccine covering MERS and some causes of the common cold in addition to all sarbecoviruses, or better yet a universal coronavirus vaccine covering all four genera of the coronavirus subfamily. The more universal the vaccine, the greater the benefits but the greater the scientific challenge. We focus on a universal COVID-19 vaccine since it strikes a balance, delivering sizable benefits without straining the boundary of scientific plausibility. It also simplifies forecasting, requiring us only to project the future path of the current pandemic rather than the arrival of future pandemics (see Glennerster et al. 2023 for the latter).

The universal COVID-19 vaccine has two benefits in the model, reducing the background COVID-19 death rate as well as reducing the spike in mortality from a VOC wave. We assume the universal COVID-19 vaccine, since it is more complex than a variant-specific booster, takes more time to develop. Still, if research and development on the universal vaccine starts on day one, it may beat the arrival of a new VOC wave and subsequent variant-specific booster.

4.2. COVID-19 Mortality

We model future COVID-19 mortality as composed of a constant background rate punctuated by random arrivals of waves caused by new VOCs. In the absence of a new VOC, COVID-19 is assumed to exhibit a background mortality rate equal to the average weekly COVID-19 deaths from April 2022 until October 2023. This is the period from the last spike in deaths due to a new VOC (i.e., the Omicron spike) until the end of our data sample. The background mortality rate is shown as the horizontal dashed line in Figure 1. This background weekly death toll is intended to be a simple way to capture a variety of ongoing factors contributing to COVID-19 deaths experienced since the Omicron wave, including seasonality, emergence of subvariants, and variant-specific boosters, such as the bivalent booster that became available in September 2022.

We assume that the weekly death toll of 1,918 continues until the random arrival of either a wave triggered by a new VOC or the end of the pandemic.

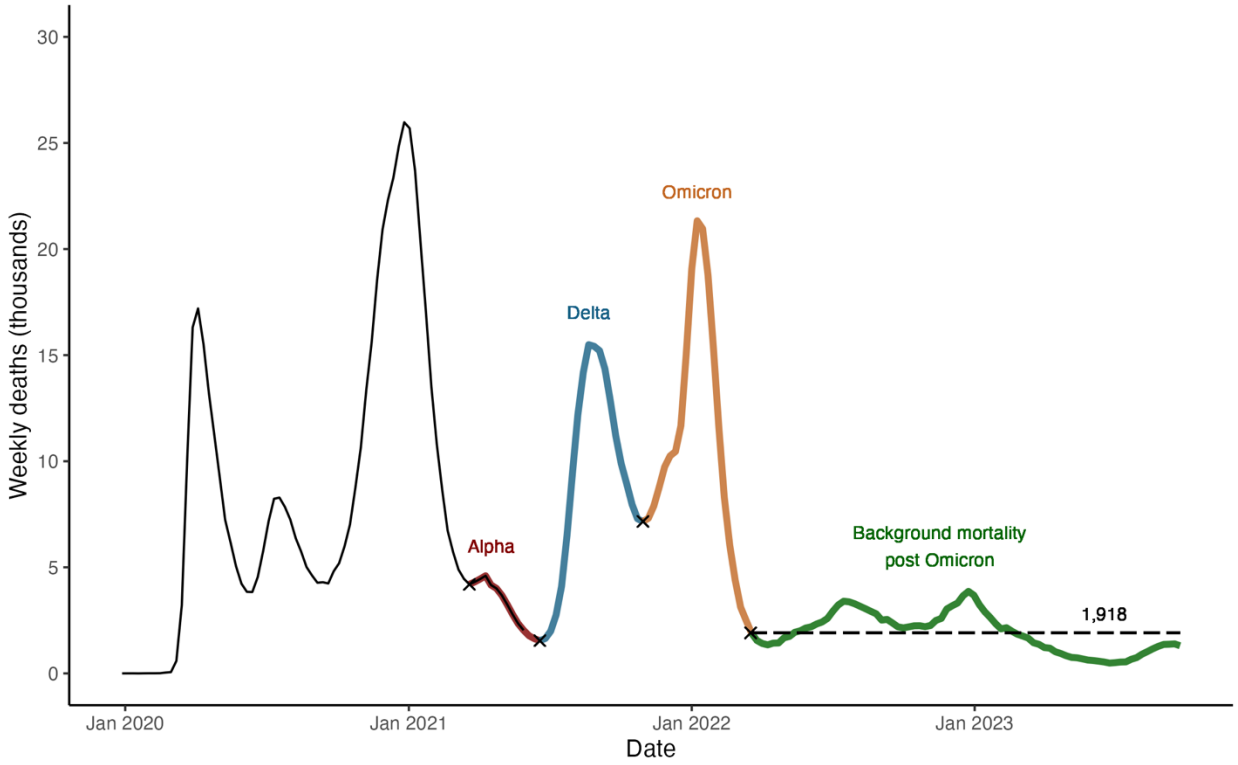

Fig. 1: Time series of weekly COVID-19 deaths. The figure graphs the weekly provisional death toll from COVID-19 from January 2020 to October 2023. The background death toll given by the horizontal dashed line is calculated as the average weekly deaths in the period after the Omicron wave peak (a period spanning from April 1, 2022, to October 7, 2023, the most recently available data point).

The constant background rate may be randomly punctuated by mortality waves. We will focus on modeling a subset of these mortality waves: those caused by the arrival of a new VOC. We have two reasons for this focus. First, putting aside the wild fluctuations in mortality early in the pandemic when the ancestral strain was dominant, in the period after the ancestral strain was replaced by VOCs, the mortality waves caused by the emergence of Alpha, Delta, and Omicron VOCs appear special, having much greater amplitudes than other waves observed during this period. Indeed, the fluctuations in mortality after the Omicron peak is sufficiently small that ironing out the fluctuations by assuming a constant background rate during that period appears to

provide a reasonable approximation. By contrast, ironing out the Omicron wave would do more violence to the data.

A second reason to focus on waves caused by the arrival of a new VOC is that VOC waves may respond differently to existing and future vaccines than waves due to other causes. By definition, the existing vaccines would have minimal efficacy against a VOC, and the ability of the status-quo program to develop variant-specific boosters will be tested. Upon the CDC determining a new VOC, a new variant-specific booster would need to start development to have any effect on reducing mortality from that point on. In this scenario, the value of advanced deployment of a universal vaccine would be well-defined.

Our procedure for estimating the contribution of VOC waves to mortality is divided into two steps: first estimating the arrival rate of waves and second estimating the shape of arriving waves (their amplitude and duration).

The first step is to estimate the arrival rate of mortality waves caused by new VOCs. Table 1 lists six designated VOCs, three of which resulted in detectable waves. A natural measure of the arrival rate of VOC waves is the number of events (three) divided by the number of weeks in the observation period. The estimate is sensitive to the number of weeks used for the denominator and may be biased by the wrong choice. A natural choice would be the number of weeks in the whole sample spanning the horizontal axis of Figure 1. The problem with using that number is that, by definition, a VOC represents a change to the ancestral strain, thus making it logically impossible for a VOC to emerge before the ancestral strain establishes itself, spreads, and mutates. Dating the observation period to the beginning of the COVID-19 pandemic overstates the period during which VOC could logically have emerged, biasing the arrival rate of a VOC wave downward. On the other hand, starting the observation period when the first VOC arrives imparts a positive selection

bias. We circumvent these biases by starting the observation period after the peak of the first (Alpha) VOC and estimating the arrival rate of subsequent VOC waves after the first. Our approach omits the Alpha peak from consideration and only considers the second and later VOC waves.

With two additional VOC waves over the 128 week period after Alpha's peak, we obtain an estimate of the probability of weekly arrival of $\hat{p} = 2/128 = 1.6\%$. A more formal method that allows the estimated arrival rate to be calculated based on covariates is provided by the literature on the analysis of recurrent events in discrete time (see Willett and Singer 2003 for a textbook treatment). Perhaps the simplest specification in this literature is the logit, writing the log odds of a wave peaking in week t as a linear function of a vector x_t of potentially time-varying covariates on the right-hand side,

$$\ln\left(\frac{p_t}{1-p_t}\right) = x_t\beta, \tag{1}$$

where β is a vector of coefficients to be estimated.

Table 2 reports the coefficient estimates for a specification with a constant arrival rate and one with a time trend. We will focus on the results in the first two columns using the same U.S. data shown in Figure 1. The coefficient estimates are difficult to interpret directly since they are in terms of log odds rather than probabilities. To aid interpretation, Figure 2 graphs the predicted probabilities derived from the coefficient estimates according to the transformation:

$$\hat{p}_t = \frac{\exp\left(x_t\hat{\beta}\right)}{1+\exp\left(x_t\hat{\beta}\right)}. \tag{2}$$

The constant specification returns the exact same estimate, $\hat{p} = 1.6\%$, obtained by dividing the number of events by weeks in the observation period. The specification with a time trend yields a sharply decreasing arrival rate, reflecting the arrival of two VOC waves within roughly a year of

the Alpha peak followed by a period of quiescence lasting over a year with no new VOC wave. The predicted arrival rate based on the specification with a time trend falls from $\hat{p}_1 = 6.5\%$ in week 1 of the observational sample to $\hat{p}_{128} = 0.1\%$ in the last week of the observational sample. Projecting beyond the observational sample to the future yields yet lower arrival rates.

Table 2 Logit estimates of arrival of new VOC wave

	U.S. data		Ten-country panel	
Variable	Constant	Time varying	Constant	Time varying
Constant	–4.14***	–2.64**	–4.29***	–3.23***
	(0.71)	(1.09)	(0.09)	(0.23)
Time trend		–0.034		–0.020***
		(0.028)		(0.005)
Observations	128	128	1,328	1,328

Estimates of coefficients from equation (1). The first two columns (using U.S. data) are estimated via a standard logit specification; the last two columns (using the ten-country panel) are estimated via a random-effects logit, adding a time-invariant random effect for each country, assumed to be normally distributed with mean 0 and variance σ^2.

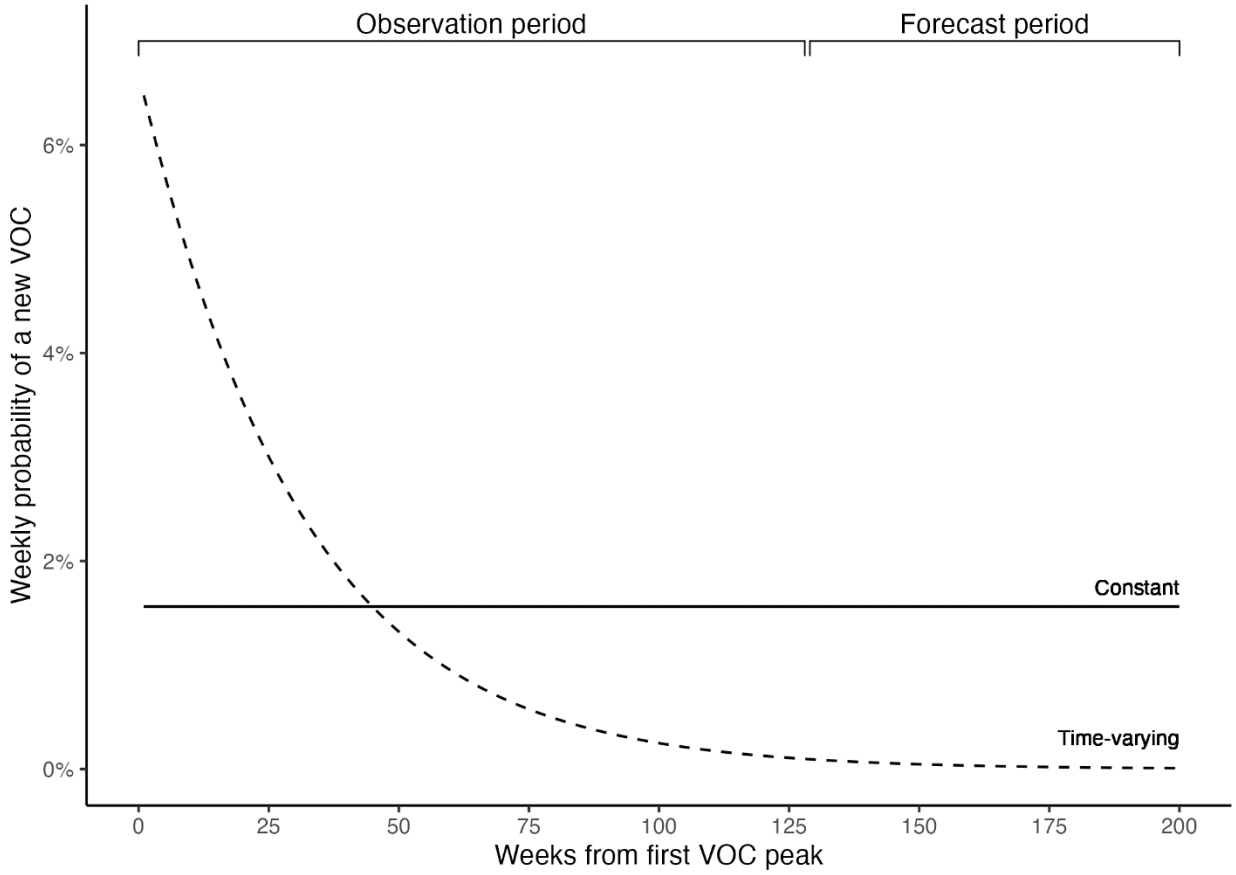

Fig. 2. Predicted probabilities of new VOC wave. Predicted probability on the vertical axis is the $\hat{p}_t$ in equation (2), computed as a function of t on the horizontal axis according to that formula. The figure shows the fit of the models both within sample (the observation period) and in the forecast period, when the universal vaccine would be relevant.

The last two columns of Table 2 provide alternative estimates of the arrival rate applying a random-coefficients logit specification to a panel of ten countries (the U.S. and nine additional countries) constructed as described in the appendix. The estimates are close to those using just the U.S. data, providing some reassurance of robustness.

Overall, the specification with a constant arrival rate predicts that future waves will be moderately likely, whereas the time-varying specification predicts they will be rare. The two specifications serve as bookends around the range of plausible assumptions on the arrival rate of future waves.

Having modeled the arrival rate of VOC waves, the next step is to model the shape of a VOC wave conditional on arrival. To do so, we use weekly data from the CDC on COVID-19 mortality during Alpha, Delta, and Omicron. The new VOC wave is assumed to be equally likely to have the shape of one of these three VOC waves experienced to date. Some work is required to extract pure wave shapes from the observed data because the waves partially overlap with each other along with fluctuations in mortality from the ancestral variant. For example, the uptick in deaths from the Omicron variant partially obscures the declining portion of the Delta wave. We leverage the fact that for all three VOC waves one or the other side of the wave is not thus obscured. We construct the complete path for the wave by assuming waves are symmetric around their peaks, taking the obscured side of the wave to have the same shape as the side that is cleanly observed. Figure 2 depicts our method for extracting the shape of the Alpha, Delta, and Omicron waves.

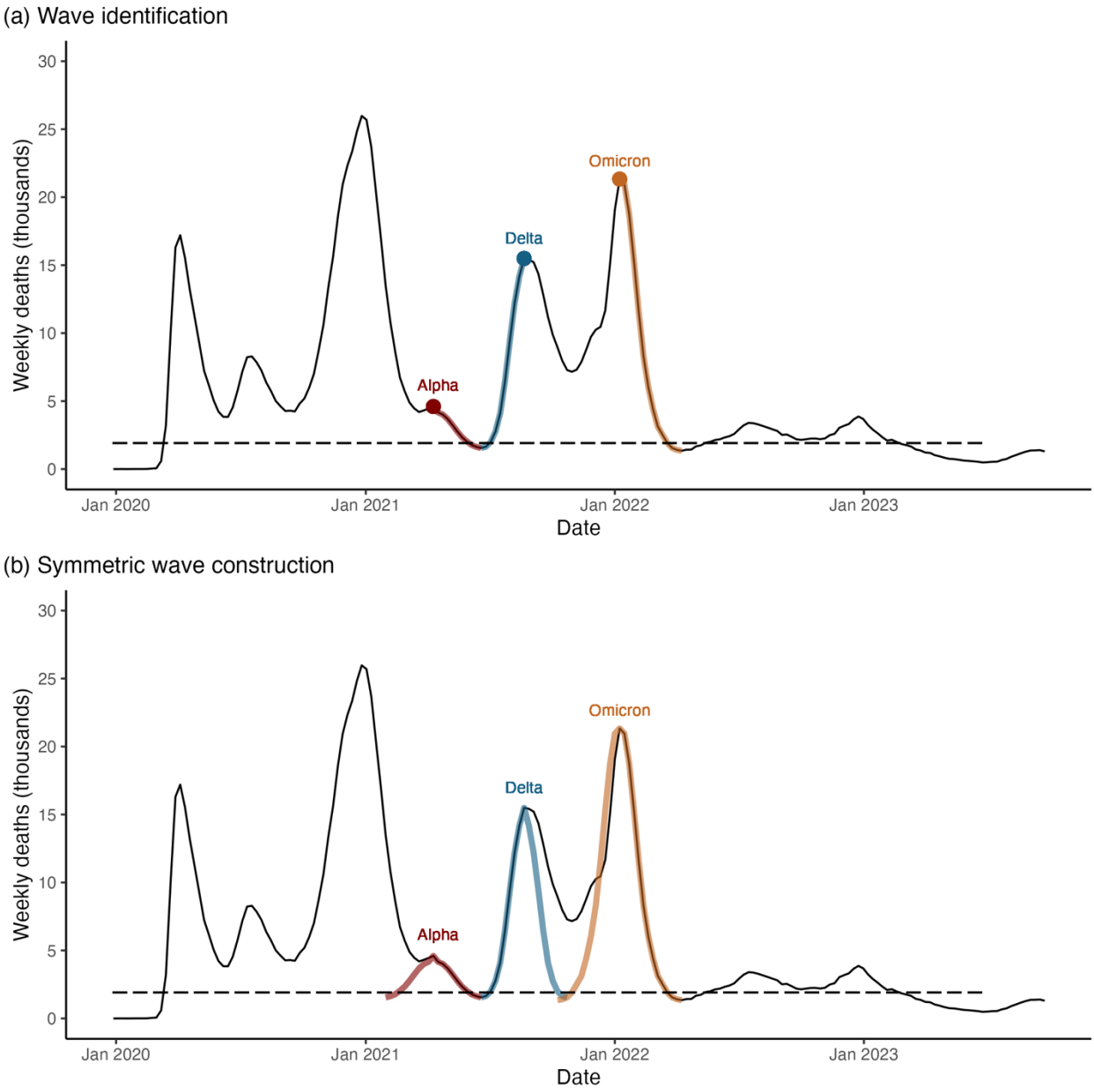

Fig. 2: Constructing VOC wave shapes. The figure shows how we construct the shape of new VOC waves used in simulations from observations of the Alpha, Delta, and Omicron waves. In both panels, the solid black curve plots a time series of weekly provisional COVID-19 deaths. The dashed horizontal line indicates the background death toll, calculated to be 1,918. In panel (a), the peaks of the Alpha, Delta, and Omicron waves are identified with dots and the sides of the waves that can be cleanly observed are highlighted with a bold color. In panel (b), the constructed wave is completed by assuming the death toll around each peak is symmetric. The side of the wave that can be cleanly observed is reflected about the peak to fill in the shape of the wave on the other side.

We can assess the goodness of fit of constructed waves by comparing them to the observed wave on the obstructed side when that obstruction is only partial, allowing part of that side to be cleanly observed. The overall fit is good. Any divergence (for example the fall from the peak of the Delta wave) if anything understates actual mortality, which would lead our analysis to generate conservative estimates.

One final adjustment is made to the constructed wave shapes in Figure 2(b) before using them in the simulations. For some of the VOC waves, the CDC designated the variant as a VOC before the resulting mortality wave began to rise above the background rate by observing elevated infection rates and international variant behavior. VOC designation can trigger a series of countermeasures including development of vaccines targeted to the variant (Centers for Disease Control and Prevention 2023a). To reflect the possibility that development of a variant-specific booster may start before mortality starts to increase in a VOC wave, as shown in Figure 3, for each of the Alpha, Delta, and Omicron waves, we shift the constructed wave so that the period between VOC designation and the wave's peak matches the same period in the data. This results in adding an anticipatory period of about ten weeks for our Alpha construction, five weeks for our Delta construction, and no anticipatory period for our Omicron construction (indeed, our Omicron construction starts when mortality is already slightly above the background rate). The constructed wave ends when the death toll returns to the background level, and the background level persists until if and when a new VOC wave is drawn in the simulation.

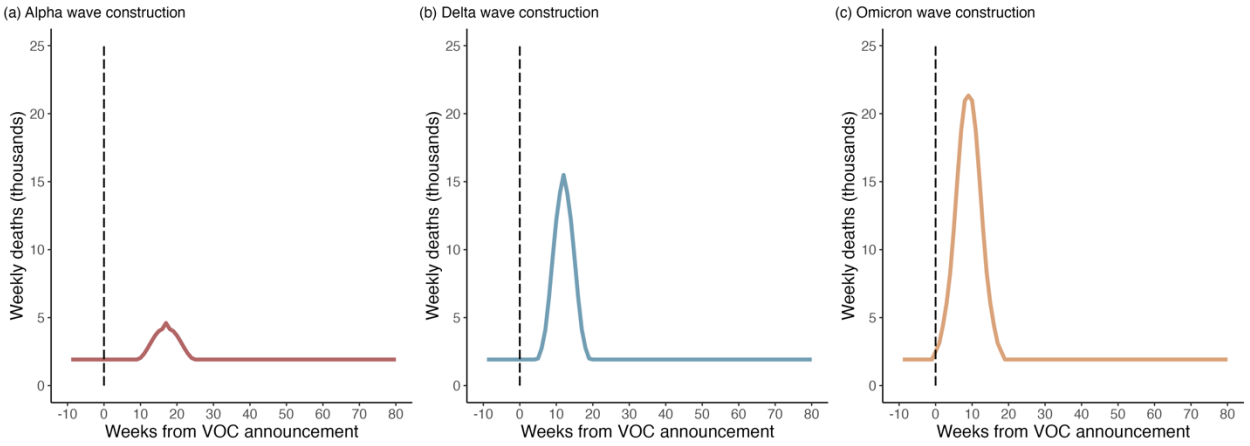

Fig. 3: Modeled VOC waves. The figure shows how the three possible future VOC waves are modeled in our simulations. We define a wave starting at the time of a VOC announcement and ending when it has returned to the steady-state death toll after peaking.

In the simulations, new VOC waves have some probability of arriving each week. Since our constructed waves last longer than a week, this entails at least a small chance that two or more waves may overlap. We compute the death toll in the event of overlapping waves by summing the background death rate and each wave's incremental death toll above the background rate. This formula avoids double counting the background rate.

4.3. Pandemic Duration

While difficult to predict when, COVID-19 mortality may eventually wane due to the development of therapeutics, technological interventions that diminish transmission, the emergence of less harmful mutations, or increasing population immunity. Case numbers could fall to the point that there is minimal death toll and little chance of the emergence of a new VOC. The features of the model introduced so far—a constant background mortality rate and waves that increase mortality above the background rate—do not incorporate the possibility that the pandemic wanes. To

incorporate this possibility, we introduce a weekly probability that the pandemic ends in the model. Specifically, the end of the pandemic is a geometric random variable with a mean of 260 weeks (about 5 years). The implied median for pandemic duration in the model is 180 weeks.

We acknowledge that the world may never be rid of COVID-19. Having a random end to the pandemic is model shorthand for the possibility that COVID-19 becomes much less of a public-health concern for whatever reason. Given the uncertainty about when this might happen, we allow for different values of the mean duration in sensitivity analyses.

Introducing a random end to the pandemic in the model tempers the assumption of a constant background mortality rate. Expected future mortality is not constant but declines geometrically at a rate given by the weekly probability the pandemic ends.

4.4. Vaccine Development

COVID-19 vaccines became available to the U.S. population within 12 months of the wide circulation of the original SARs-CoV-2 virus. Likewise, the Omicron booster became available in the United States within a year of the wide circulation of the Omicron variant. These development timelines were hailed as scientific breakthroughs, yet still, hundreds of thousands of U.S. deaths occurred between the emergence of the pathogen and the development of a vaccine (Figure 4). The expected development timelines of future variant-specific boosters and a universal vaccine can be informed by the prior experience with COVID-19 vaccines.

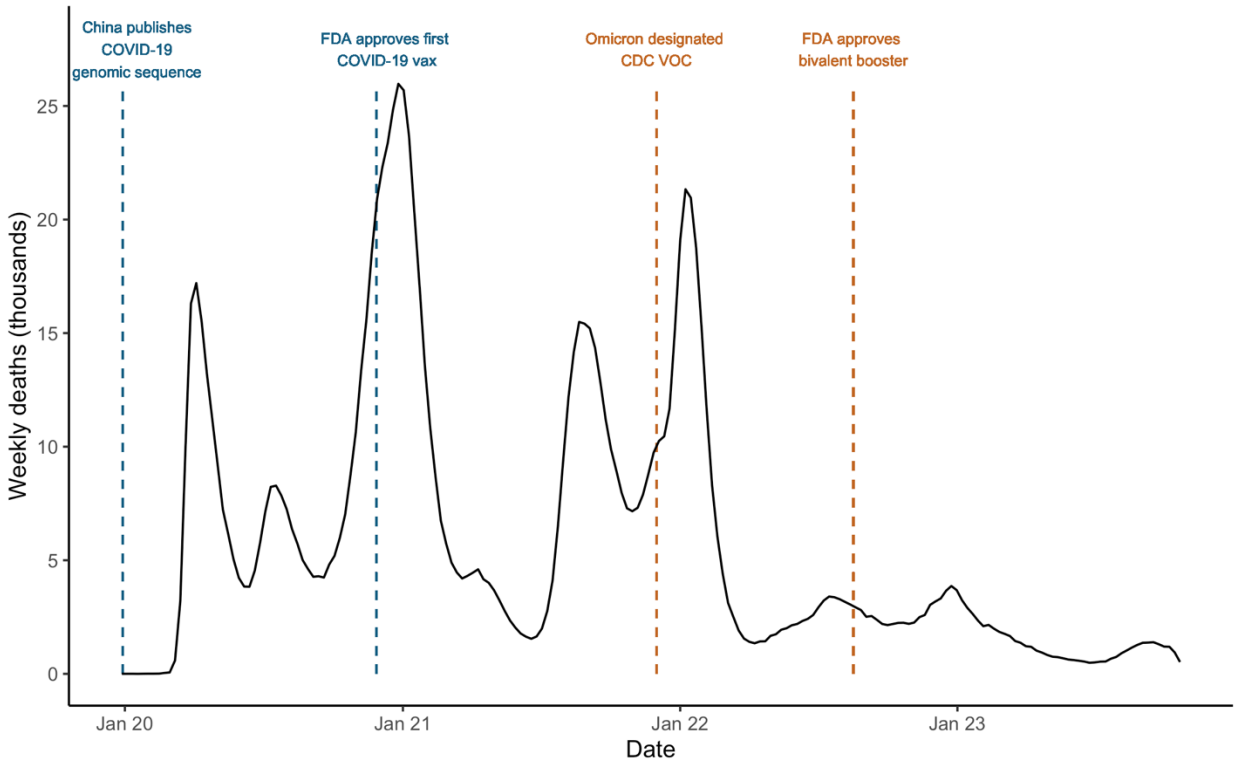

Fig. 4: Landmarks in COVID-19 vaccine development. The figure uses dotted lines to demarcate key events in the development COVID-19 vaccines. Weekly COVID-19 mortality graphed as a solid curve contextualizes the events relative to various COVID-19 waves.

Agarwal et al. (2021) suggest that streamlined regulatory procedures, rapid and widespread sharing of disease information, technology advancements, at-risk investment, and operational excellence were all key factors enabling the timeline of COVID-19 vaccine development to be shortened to a year. While many of these factors could also apply to the development of a universal COVID-19 vaccine, the advanced technological features of mRNA vaccines that the authors suggest are responsible for cutting up to a year off the development timeline may not apply to a universal vaccine. To be conservative, we increase the mean development time for the universal COVID-19 vaccine from one to two years. We model the arrival of a universal vaccine as Poisson random variable with parameter $\lambda_u = 104$ weeks (equal to the mean arrival time for Poisson

random variable) starting from the first week of the simulation, which we take to be the time of this writing (October 2023).

We expect a variant-specific booster would be able to take full advantage of the accelerated timeline from the initial COVID-19 vaccines and subsequent boosters. Even further, pandemic preparedness organizations are working to continue accelerating the timeline of vaccine development to a goal of 100 days from the sequencing of a new pathogen (International Pandemic Preparedness Secretariat no date, Coalition for Emergency Preparedness Innovations no date). A review of their proposed plan determined that a vaccine development timeline of 250 days would be feasible but optimistic (Saville et al. 2022). We chose to use this estimate of 250 days as the mean timeline of a variant-specific booster. An ambitious estimate of a booster development results in a conservative estimate of the incremental value of a universal vaccine. A variant-specific booster cannot start development until the new variant is identified and sequenced. Reflecting the preceding considerations, the arrival of a booster vaccine is specifically modeled as a Poisson random variable with mean $\lambda_b = 36$ weeks (36 weeks approximately equals 250 days expressed in the unit of time used in the model), starting from the week that a new VOC is identified. For readers who believe this is too optimistic or pessimistic of outlook, sensitives of this parameter presented in Section 5.3 show little impact on the benefits estimate.

We calculate benefits are conditional on a successfully developed and deployed universal COVID-19 vaccine. This is a useful input into calculations later in the paper of expected program benefits. In particular, Section 6 evaluates the expected benefits of an AMC to incentivize vaccine development. This is done by taking the estimated benefit of a successful universal vaccine as an input and multiplying it by the incremental probability that the AMC leads to a successful universal vaccine relative to the status quo.

4.5.Vaccine Efficacy

COVID-19 vaccines have historically been about 90% effective at preventing severe disease and mortality in the variant to which they are tailored (Jara et al. 2023; Tenforde et al. 2022). We assume subsequent booster and universal vaccines would be similarly efficacious, if not superior. The technical specification of a universal COVID-19 target vaccine would likely be benchmarked to the performance of other available variant-specific vaccines. If a universal vaccine is less effective at preventing severe disease, it is not clear that the public would or should prefer the universal vaccine. Hence, we model both booster and universal vaccines as preventing mortality by 90%.

Because the universal vaccine is effective against all COVID-19 strains, it can begin providing benefits by reducing background COVID-19 deaths as soon as it is released. Reductions in mortality can occur before, during, and after a new VOC wave. If a universal vaccine is developed during a non-peak time of cases or during a peak but before a booster vaccine is developed, we assume that it will take 100% market share. If a universal vaccine is developed during a peak but after a booster vaccine is developed, we assume that there will be a 13-week (three-month) delay in universal vaccine deployment. This simulates the time needed to repurpose the already deployed manufacturing capacity. Incorporating this delay also simplifies the model and reduces the need to make assumptions about the market share of each vaccine.

We model the booster vaccine as only offering benefits during the spike of deaths caused by a new VOC. The background steady-state rate of deaths following the spike caused by a VOC is estimated from the number of deaths experienced since the Omicron surge. We assume the steady-state weekly death toll already encompasses the reduction in deaths from waning immunity of previous boosters and additional boosters being developed such as the bivalent booster approved

in September 2022. Hence, allowing a new booster vaccine to offer benefits during this period would account for a duplicative effect.

4.6. Valuing Lives

We assume that preventing a single COVID-19 death is worth $13.5 million, which is an inflation adjustment of the U.S. Federal Emergency Management Administration's estimate of $11.6 million in 2020 dollars (Federal Emergency Management Administration 2022). This estimate is close to others used in the literature and across federal agencies. Kniesner and Viscusi (2019) calculated that the value of a statistical life in the United States is worth $10 million. The Environmental Protection Agency suggests using a value of $7.4 million in 2006 dollars which inflation-adjusted is $11 million in 2023 dollars. In 2016, the Department of Agriculture and the FDA valued life at $8.9 million and $9.5 million, respectively (Merrill 2017).

4.7. Other Pandemic Losses

Our estimates of pandemic losses focus only on mortality, not morbidity, economic-output losses, or learning losses. Such additional losses can be substantial. For example, Glennerster, Snyder, and Tan (2023) estimate average annual global losses of over $700 billion from pandemics going forward, of which they attribute 73% to mortality losses and 27% to economic output and learning losses. Valuing a universal vaccine on just averted deaths provides a conservative estimate.

4.8. Model Parameters

A complete list of our model parameters is included in Table 1. Section 5.3 presents the results of a sensitivity analysis of our model to these parameters.

Table 3 Model parameters

Parameter	Description	Baseline value
Value of statistical life, v	Economic value used to monetize benefit of avoiding a fatality	$13.5 million
Vaccine efficacy, e	Reduction in mortality risk for immunized person	90%
Mean pandemic duration, d	Pandemic end modeled as a geometrically distributed random variable with parameter $1/d$	364 weeks
Mean development time of universal vaccine, λ_u	Arrival of universal vaccine modelled as a Poisson random variable with parameter λ_u	104 weeks
Mean development time of variant-specific booster, λ_b	Arrival of variant-specific booster modeled as a Poisson random variable with parameter λ_b	36 weeks

5. Monte Carlo Simulations

5.1. Setup

To evaluate the social value of a universal COVID-19 vaccine over the status quo of variant-specific boosters, we conduct 100,000 Monte Carlo simulations. The simulations are run by drawing from the distributions of the random arrival of a universal COVID-19 vaccine and the random arrival of new VOC waves. Conditional on a new VOC wave arriving and no universal COVID-19 vaccine having yet been developed, we draw from the distribution of the random arrival of a specific booster. A random draw from the geometric distribution to determine when the pandemic ends.

All results are expressed as dollar values in present value terms assuming a real annual social discount rate of 4%. We take this to be a simple discount rate, translated into a rate per week (the unit of time in the simulation) by dividing 4% per year by 52 weeks per year.

5.2. Baseline Simulation Results

The simulation results are summarized in Table 4 (incremental benefits) and Table 5 (additional outcome variables from the simulations). The mean benefit from a universal COVID-19 vaccine over the status quo of variant-specific boosters depends on how the arrival rate of new VOC waves is modeled. Assuming a constant arrival rate, waves arrive fairly frequently, with an average of 2.7 arriving after the universal vaccine is developed. The incremental benefit has a mean of $2.6 trillion. About a third of the incremental benefit is from averting deaths due to waves and the remaining two-thirds is due to reducing the background death toll.

The estimated arrival rate when allowed to be time-varying is sharply decreasing. Forecasted into the future, waves are expected to be extremely rare according to this model, an average of only 0.03 per simulation and only .001 arriving after the development of a universal vaccine. With fewer waves, the death toll is lower and fewer are the deaths averted by a universal vaccine. The benefit of the universal vaccine is thus lower, about 60% of the incremental benefit from the constant-arrival-rate model, with a mean of $1.5 trillion. With so few waves, very little of the incremental benefit is due to averting deaths during the wave; essentially all of it comes from reducing the background death toll.

Table 4 Distribution of incremental benefits of a universal COVID-19 vaccine across baseline simulations

	Incremental universal COVID-19 vaccine benefit (present value, trillion $)	
Statistic	Constant wave arrival rate	Time-varying wave arrival rate
Mean	2.63	1.50
Median	1.02	0.66
75th percentile	4.21	2.41
90th percentile	7.78	4.38
99th percentile	14.44	7.97

Table 5 Additional outcomes across baseline simulations

Variable	Constant wave arrival rate	Time-varying wave arrival rate
Mean number of waves	4.0	0.03
Percent of simulations with universal vaccine before end	67%	67%
Mean number of waves after universal vaccine developed	2.7	0.001
Mean incremental benefit from universal vaccine from wave deaths	$1.1 trillion	$256 million
Mean percent of incremental benefit of averting wave deaths	34%	0.01%

A key insight drawn from the simulations is that a variant-specific booster rarely arrives in time to quell the spike in deaths associated with a new VOC wave. Despite the optimistic timeframe (36 weeks) assumed for the development of the variant-specific booster, given that development of the booster can only start after the VOC has been identified, at which point the mortality wave is already taking off, in fewer than 1% of runs does the booster arrive before the mortality from the wave has returned to baseline rates. The key insight from the simulations aligns with the experience during the Omicron variant. The bivalent booster tailored to the Omicron strains was not released until nine months after Omicron was identified as a VOC.

The incremental benefit of a universal vaccine over the status quo has a skewed distribution with a long right tail. The long tail in incremental benefits reflects randomness in pandemic duration, which also has a long right tail. The median incremental benefit is only about 40% of the mean. The 99% percentile is more than five times the mean. The duration of the pandemic in the 99th percentile simulation is 22 years. The universal vaccine has substantial incremental value in typical (median) simulations but extraordinary value in outlying simulations. While scenario in which the pandemic continues to generate mortality waves for decades may be quite unlikely, it is still valuable to have some insurance against them in the form of an effective vaccine.

5.3. Sensitivity to Model Parameters

Table 6 presents the sensitivity of incremental benefits to changes in model parameters. The results are most sensitive to how the arrival rate of new VOC waves is modeled, whether a constant or a time-varying rate, reflected in the separate results by column. As noted above, the arrival rate of waves is moderately high with a constant arrival rate but forecasted to the future falls virtually to zero with a time-varying rate. Pandemic harm, and the benefits of a universal vaccine to mitigate this harm, is bookended by the two specifications, ranging between $1.5 trillion and $2.6 trillion.

The table's rows report changes to other model parameters. Even the fairly substantial changes considered have relatively modest effects on the results, providing some confidence in their robustness. Changes in vaccine efficacy e by ten percentage points in one direction or the other leads to about a 10% change in incremental benefits in the expected direction. Changes to λ_b, the mean development time of the variant-specific booster, have little effect on the results because the boosters' main effect is to quell mortality from a new VOC wave but typically arrive too late to cut into the wave's peak.

Changes to λ_u, the mean development time of the universal vaccine, have a significant impact on incremental benefits. The faster the vaccine is available, the more time it can provide benefits before the pandemic ends. Cutting a year off the mean development time increases incremental benefits by over a quarter. Increasing the mean development time by a year decreases incremental benefits by around 20%.

The lowest estimate appearing in the table appears in the column for the specification with a time-varying arrival rate in the row that considers a three-year mean pandemic duration for the universal vaccine. Even in that conservative entry, we see that new benefits from a universal vaccine are estimated to be $717 billion.

Table 6 Sensitivity to model parameters

Parameter	Mean incremental benefit from universal vaccine (trillion $)	
	Constant wave arrival rate	Time-varying wave arrival rate
Baseline scenario	2.63	1.50
Vaccine efficacy e (baseline 90%)		
Reduce to 80%	2.34	1.34
Increase to 100%	2.92	1.67
Mean pandemic duration d (baseline 5 years)		
Reduce to 3 years	1.25	0.72
Increase to 7 years	3.90	2.25
Mean development time of universal vaccine λ_u (baseline 2 years)		
Reduce to 1 year	3.34	1.91
Increase to 3 years	2.07	1.18
Mean development time of booster vaccine λ_b (baseline 36 weeks)		
Reduce to 14 weeks	2.55	1.50
Increase to 52 weeks	2.62	1.50

See Table 3 for parameter definitions. For each sensitivity analysis, all other parameters besides the one indicated are held constant at the baseline value.

6. Incentivizing Development with an Advance Market Commitment

This section identifies market failures that might lead to underinvestment in research, development, and production of a universal COVID-19 vaccine despite its large estimated social value presented in Section 5. We discuss a policy, an advance market commitment (AMC), that holds promise to incentivize its acceleration. An AMC is a legally binding commitment to purchase or subsidize a prespecified quantity of a vaccine at a prespecified price or subsidy rate once it is developed if it meets certain criteria. This section discusses some of the pros and cons of AMCs in the context of funding a universal COVID-19 vaccine.

6.1. Case for Public Subsidy

Several arguments can be offered for the need for public support to provide adequate incentives for commercial firms to develop a universal COVID-19 vaccine. Across a broad range of markets, not just vaccines, innovation tends to be underprovided since patents and other forms of intellectual property only allow innovators to capture a portion of the social benefits of an innovation (Arora et al. 2008). The high social returns to innovation observed in many areas are evidence of underinvestment in innovation (Jones and Summers 2021).

The market for vaccines presents a stronger case for public subsidy than the average market. Vaccines that prevent infection and transmission provide a positive epidemiological externality, which the recipient of a dose may be unwilling to pay for (see, e.g., Goodkin-Gold et al. forthcoming). Kremer and Snyder (2015) argue that drugs bought by consumers who have contracted the disease may extract more revenue from consumers than vaccines bought before.

Because of the high social returns, governments often subsidize consumer purchases or buy vaccines for citizens outright. However, governments face a time inconsistency problem: they may value a vaccine highly in anticipation but once an inventor has sunk resources into development, the government faces pressure to exercise their monopsony power to hold down prices. Knowing this, innovators will be reluctant to invest in the first place. This time inconsistency is exacerbated when a vaccine is most useful during a public health emergency (as a universal COVID-19 vaccine would be). During these emergencies, there is strong societal pressure to keep prices well below social value (Roth 2007). For example, during the initial period of COVID-19 vaccine supply shortages, Castillo et al. (2021) estimated a course of the original COVID-19 vaccine to have an average social value of $5,800 globally, eclipsing the $6 to $40 prices manufacturers were charging at the time. Without intervention, the private market will

produce a smaller quantity than is socially optimal because of the standard monopoly price distortion where a producer of a product with a patent faces a downward-sloping demand curve. The challenge of optimal production in the face of demand uncertainty for a universal COVID-19 vaccine illustrates how these market failures interact. There is a high insurance value to society of having high production of the vaccine to cover the situation when a future wave leads to higher-than-average demand for the vaccine. The innovator does not get rewarded for this high insurance value of large production. Instead, if they produce a large quantity, they get excess supply in low-demand scenarios, which puts downward pressure on the price for all their sales while under the high-demand scenario (a deadly wave) they will be unable to raise their price because of social pressure.

6.2. Case for an AMC

We have argued that government or philanthropic support is needed to overcome the market failures to incentivize the development of a universal COVID-19 vaccine. Here we discuss the pros and cons of providing the support through an AMC. An AMC is part of a broader class of incentive mechanisms often referred to as "pull funding" that tie payment to the achievement of an outcome (in this case purchase of an effective vaccine). "Push funding," by contrast, provides grant funding for inputs such as researcher team effort or covering the cost of a clinical trial; the payment is made whether or not a product is eventually produced successfully. A key advantage of an AMC is that it places the burden of innovation risk and market risk on the entity with the most relevant information: the innovator has private information on the likely success of their product, and they bear the risk their vaccine will fail; the funder knows how much they value the vaccine and takes the risk that an alternative solution may come along and make the vaccine less

valuable. This contrasts with a more standard grant to an innovator where the funder has to pick which candidate vaccine to fund, i.e. judges innovation risk. An AMC also solves the time inconsistency and monopoly pricing distortions mentioned above. By setting a legally binding price commitment in advance of innovators deciding whether to invest, the AMC solves the time inconsistency problem. An AMC solves the monopoly pricing problem by committing to a price/quantity bundle that is sufficiently large to cover the fixed costs of development but in exchange requires the innovator to produce at high quantity.

6.3. Estimating AMC Benefits

Our previous estimates of the social benefit of a universal COVID-19 vaccine were computed conditional on its successful development, in effect setting the probability of successfully developing a universal vaccine to 100%. An AMC does not guarantee that a universal vaccine would succeed, however, even if it incentivizes more investment. Nor does the absence of an AMC guarantee that no universal vaccine would be developed, as evidenced by the dozens of universal coronavirus candidates in preclinical trials (Dolgin 2022) despite the current absence of an AMC. Translating the incremental benefits from a product (in this case, a universal vaccine) to the incremental benefits from a funding program incentivizing the product (in this case, an AMC) requires several additional steps.

Several approaches can be taken to modeling the incremental benefits of an AMC relative to the status quo. One approach is to specify that the AMC increases the probability that a universal COVID-19 vaccine is developed and rolled out to the specified population by some $\Delta\pi \in [0\%, 100\%]$. The first panel of Figure 5 provides the underlying information needed to complete the calculation. The panel graphs the incremental benefits of a universal COVID-19 vaccine

relative to the status-quo booster program as a function of the universal vaccine's probability of success (π). The graph starts at a value of zero when the universal vaccine certainly fails ($\pi = 0\%$) and increases linearly with π from there, extending up to the full benefit reported in Table 6 ($2.6 trillion in the specification with a constant wave arrival rate, $1.5 trillion in the specification with a time-varying arrival rate) for a universal vaccine that always succeeds ($\pi = 100\%$).

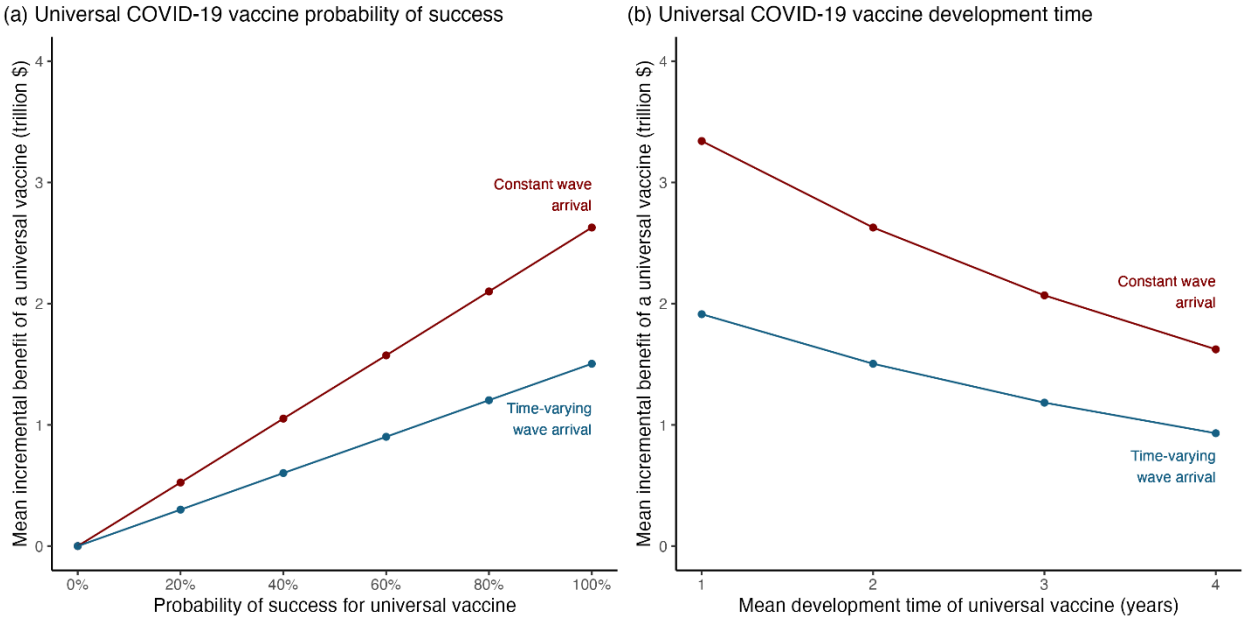

Fig. 5. Translating incremental benefit from a universal vaccine into incremental benefit from an AMC. Panel (a) plots the incremental benefit of a universal COVID-19 vaccine as a function of its probability of success. Panel (b) plots the incremental benefit of a universal COVID-19 vaccine as a function of its mean development time from simulations that model the vaccine's development timeline as a Poisson random variable with the mean development time along the x-axis.

The incremental benefit an AMC relative to the status quo can be read off the graph as a rightward shift along the line from one point to another, depending on how much the AMC increases the probability of developing a universal vaccine. For example, suppose it is 20% likely that a universal vaccine would be developed even in the absence of an AMC, and AMC incentives increase this probability to 60%. Then social benefits increase from $300 billion to $900 billion in

the model with time-varying wave arrival and increase from $526 billion to $1.578 trillion in the model with constant wave arrival. Thus, the incremental benefit of the AMC in this numerical example is $900 billion − $300 billion = $600 billion in the model with time-varying wave arrival and $1.578 trillion − $526 billion = $1.052 trillion in the model with constant wave arrival. Given the linearity of the incremental social value of a universal vaccine in its probability of success, the incremental value of the AMC can be simply computed by multiplying the results from Table 6 for a certainly successful universal vaccine by $\Delta\pi$, the increment to the probability of success due to the AMC.

An alternative approach to modeling the incremental benefit of an AMC is to specify that it accelerates the development time of the universal vaccine. Ahuja et al. (2021) suggested that an AMC designed to respond to a pandemic should only offer payment for vaccines delivered within a certain time frame to encourage scaling up manufacturing capability. An AMC for a universal COVID-19 vaccine might incorporate feature directly or indirectly via a sunset provision. The acceleration from an AMC was successful in the pneumococcal vaccine which resulted in widespread distribution five years faster than the rotavirus vaccine which was not supported by an AMC (Kremer et al. 2020).

The incremental benefit of an AMC from this perspective can read off the second panel of Figure 5, which plots the incremental benefits of a universal COVID-19 vaccine under various development timelines. The faster a universal vaccine is developed, the sooner it can reduce mortality from background deaths and quell VOC waves. The incremental benefit of an AMC that accelerates universal vaccine development can be read as a leftward shift from one point to another along a curve. For example, suppose the mean arrival time of a universal vaccine is four years in the absence of an AMC and two years in its presence. Then the incremental benefit of the AMC is

$1.504 trillion − $931 billion = $573 billion in the model with time-varying wave arrival and $2.628 trillion − $1.623 trillion = $1.005 trillion in the model with constant wave arrival.

6.3. Costing an AMC

Our analysis suggests a universal COVID-19 vaccine is highly valuable. How much should a funder be willing to pay for it? We seek benchmarks for the cost of procuring a relatively novel vaccine. One such benchmark can be drawn from the initial contracts offered for the COVID-19 vaccines, also novel at the time. According to the Congressional Research Service (2021), the contracts offered by the U.S. government under Operation Warp Speed involved substantial fixed and variable payments. The U.S. government provided development funding for Moderna ($954 million) and Johnson & Johnson ($456 million). In procurement contracts, the U.S. government paid $19.90 per dose in the Pfizer contract for 300 million doses (total of $5.97 billion), $16.47 in the Moderna contract for 300 million doses (total of $5.89 billion), and $10 in the Johnson and Johnson contract for 100 million doses (total of $1.46 billion) (U.S. Department of Health and Human Services, no date). Contributing to the higher price of the Pfizer and Moderna was the novelty of those mRNA vaccines. Assuming the AMC purchases enough of the universal vaccine that to cover everyone in the United States who wishes to receive it, that roughly half of the U.S. population (165 million) does so, basing the price on the original contract with Pfizer, and ignoring discounting, the AMC would require $6.4 billion in funding.

The Pfizer contract is not a perfect benchmark for an AMC for a universal COVID-19 vaccine, differing on several dimensions, some which would lead to higher program costs, some lower. The Pfizer vaccine was developed under pandemic conditions at unprecedented speed, pushing up costs. An alternative way to estimate the size of AMC needed is the size of market that

pharmaceutical companies typically need to invest in development and production of novel pharmaceuticals. By reviewing pharmaceutical company spending on pharmaceuticals marketed to rich countries, Levine, Kremer, and Albright (2005) suggest that $3 billion would be sufficient to attract pharmaceutical company investment. Adjusted for inflation, the appropriate amount would be $4.7 billion. This is similar to the funding suggested by the original Operation Warp Speed contracts.

Setting the optimal size for the AMC fund involves guesswork: it is impossible for the funder to know the firm's cost of developing and producing the final vaccine or the probability that its considerable investment does not result in a successful vaccine. While economizing on program expense is an important consideration, it is not the sole consideration; the optimal program for the funder is not necessarily achieved by ensuring price is as close as possible to the vaccine's marginal cost (or even its average cost). The loss function from getting the optimal price wrong may be asymmetric: if the price is set too low, firms may not be adequately incentivized to develop a vaccine and enormous social value may be lost; on the other hand, even if the price ends up being substantially above a successful firm's costs, it is still likely to be well below the social value of the vaccine.[2]

AMC funds would not be paid out if a universal vaccine fails to be developed, but other unmodeled costs may not be thus saved, for example, the up-front costs in designing the program (time and money) may have to be sunk and political capital expended. The expected benefits from

[2] Snyder, Hoyt, and Gouglas (2023) derive the optimal vaccine-funding mechanism under asymmetric information, showing it has the structure of a reverse Vickrey auction with reserve, inducing an endogenous number of candidates to invest. To apply to the present context involving a complex mortality pattern would require extending their static model to a dynamic model.

the program presented in Section 6.3 can help inform policymakers whether such up-front investments are worthwhile.

The costing exercise has so far focused on the total costs of an AMC program. This is a useful number to know for budgeting purposes, but perhaps more useful is the AMC's incremental cost compared to status-quo spending. The status quo involves spending on variant-specific boosters, which would be saved if supplanted by a universal vaccine. To the extent that the incremental-benefits calculation allowed for a positive probability that a universal COVID-19 vaccine is rolled out even in the absence of an AMC, to compare apples to apples, the incremental-cost exercise should include in status-quo spending any push funding underway for a universal COVID-19 vaccine as well as some probability of expenditures a successful universal vaccine. After canceling out expenditures that occur whether or not an AMC is undertaken, remaining incremental costs for AMC include a higher probability of the expenditures involved in procuring a successful universal vaccine. If the AMC program required a price premium to adequately spur incentives, this premium needs to be added to the incremental AMC costs. In any event, the incremental costs of an AMC program are less than its total costs, which according to any of the benchmarks considered in this section are several orders of magnitude less than the incremental AMC benefits.

6.4. Cannibalizing Suppliers' Other Products

Incumbent booster manufacturers may be the most promising innovators in a universal COVID-19 vaccine. However, they may hesitate to invest in an innovation that will cannibalize profits from booster sales—an instance of the Arrow (1962) replacement effect. To secure incumbents' active participation, the AMC may need to offer a higher unit price to offset cannibalized sales.

Any concern about the Arrow replacement effect is mitigated by the intensity of competition the AMC is expected to generate. The more firms that are expected to enter, the more likely the AMC is to succeed without the participation of any given booster manufacturer. Even if an existing booster manufacturer has a disproportionate chance of being the pivotal AMC supplier, their fear of losing business to a potential entrant or a rival booster manufacturer may provide sufficient investment incentives for them to actively invest in a universal vaccine without having to compensate them much for cannibalization.

Another consideration that mitigates the Arrow replacement effect is that booster sales are currently relatively weak. Only 17% of the eligible population has received the new booster as of this writing (Centers for Disease Control, 2023b), a much smaller proportion than the market that would be guaranteed for a universal vaccine through an AMC. Even a monopoly manufacturer would be willing to trade the small booster market for the market guaranteed for a universal vaccine.

A formal treatment of the optimal adjustment to AMCs to account for cannibalization is outside the scope of this paper. Qualitatively, the dominance of two key incumbents (Moderna and Pfizer) in the booster market and the prospects that they will be important innovators in future COVID-19 vaccines suggests that some attention be paid to cannibalization concerns in the present context, arguing for leaning towards a marginally higher AMC commitment. It is worth reiterating that a careful accounting of incremental costs and benefits should offset any increase in the AMC expense against government savings from the expense of paying for recurring boosters.

6.5. Cannibalizing Support for Therapeutics

Vaccines and therapeutics are substitutes in the market for a given disease. A vaccine that substantially reduced infection and illness from a disease would shrink the market for therapeutics for that disease. An AMC for a universal COVID-19 vaccine may draw some private investment away from innovating in COVID-19 therapeutics.

Vaccines and therapeutics are both valuable, both likely to be undersupplied by the market, and thus both worth at least considering an AMCs to support their development. We have focused on vaccines for the reasons offered in Section 6.1. However, a comprehensive policy may simultaneously provide support for new vaccines and new therapeutics. The arguments for why an AMC is a good funding structure for vaccines also apply well to new therapeutics. Of course, a funder could provide an AMC for a new vaccine while providing other types of support for therapeutics. For instance, research grants could be offered to labs working on new antivirals or public campaigns could raise awareness about existing therapeutics like Paxlovid.

6.6. Ensuring Universality

Our analysis focused on the benefits of a universal COVID-19 vaccine. Other commentators have advocated even more ambitious targets for a universal vaccine. For example, Morens, Taubenberger, and Fauci (2022) call for a universal Betacoronavirus vaccine that would prevent SARS, COVID-19, MERS, and infection by viral drift and recombination variants.

Verifying that a vaccine has attained the desired level of universality is challenging since it requires assessing whether the vaccine is effective not just against the major variant circulating in the population but against target pathogens not currently in wide circulation and—even more challenging—against variants yet to emerge.

One way to address this challenge is to stage the AMC payments. The first payment could be based upon achieving one or more provisional indicators of universality. At a minimum, the vaccine must achieve a threshold efficacy against strains of COVID-19 currently circulating in the population similar (say within 5 percentage points) to existing boosters specific to the variant if such exist or, if not, to the historical efficacy of COVID-19 boosters. Another provisional indicators could be expert evaluation at the FDA establishing that the vaccine technology has a strong claim to providing near universal protection against likely COVID-19 variants based on biological principles.

The second payment could be based on the universal vaccine's real-world performance over several years. For instance, the payment could be conditioned on the vaccine attaining the threshold efficacy against new VOCs that emerge. The universal vaccine would be required to have similar efficacy to boosters specific to the new variant if such exist or, if not, to the historical efficacy of COVID-19 boosters. The universal vaccine would be expected to have substantially higher efficacy against than boosters designed for older variants.

7. Conclusion

Averaged across Monte Carlo simulations of our baseline model, we calculated that a successful universal COVID-19 vaccine would increase social benefits by $1.5 trillion in the United States over the status-quo program of developing variant-specific boosters. This estimate is based on a forecast that background COVID-19 mortality is very unlikely to be punctuated by a future wave. The social benefit gain rises to $2.6 trillion when based on a less conservative forecast that assumes that mortality waves will continue to arrive at a constant rate.

The gain from the universal COVID-19 vaccine eclipses the likely cost of a program to fund its development. While more work would need to be done to determine the optimal size of the AMC, one back-of-the envelope calculation put the total cost at $4.7 billion, another at $6.4 billion; either number is still several orders of magnitude less than the social gain from a universal COVID-19 vaccine.

Of course, the economic case for undertaking an AMC should consider not its total costs and benefits but its incremental costs and benefits over the status quo. While an AMC will likely increase the chance that a universal COVID-19 vaccine is developed and accelerate its arrival, there is some chance that the modest level of status-quo funding leads a universal COVID-19 vaccine to be developed even in the absence of an AMC. The text provided some figures that can be used to translate the incremental benefits of a universal vaccine into the incremental AMC benefits under various assumptions about how much the AMC increases the probability of success of a universal vaccine and accelerates its arrival. The text discusses what costs can be considered incremental to the AMC and what costs would be borne in any event.

The analysis in the paper focused on the benefits and costs of a program just for the United States and just for COVID-19 because of data availability. A larger international program would produce proportionately more social value (but would require a certain level of international cooperation to effect). A vaccine that was yet more universal, say covering other Betacoronavirus such as SARS and MERS (Morens, Taubenberger, and Fauci 2022) or other genera of coronavirus would also be more valuable and may be an even better AMC target depending on scientific opportunities.

The launch of an AMC for a universal COVID-19 vaccine (or better yet a universal coronavirus vaccine) thus offers the possibility of an enormous return on investment and the

chance to save many lives in the United States and even more lives across the globe. The structure of AMCs limits the downside risk of failure: if the AMC does not result in a universal COVID-19 vaccine funders make no payments. The use of an AMC also offers an important opportunity to learn about the rate at which pharmaceutical companies can develop and produce vaccines for viral threats. The value of this information for planning and preparing for future pandemics is hard to quantify but could be quite large.

References

Abbasian, MH, Mahmanzar M, Rahimian K, Mahdavi B, Tokhanbigli S, Moradi B, Sisakht MM, Deng Y (2023) Global landscape of SARS-CoV-2 mutations and conserved regions. Journal of Translational Medicine 21: 152.

Agrawal G, Hermann R, Moller M, Poetes R, Steinmann M (2021) Fast-forward: will the speed of COVID-19 vaccine development reset industry norms? McKinsey & Company. [Internet.] https://www.mckinsey.com/industries/life-sciences/our-insights/fast-forward-will-the-speed-of-covid-19-vaccine-development-reset-industry-norms.

Ahuja A, Athey S, Baker A, Budish E, Castillo JC, Glennerster R, Kominers SD, Kremer M, Lee J, Prendergast C, Snyder CM, Tabarrok A, Tan BJ, Więcek W (2021) Preparing for a Pandemic: accelerating vaccine availability. American Economic Association Papers and Proceedings 111: 331–335.

Alfani G (2022) Epidemics, inequality, and poverty in preindustrial and early industrial times. Journal of Economic Literature 60(1): 3–40.

Arora A, Ceccagnoli M, Cohen WM (2008) R&D and the patent premium. International Journal of Industrial Organization 26(5): 1153–1179.

Arrow, K (1962) Economic welfare and the allocation of resources for invention. In R Nelson, ed., The Rate and Direction of Inventive Activity. Princeton University Press.

Baker A, Chaudhuri E, Kremer M (2021) Accelerating Vaccinations. International Monetary Fund. [Internet.] https://www.imf.org/en/Publications/fandd/issues/2021/12/Accelerating-Vaccinations-Baker-Chaudhuri-Kremer.

Barro R, Ursúa J, Weng J (2020) The coronavirus and the Great Influenza Pandemic: lessons from the "Spanish Flu" for the coronavirus's potential effects on mortality and economic activity. National Bureau of Economic Research working paper no. 26866.

Berndt ER, Glennerster R, Kremer M, Lee J, Levine R, Weizsäcker G, Williams H (2007) Advance market commitments for vaccines against neglected diseases: estimating costs and effectiveness. Health Economics 16(5): 491–511.

Berndt, ER, Hurvitz JA (2005) Vaccine advance-purchase agreements for low-income countries: practical issues" Health Affairs 24(3): 653–665.

Burger L (2022) BioNTech, Pfizer to start testing universal vaccine for coronaviruses. Reuters. [Internet.] https://www.reuters.com/business/healthcare-pharmaceuticals/biontech-pfizer-starting-testing-universal-coronavirus-vaccine-h2-2022-06-29/.

Castillo JC, Ahuja A, Athey S, Baker A, Budish E, Chipty T, Glennerster R, Kominers SD, Kremer M, Larson G, Lee J, Prendergast C, Snyder CM, Tabarrok A, Tan BJ, Więcek W (2021) Market design to accelerate COVID-19 vaccine supply. Science 371(6534): 1107–1109.

Centers for Disease Control and Prevention (2023a) COVID-19: SARS-CoV-2 variant classifications and definitions. May 11. [Internet.] https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html.

Centers for Disease Control and Prevention (2023b) COVID-19: vaccinations in the United States. September 1. [Internet.] https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-booster-percent-pop5.

Centers for Disease Control and Prevention (2023c) Influenza vaccination coverage for persons 6 months and older. [Internet.] https://www.cdc.gov/flu/fluvaxview/interactive-general-population.htm.

Centers for Disease Control and Prevention (2023d) COVID-19 vaccinations in the United States, jurisdiction. [Dataset.] May 12. https://data.cdc.gov/Vaccinations/COVID-19-Vaccinations-in-the-United-States-Jurisdi/unsk-b7fc.

Centers for Disease Control and Prevention (n.d.) COVID data tracker: trends in United States COVID-19 hospitalizations, deaths, emergency department (ED) visits, and test positivity by geographic area. [Dataset.] https://www.cdc.gov/nchs/nvss/vsrr/covid19/index.htm.

Chalkidou, K, Kettler H, Ramakrishnan G, Silverman R, Towse A (2020) Leave no one behind: using a benefit-based advance market commitment to incentivise development and global supply of COVID-19 vaccines. Center for Global Development working paper. [Internet.] https://www.cgdev.org/publication/leave-no-one-behind-using-benefit-based-advance-market-commitment-covid-vaccine

Coalition for Emergency Preparedness Innovations (n.d.) CEPI's 100 days mission. https://100days.cepi.net/

Congressional Research Service (2021) Operation warp speed contracts for COVID-19 vaccines and ancillary vaccination materials. CRS Report no. IN11560 version 7. March 1. [Internet.] https://crsreports.congress.gov/product/pdf/IN/IN11560

Cutler DM, Summers LH (2020) The COVID-19 pandemic and the $16 trillion virus. Journal of the American Medical Association 324(15): 1495–1496.

Disease X Act, S.2640, 117th Congress (2021) [Internet.] https://www.congress.gov/bill/117th-congress/senate-bill/2640.

Dolgin E (2022) Pan-coronavirus vaccine pipeline takes form. Nature Reviews Drug Discovery 21(5): 324–326.

Environmental Protection Agency (2014) Mortality Risk Valuation: Overviews and Factsheets. [Internet.] https://www.epa.gov/environmental-economics/mortality-risk-valuation.

Fan V, Summers L, Jamison DT (2018) The loss from pandemic influenza risk. In DT Jamison, H Gelband, S Horton, P Jha, R Laxminarayan, CN Mock, R Nugent, eds., Disease Control Priorities (third edition): Volume 9, Disease Control Priorities. Washington, DC: World Bank.

Federal Emergency Management Agency (2022) FEMA benefit-cost analysis sustainment and enhancements: draft standard economic value report. Version 11.0. [Internet.] https://www.fema.gov/sites/default/files/documents/fema_standard-economic-values-methodology-report_092022.pdf.

Ferdinands JM, Rao S, Dixon B, Mitchell P, DeSilva M (2022) Waning 2-dose and 3-dose effectiveness of mRNA vaccines against COVID-19—associated emergency department and urgent care encounters and hospitalizations among adults during periods of Delta and Omicron variant predominance—VISION Network, 10 States, August 2021–January 2022. Morbidity and Mortality Weekly Report 71(7): 255–263.

Flu Vaccine Act, H.R. 6025, 117th Congress (2021) [Internet.] https://www.congress.gov/bill/117th-congress/house-bill/6025.

Food and Drug Administration (2021) FDA authorizes booster dose of Pfizer-BioNTech COVID-19 vaccine for certain populations. September 22. [Internet.] https://www.fda.gov/news-events/press-announcements/fda-authorizes-booster-dose-pfizer-biontech-covid-19-vaccine-certain-populations.

Food and Drug Administration (2022) Coronavirus (COVID-19) update: FDA authorizes Moderna, Pfizer-BioNTech bivalent COVID-19 vaccines for use as a booster dose. August 31. [Internet.] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-moderna-pfizer-biontech-bivalent-covid-19-vaccines-use.

Food and Drug Administration (2023) FDA takes action on updated mRNA COVID-19 vaccines to better protect against currently circulating variants. September 11. [Internet.] https://www.fda.gov/news-events/press-announcements/fda-takes-action-updated-mrna-covid-19-vaccines-better-protect-against-currently-circulating.

GISAID (2023) hCoV-19 Variants Dashboard: VOC/VOI/UM Relative Frequencies Over Time [Internet.] https://gisaid.org/hcov-19-variants-dashboard.

Glennerster R, Snyder CM, Tan BJ (2023) Calculating the costs and benefits of advance preparations for future pandemics. IMF Economic Review 71(3): 611–648.

Goodkin-Gold, M, Kremer M, Snyder CM, Williams H (forthcoming) Optimal vaccine subsidies for epidemic diseases. Review of Economics and Statistics.

International Pandemic Preparedness Secretariat (n.d.) 100 days mission. [Internet.] https://ippsecretariat.org.

Jara A, Cuadrado C, Undurraga EA, García C, Nájera M, Bertoglia MP, Vergara V, Fernández J, García-Escorza H, Araos R (2023) Effectiveness of the second COVID-19 booster against Omicron: a large-scale cohort study in Chile. Nature Communications, 14(1): Article 1.

Jones BF, Summers LH (2021) A calculation of the social returns to innovation. Chapter 1 in A. Goolsbee and BF Jones, eds. Innovation and Public Policy. University of Chicago Press.

Jones R, Tasolides J (2023) CDC likely to recommend annual COVID shot in the fall, director says. Spectrum News NY1, July 27. [Internet.]
https://ny1.com/nyc/all-boroughs/news/2023/07/27/cdc-director-covid-shot-annual-

Kremer M (2000a) Creating markets for new vaccines. Part I: rationale. Innovation Policy and the Economy 1: 35–72.

Kremer M (2000b) Creating markets for new vaccines. Part II: design issues. Innovation Policy and the Economy 1: 73–118.

Kremer M, Glennerster R (2004) Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Disease. Princeton University Press.

Kremer M, Levin J, Snyder CM (2020). Advance market commitments: insights from theory and experience. American Economic Association Papers and Proceedings 110: 269–273.

Kremer M, Levin J, Snyder CM (2022). Designing advance market commitments for new vaccines. Management Science 68 (7): 4786–4814.

Kremer M, Snyder CM (2015) Preventives versus treatments. Quarterly Journal of Economics 130(3): 1167–1239.

Kremer M, Williams H (2010) Incentivizing innovation: adding to the tool kit. Innovation Policy and the Economy 10: 1–17.

Kniesner TJ, Viscusi WK (2019) The value of a statistical life. Oxford Research Encyclopedia of Economics and Finance. [Internet.]
https://doi.org/10.1093/acrefore/9780190625979.013.138.

Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, Hengartner N, Giorgi EE, Bhattacharya T, Foley B, Hastie KM, Parker MD, Partridge DG, Evans CM, Freeman TM, de Silva TI, McDanal C, Perez LG, Tang H, Montefiori DC, et al. (2020) Tracking

changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell 182(4): 812-827.

Levine R, Kremer M, Albright A (2005) Making Markets for Vaccines. Center for Global Development.

Mathieu E, Ritchie H, Rodés-Guirao L, Appel C, Giattino C, Hasell J, Macdonald B, Dattani S, Beltekian D, Ortiz-Ospina E, Roser M (2020) Coronavirus pandemic (COVID-19). *Our World in Data*. [Dataset.] https://ourworldindata.org/covid-deaths.

Merrill D (2017) No one values your life more than the federal government. Bloomberg.Com. October 19. [Internet.] https://www.bloomberg.com/graphics/2017-value-of-life/.

Medicines and Healthcare Products Regulatory Agency (2022) First bivalent COVID-19 booster vaccine approved by UK medicines regulator. August 15. [Internet.] https://www.gov.uk/government/news/first-bivalent-covid-19-booster-vaccine-approved-by-uk-medicines-regulator.

Morens DM, Taubenberger JK, Fauci AS (2022) Universal coronavirus vaccines—an urgent need. New England Journal of Medicine 386(4): 297–299.

Msemburi W, Karlinsky A, Knutson V, Aleshin-Guendel S, Chatterji S, Wakefield J (2023) The WHO estimates of excess mortality associated with the COVID-19 pandemic. Nature 613(7942): 130–137.

Ng KW, Faulkner N, Finsterbusch K, Wu M, Harvey R, Hussain S, Greco M, Liu Y, Kjaer S, Swanton C, Gandhi S, Beale R, Gamblin SJ, Cherepanov P, McCauley J, Daniels R, Howell M, Arase H, Wack A, Kassiotis G, et al. (2022) SARS-CoV-2 S2–targeted vaccination elicits broadly neutralizing antibodies. Science Translational Medicine 14(655): eabn3715.

Roth AE (2007) Repugnance as a constraint on markets. Journal of Economic Perspectives 21(3): 37–58.

Sah P, Alfaro-Murillo JA, Fitzpatrick MC, Neuzil KM, Meyers LA, Singer BH, Galvani AP (2019) Future epidemiological and economic impacts of universal influenza vaccines. Proceedings of the National Academy of Sciences 116(41): 20786–20792.

Saville M, Cramer JP, Downham M, Hacker A, Lurie N, Van der Veken L, Whelan M, Hatchett R (2022) Delivering pandemic vaccines in 100 days—what will it take? New England Journal of Medicine 387(2): e3.

Snyder CM, Begor W, Berndt ER (2011) Economic perspectives on the advance market commitment for pneumococcal vaccines. Health Affairs 30(8): 1508–1517.

Snyder CM, Hoyt K, Gouglas D (2023) An optimal mechanism to fund the development of vaccines against emerging epidemics. Journal of Health Economics 91 (102795): 1–22.

Snyder CM, Hoyt K, Gouglas D, Johnston T, Robinson J (2020) Designing pull funding for a COVID-19 vaccine. Health Affairs 39(9): 1633–1642.

Tenforde MW, Self WH, Gaglani M, Ginde AA, Douin DJ, et al. (2022) Effectiveness of mRNA vaccination in preventing COVID-19-associated invasive mechanical ventilation and death—United States, March 2021–January 2022. Morbidity and Mortality Weekly Report 71(12): 459–465.

UNESCO, The World Bank, and United Nations Children's Fund (2021) The state of the global education crisis: A path to recovery. [Internet.] https://doi.org/10.54675/JLUG7649.

U.S. Department of Health and Human Services (2023) NIH clinical trial of universal flu vaccine candidate begins. National Institutes of Health. September 15. [Internet.] https://www.nih.gov/news-events/news-releases/nih-clinical-trial-universal-flu-vaccine-candidate-begins

U.S. Department of Health and Human Services (n.d.) BARDA COVID-19 Medical Countermeasure Portfolio. [Internet.] https://www.medicalcountermeasures.gov/app/barda/coronavirus/COVID19.aspx.

Vogel G (2022) Omicron shots are coming—with lots of questions. Science 377(6610): 1029–1030.

Ward T, Glaser A, Johnsen A, Xu F, Hall I, Pellis L (2021) Growth, reproduction numbers and factors affecting the spread of SARS-CoV-2 novel variants of concern in the UK from October 2020 to July 2021: A modelling analysis. BMJ Open, 11(11): e056636.

Willett JB, Singer JD (2003) Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence. Oxford University Press.

World Bank (n.d.) Advance market commitment. [Internet.] https://fiftrustee.worldbank.org/en/about/unit/dfi/fiftrustee/fund-detail/amc

World Health Organization (n.d.) Tracking SARS-COV-2 variants. [Internet.] https://www.who.int/activities/tracking-SARS-CoV-2-variants

Wu N, Joyal-Desmarais K, Ribeiro PAB, Vieira AM, Stojanovic J, Sanuade C, Yip D, Bacon SL (2023) Long-term effectiveness of COVID-19 vaccines against infections, hospitalisations, and mortality in adults: Findings from a rapid living systematic evidence synthesis and meta-analysis up to December, 2022. Lancet Respiratory Medicine, 11(5), 439–452.

Yuen C-K, Wong W-M, Mak L-F, Lam J-Y, Cheung L-Y, Cheung DT-Y, Ng Y-Y, Lee AC-Y, Zhong N, Yuen K-Y, Kok K-H (2023) An interferon-integrated mucosal vaccine provides pan-sarbecovirus protection in small animal models. Nature Communications 14(1): Article 1.

Appendix: International Panel on VOC Wave Arrival Rates

To evaluate the robustness of the VOC arrival rates estimated in Section 4.2, we used global COVID-19 tests and death data to estimate the arrival of VOC waves in nine countries in addition to the United States. The countries in our panel included Brazil, Canada, Denmark, France, Germany, Japan, Spain, Sweden, and the United Kingdom.

We followed an equivalent methodology to identify variant waves as we did for the United States. Variants that were identified by the World Health Organization as VOCs and accounted for at least 50% of positive COVID-19 tests in a given country (GISAID) were considered of interest. We used confirmed COVID-19 deaths data from Our World in Data to identify the magnitude and timing of mortality waves following the arrival of each variant of concern (Mathieu et al., 2020), as shown in Figure A1. In the ten countries of our panel, Alpha, Gamma, Delta, and Omicron caused detectable mortality waves.

We estimate the arrival rate of variant waves using the logit specification defined in equation (1) with country-level fixed effects. The results from this estimation are reported in Table 2. Figure A2 graphs the predicted probabilities derived from the coefficient estimates according to the transformation in equation (2). The projections using the ten-country panel are very similar to projections from the United States alone. Hence, our analysis and results of the benefits of a universal COVID-19 vaccine during anticipated variant wave arrivals are likely to be applicable to other countries (with appropriate scaling to reflect population, value of a statistical life, and background deaths in other countries).

.

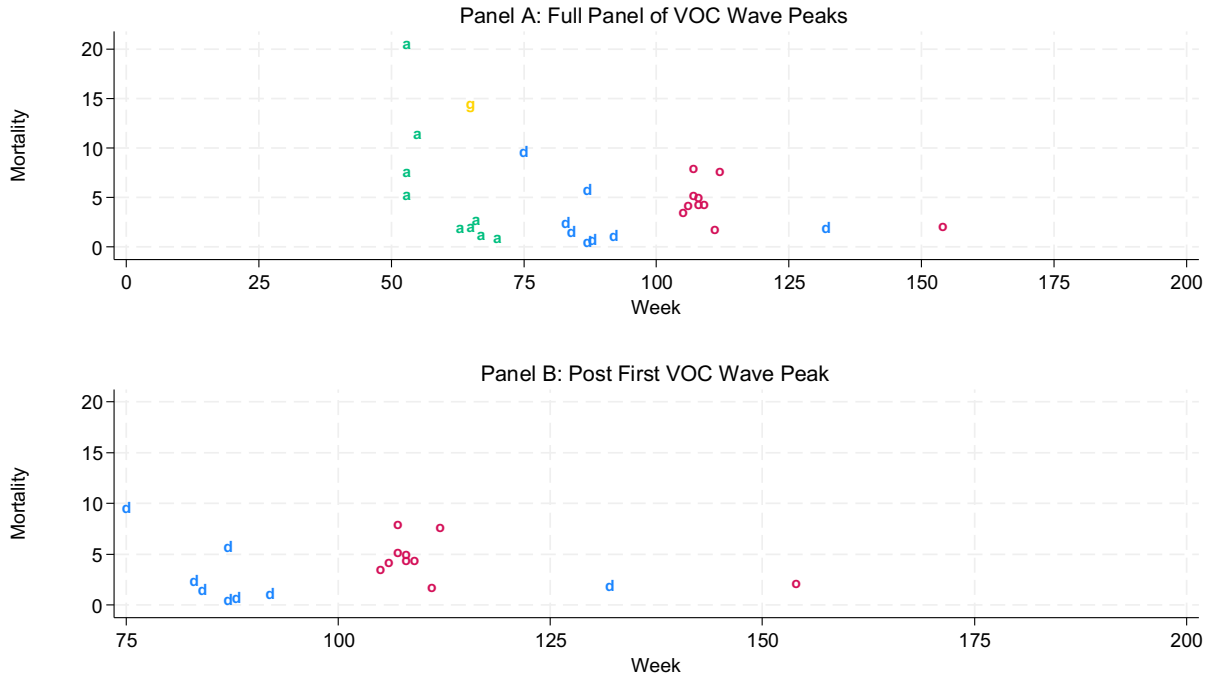

Fig. A1: Peak in mortality caused by new VOC wave in panel of countries. Letters mark the arrival of mortality peak caused by new VOC waves across panel of countries. The height of the letter represents the intensity of mortality, given by deaths in that week per million people in the country's population. The letter "a" denotes the Alpha VOC, "d" Delta, "g" Gamma, and "o" Omicron. The top panel shows the full time series back to the January 20, 2020 start of the pandemic, labeled week 1. The bottom panel shows the truncated time series omitting country data up to an including the peak of the first VOC wave in that country. The scale of the horizontal axis is thus narrower in the bottom panel.

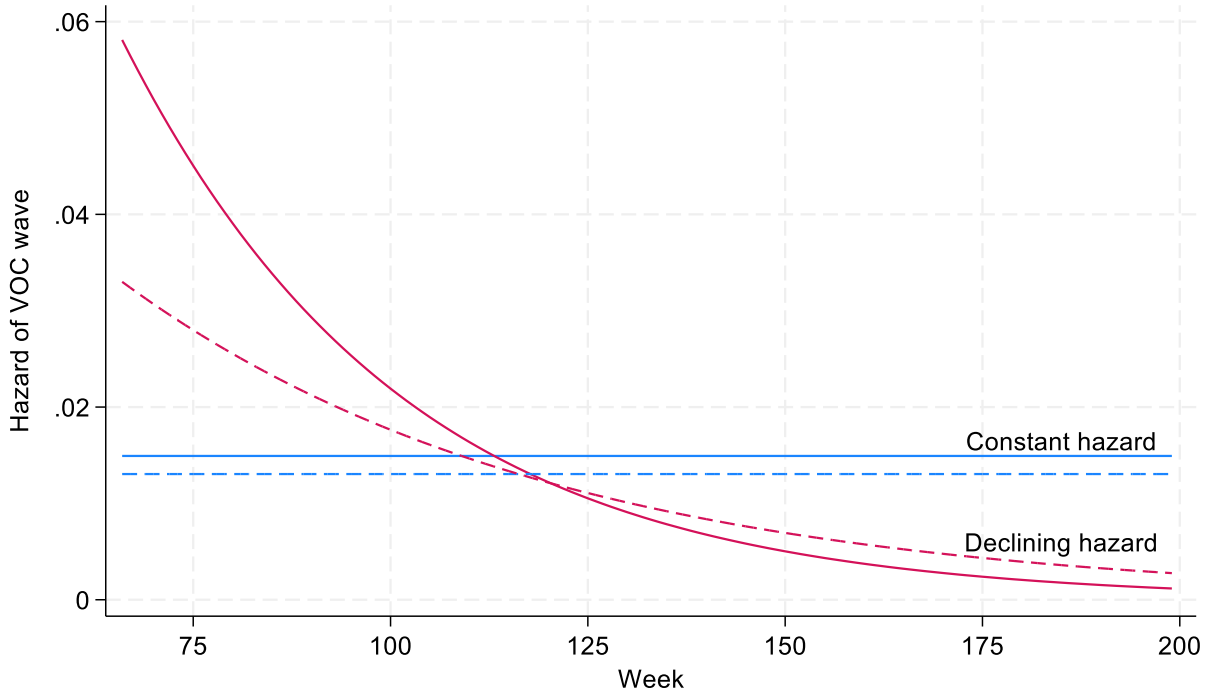

Fig. A2: Estimated hazard of wave caused by new VOC. Graphs of hazard rate of wave caused by new VOC over sample period based on estimates from Table 2. Solid curves are based on estimates using only U.S. data and dashed curves are based on panel of ten countries. Simulations project these hazard rates into future starting in week 200.