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Article

Keywords:

Posted Date: July 1st, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10141341/v1>

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Additional Declarations: **Yes** there is potential Competing Interest. PD, RJ and KDH declare receipt of personal fees from WHO for consultancies on integrated epidemiological–economic modelling and pandemic vulnerabilities, respectively. GF declares receipt of personal fees from WHO and Imperial College London for consultancies. KDH declares receipt of personal fees from WHO, Pfizer, GSK and Munich Re for work unrelated to this study, payments for expert testimony from Infected Blood Inquiry (UK) and stocks from Astra Zeneca. CW has received personal consultancy fees from SecureBio for work relating to novel pathogen surveillance and from Blueprint Biosecurity for work relating to pandemic preparedness.

Costs and impacts of vaccine preparedness investments for SARS-X pandemics

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Abstract

Investments in preparedness made in advance of the next pandemic can both save millions of lives and avert substantial economic losses. Using recent data, we estimated investment costs and modelled pandemic losses for future SARS-X outbreaks, combining epidemiological with economic and educational outcomes within an idealised framing of population and policy response. The counterfactual expected loss due to SARS-X pandemics within this frame, assuming pre-COVID-19-like levels of vaccine investment, had interquartile range 0.39–1.1% of global GDP per year. Through a quantitative scenario analysis of investment options, we found that reducing time to vaccine availability, whether broadly protective or strain specific, yielded the largest reductions in expected pandemic losses; combining R&D investments with manufacturing capacity reservations produced greater impacts than either intervention alone; and improving global distribution equality generated measurable benefits without increasing preparedness costs.

Abbreviations

AMC	Advanced market commitment
AMR	Anti-microbial resistance
BAU	Business as usual
BPSV	Broadly protective sarbecovirus vaccine
CEPI	Coalition for Epidemic Preparedness Innovations
COGS	Cost of goods supplied
GDP	Gross domestic product
GVA	Gross value added
HIC	High-income countries
IQR	Interquartile range
LIC	Low-income countries
LIR	Loss under ideal response
LLMIC	Low- and lower-middle-income countries
LMIC	Lower-middle-income countries
NGFS	Network for Greening the Financial System
NPI	Non-pharmaceutical intervention
R&D	Research and development
SARS	Severe acute respiratory syndrome
SSV	Strain-specific vaccine
UMIC	Upper-middle-income countries
USD	US dollars
VSL	Value of a statistical life
WHO	World Health Organization
YLL	Years of life lost

Introduction

The rapid development of COVID-19 vaccines was a remarkable achievement of science and humanity. It was estimated that vaccines prevented almost 20 million COVID-19 deaths globally between December 2020 and December 2021 and, additionally, that 45% of deaths could have been averted had the COVAX coverage target been met in every low-income country.¹ Beyond saving lives, vaccines also reduced the need for non-pharmaceutical interventions (NPIs), such as stay-at-home orders, testing, contact tracing, and business and school closures. Because many NPIs are associated with high economic and social losses,² mass vaccination can yield significant economic gains during a pandemic.

Building on years of prior research on the viral family and mRNA technologies, the COVID-19 vaccines were developed rapidly following the emergence of SARS-CoV-2. They were made available at scale within one year of development beginning, following rapid conversion of manufacturing capacity and with access initially concentrated in high-income countries. Several avenues with potential to improve international pandemic response have been identified, including development of broadly protective sarbecovirus vaccines (BPSVs),³ reserving manufacturing capacity,⁴ redressing regressive distribution of vaccine products among nations, and the “100 Days Mission”, the ambition to have the capability to develop effective, strain-specific vaccines (SSVs) within 100 days of a novel virus with pandemic potential being sequenced.⁵ BPSVs are envisaged to confer protection that is a priori unknown and assumed to be limited against a broad array of possible Sarbecoviruses, denoted SARS-X. SSVs, in contrast, are those developed reactively and with specificity, and are therefore expected to have higher effectiveness. Capacity reservations are advance agreements between manufacturers and purchasers in which, for a small annual cost, the purchaser can buy SSV doses at a pre-arranged price in the event of an outbreak, and the manufacturer remains prepared to quickly convert production to the new vaccine.

The objective of this work was to model the costs and health and economic impacts of various investments into vaccine technology for SARS-X pandemics, building on recent literature estimating global impacts of vaccines.^{6,7,1} Prior literature has focused on macro estimates of pandemic costs. In this work, we endogenised vaccine timing and delivery within epidemic dynamics. Specifically, we modelled advance investments into vaccine research,

development and manufacture that would enable: (a) BPSVs to be held in an investigational reserve, and tested for efficacy and delivered to populations aged over 64 in the event of a SARS-X outbreak, and (b) SSVs to be developed reactively in a shorter time than was achieved in response to COVID-19. We defined ten scenarios representing different types and levels of investment, including BPSVs, capacity reservations, SSVs available in 100 or 200 days, and greater equality in timely vaccine distribution globally. For each scenario, we estimated investment costs and modelled the losses and response costs due to future SARS-X pandemics. We compared investment scenarios to a counterfactual business-as-usual (BAU) scenario with no advance investments beyond capacity reservations that already exist.

The costs of advance investments and pandemic response were estimated using COVID-19 data, expert insight, and previous research.⁸ Pandemics were modelled using existing methods to project probabilities of pandemics with different severities,^{9,10} to which we associated health and economic losses using an economy-structured epidemiological model.¹¹ We modelled population and policy responses that were constructed as internally *ideal*: that is, the best they could reasonably be, in terms of policy response and availability and delivery of vaccines (see Box 1). With results derived under an idealised response framework, ours is a comparative analytical construct rather than a prediction of real-world outcomes. We use a partial, vaccine-mediated lens, considering only R&D, manufacturing and delivery levers, and not the broader preparedness system they are part of, encompassing surveillance, regulatory systems and broader ecosystem readiness. Health systems and 100 day mission capabilities strengthening costs were not included.

Our results show how targeted investments can reduce some of the losses associated with future SARS-X pandemics, albeit within a narrow frame, and under several other assumptions.

Box 1: Modelling pandemic losses averted by advance preparedness investments into vaccines

We used a dynamic epidemic model to capture impacts of vaccines. To implement such a model, one must specify the actions of policy makers and populations during the emergency. Due to the difficulty of anticipating the ways in which, and the likelihood with which, decision-makers will make mistakes and suboptimal choices, we chose to construct the model with *idealised* responses; that is, we chose a narrow analytical frame in which to make comparisons (see Figure B.1 for this frame in context). We defined ΔLIR as the difference (Δ) in pandemic losses under ideal policy and population response (LIR). Scenarios were therefore designed with vaccine administration and uptake as high as the best examples during the COVID-19 pandemic; the declaration of an international health emergency was made quickly; we modelled four different epidemic-mitigation strategies for each epidemic and selected the one that yielded the lowest societal losses; and we assumed that effective vaccines were developed through R&D and distributed to countries according to the specifications of each scenario.

The real-world gains from these investments would inevitably differ from the modelled ΔLIR , which is restricted to a narrow analytical frame that excludes several key determinants of vaccine impact. For example, gains would be lower if vaccine uptake is less than we modelled or if mitigation is highly effective, and higher if mitigation measures are poorly implemented. A high pathogen mutation rate could reduce vaccine efficacy, meaning that advance investments that shorten the time to vaccine availability would yield greater gains.

We estimated values for LIR using a combination of projection, resampling and aggregation. We did not model country and population decisions individually or in detail, but instead modelled synthetic countries and approximated global ΔLIR using aggregation. ΔLIR represents annualised societal gains relative to the business-as-usual scenario (within the ideal-response frame). Values are annualised in order to average the impacts of discrete pandemic events over multi-decade time horizons in which many years would see no events, and a small number of years would see large and impactful events.¹² These quantities should therefore be interpreted not as estimates of returns on investments, but as estimates of differences in losses within the modelled frame. In supplementary material (Section C.2), we present LIR values given SARS-X pandemics of varying severity, from mild (“once in thirty years”) to severe (“once in hundred years”), as well as compositions of LIR and ΔLIR , which were both driven primarily by lives lost.

Results

We estimated costs across different categories of spending: R&D and manufacturing capacity reservations before an outbreak, which are elective investment costs; and procurement and delivery, which will be necessary costs in pandemic events and will be impacted by prior investment choices. These costs arise at different times and with different frequencies: some costs occur once only (upfront, or one-off, costs), some occur annually, and some occur only in the event of a pandemic.

We explored investments' impacts by constructing scenarios. Scenarios were defined as combinations of investments made outside pandemics, and dose distribution during outbreaks. The scenarios we considered are given in Table 1. Investments were translated into profiles of vaccine coverage according to the scenario definition (Figure 1), which determine their impacts in the event of an outbreak. We approximated these impacts by modelling the health and economic losses that would be incurred during epidemics given these profiles. We defined loss under ideal response (LIR) to represent the annualised societal loss given the probability for SARS-X pandemics to occur, and Δ LIR to represent annualised differences in expected losses relative to the business-as-usual counterfactual.

When presenting results, we provide preparedness costs (one-off costs and annual costs) and response costs in 2025 USD, and Δ LIR as a % of global GDP per year. We take this approach because costs in USD are assumed fixed, whereas GDP is expected to grow each year. We provide examples (Table C.15) and a spreadsheet in Supplementary Material which allows interested readers to convert Δ LIR to monetary values based on their specific assumptions regarding growth and discount rates, and the duration over which costs accumulate. Numerical results are rounded to two significant figures (omitting trailing zeros). Uncertainty ranges, which come from 10,000 Monte Carlo simulations, are given as interquartile ranges (IQR) unless specified otherwise.

Business as usual with limited advance vaccine investments

The BAU scenario was defined to have properties similar to observed preparedness and response during the COVID-19 pandemic, with no BPSV, and the SSV becoming available 365 days

Table 1: **Advance vaccine investment scenarios.**

Investment Scenario	BPSV ^a	Time to SSV (days) ^b	Additional reserved capacity (billion doses) ^c	SSV distribution (unreserved doses) ^d	LLMIC administration rate (% per week) ^e
BAU	No	365	0	HIC first	2
BPSV SCENARIO					
S01	Yes	365	0	HIC first	2
CAPACITY-RESERVATION-ONLY SCENARIOS; 365 DAYS TO SSV					
S02	No	365	0.7	HIC first	2
S03	No	365	2	HIC first	2
200-DAYS-TO-SSV SCENARIOS					
S04	No	200	0	HIC first	2
S05	No	200	0.7	Equal	2
S06	No	200	2	Equal	2
100-DAYS-TO-SSV SCENARIOS					
S07	No	100	0	HIC first	2
S08	No	100	0.7	Equal	2
S09	No	100	2	Equal	2
EQUALITY + DELIVERY SCENARIO					
S10	No	365	0	Equal	4

^a If “Yes”, BPSV doses are given to all adults aged 65 and older in the event of an outbreak. If “No”, BPSVs are neither costed nor deployed in the impact model.

^b “Time to SSV” is the time required (in days) from sequencing of the pathogen to developing a strain-specific vaccine ready for initial authorization and manufacturing at scale.

^c “Additional reserved capacity” is the volume of SSV doses to be manufactured per year for an agreed price in the event of an outbreak in addition to an existing reservation of 500M doses that is reserved by HIC in BAU and all other scenarios. Manufacturing commences within five weeks of authorisation, which is faster than that for unreserved doses. The cost per dose from reserved capacity is less than that from unreserved capacity. Distribution across countries of doses from additional reserved capacity is proportional to eligible populations.

^d “SSV distribution (unreserved doses)” refers to the global distribution of SSV doses from capacity that was not reserved. Doses either go to HIC first, or are distributed equally, i.e. proportional to population. BPSVs are distributed proportional to eligible populations.

^e “LLMIC administration rate” is the number of doses per 100 population that is administered per week in LLMIC. A higher rate is achieved in S10 via improvements to health system capacity. We assume under all scenarios that the administration rate is 7% in HIC and UMIC.

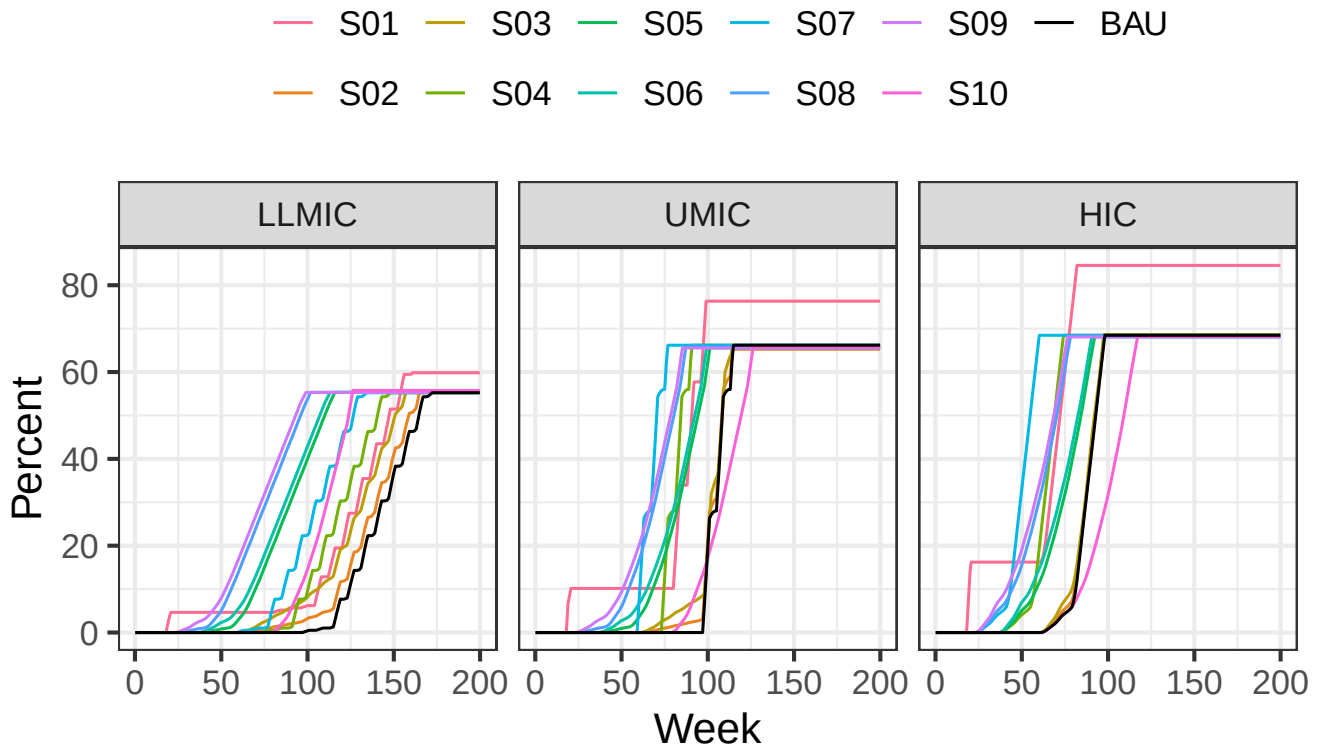


Figure 1: **Vaccine delivery by country income level and scenario.** The y axis shows the cumulative vaccine coverage of the population (doses per hundred people) for both BPSV and SSV 2nd dose. Because it counts BPSV doses per hundred people and SSV second doses per hundred people, coverage is higher in the scenario with BPSV (S01).

after the pathogen is sequenced. In BAU, SSVs are delivered first to high-income countries (HIC), where distribution proceeds at a faster rate than in low- and lower-middle-income countries (LLMIC).

Preparedness costs for BAU were 270 million USD per year for existing capacity reservations, and 570–610 billion USD for response in the event of a pandemic (Table C.10). There were no one-off preparedness costs in BAU. We estimated LIR under BAU to be 0.39–1.1% of global GDP per year, with average deaths per thousand population ranging between 0.023 and 0.063 (Table C.14).

Costs and impacts of advance vaccine investments

Costs for each discrete investment we considered, by type and timing, are shown in Figure 2 as compared to BAU. Costs for scenarios, which are combinations of investments, are shown aggregated in Figure 3, and numerically in Table 2. All scenarios had a positive effect on pandemic impacts, and some reduced response costs in the event of a pandemic.

Table 2: Cost and impact results compared to BAU. Upfront costs are one-off costs and are expressed in present-value USD. Annual costs recur each year and are given in USD. Response costs are incurred in the event of a pandemic and are given in USD. See Table C.10 for discounted values. Upfront and annual costs are preparedness investments made actively by governments or investors, whereas response costs are consequences of outbreaks and impacted by prior investment choices. Δ LIR values represent annualised differences in expected losses under model assumptions, and are expressed as a percentage of global GDP per year. Results are given as IQRs rounded to two significant figures (trailing zeros omitted). Single values are given for cases for which the uncertainty modelled did not differentiate the two quantiles.

Scenario	Upfront, million USD	Annual, million USD per year	Response, million USD per pandemic	Δ LIR, % global GDP per year
BPSV SCENARIO				
S01	210–370	0.17	19,000–23,000	0.038–0.11
CAPACITY-RESERVATION-ONLY SCENARIOS; 365 DAYS TO SSV				
S02	0	370	-34,000	0.0039–0.011
S03	0	1,100	-110,000	0.0069–0.019
200-DAYS-TO-SSV SCENARIOS				
S04	3,200–3,300	0	-74–85	0.016–0.044
S05	3,200–3,300	370	-37,000	0.024–0.066

Scenario	Upfront, million 2025 USD, present value	Annual, million 2025 USD per year	Response, million 2025 USD per pandemic	Δ LIR, % global GDP per year
S06	3,200–3,300	1,100	-94,000–-93,000	0.028–0.076
100-DAYS-TO-SSV SCENARIOS				
S07	7,600–8,600	0	1,400–1,600	0.028–0.077
S08	7,600–8,600	370	-41,000	0.04–0.11
S09	7,600–8,600	1,100	-100,000	0.046–0.13
EQUALITY + DELIVERY SCENARIO				
S10	0	0	-11,000	0.0076–0.021

Broadly protective sarbecovirus vaccine

BPSVs are expected to have lower effectiveness than their strain-specific counterparts, and are proposed to be distributed to vulnerable populations following a successful expedited Phase 3 trial after the onset of the outbreak. We modelled pandemic response assuming BPSVs and SSVs would be produced using the same platform, meaning that prior conversion of manufacturing to BPSVs led to faster conversion of existing manufacturing for the production of SSVs.

The upfront one-off cost of developing a successful BPSV candidate was 210–370 million USD, which equates to 0.0002–0.0003% of global GDP in 2025, and the annual cost of maintaining the investigational reserve for clinical trials was 0.17 million USD per year (Table C.10). A pandemic response with two vaccines, a BPSV followed by a SSV, will have additional costs in both preparedness and response (Figures 2 and 3). We estimated the additional response costs in the event of a pandemic to amount to 19–23 billion USD in real terms (which is around 0.02% of 2025 GDP). These investments yielded a Δ LIR of 0.038–0.11% of global GDP per year (Table 2)

Capacity reservations

Vaccine procurement and delivery costs exceeded other costs by several orders of magnitude in real terms: SSV procurement cost 410 billion USD and delivery 190–250 billion USD in BAU in real terms. Capacity reservations reduced the cost of procurement during pandemic response (Figure 2), and led to faster manufacturing transition, making doses available earlier

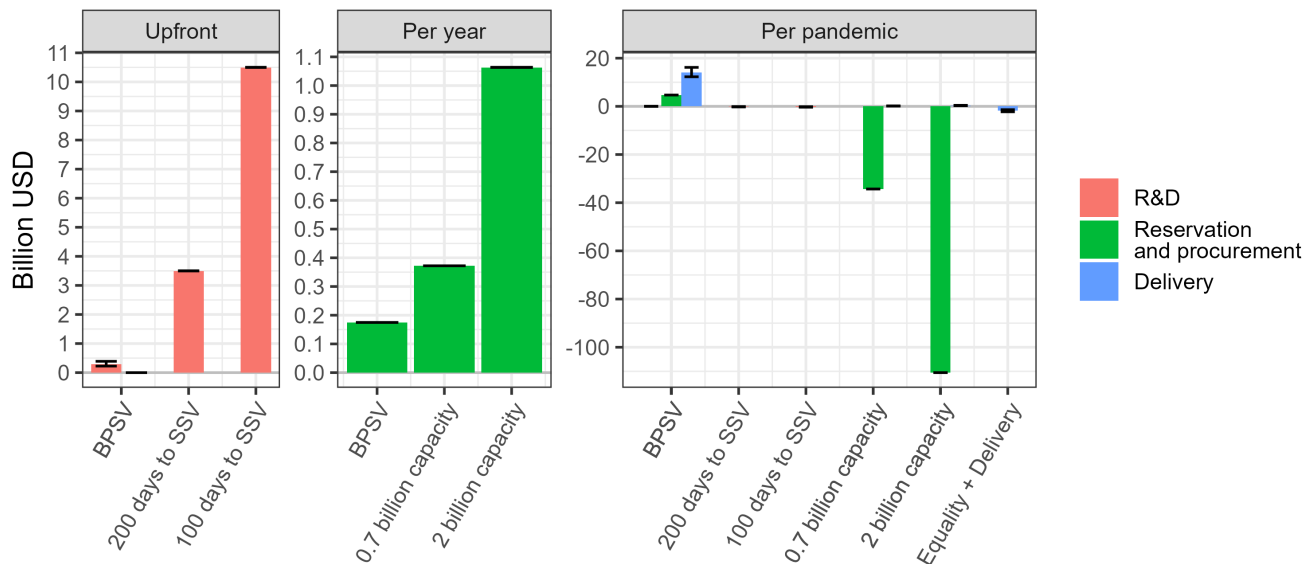


Figure 2: **Preparedness and response costs for different types of investment.** Costs shown are relative to “business as usual” counterfactuals: no upfront costs; annual costs of a 500-million-dose capacity reservation; and no BPSV in pandemic response. Costs are shown separated by type and when they are incurred: whether upfront, annual, or only in response to a pandemic. Response (Per pandemic) costs are discounted to the first year in which they occur (the start of the pandemic). Upfront and annual costs (Per year) are presented without discounting. Types of investment are (1) BPSV, for which there are R&D and investigational-reserve upfront costs, investigational-reserve recurring costs, and R&D, procurement and delivery response costs; (2) accelerating time to SSVs, aiming for either 200 or 100 days, which involve upfront R&D costs and affect delivery costs; (3) additional capacity reservations, which come with additional annual costs and affect procurement and delivery costs; and (4) equal distribution, which impacts delivery costs. Bar heights show medians and error bars IQRs. Numeric values are given in Table C.9.

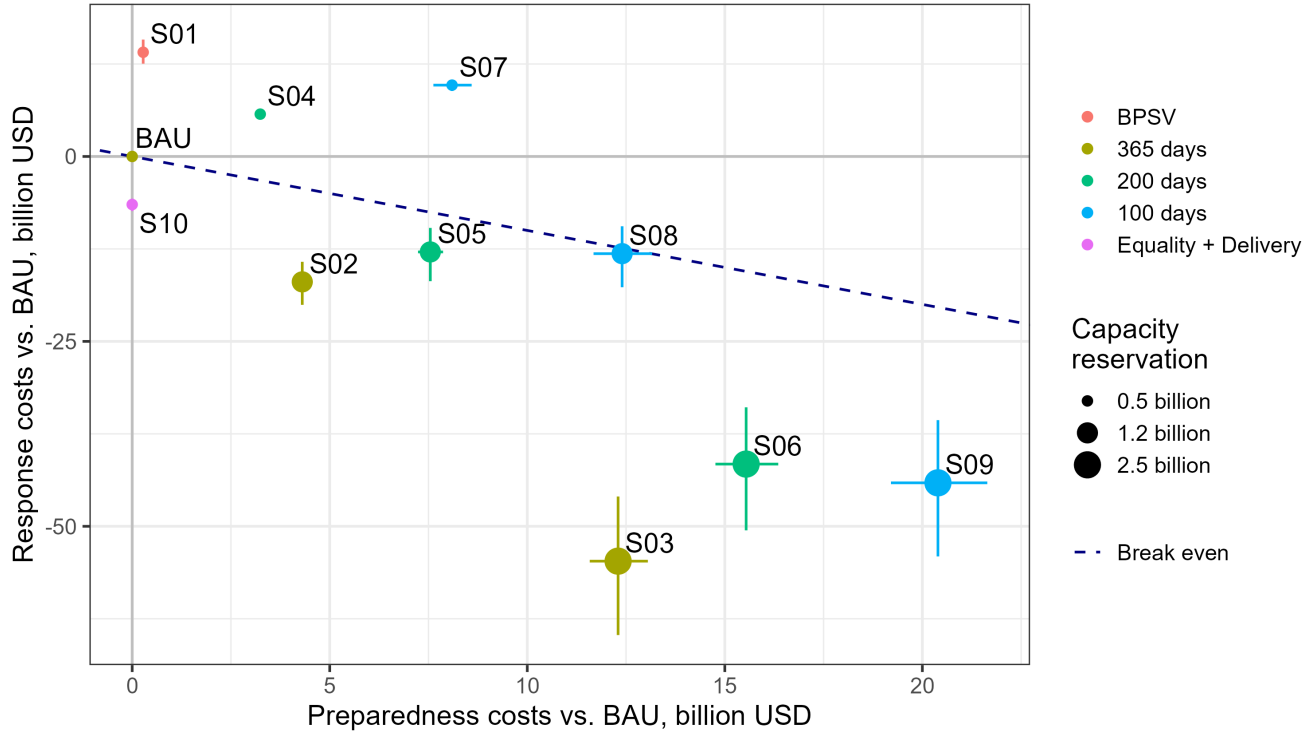


Figure 3: **Preparedness and response costs for scenarios compared to BAU for an outbreak in year 15.** Preparedness vs Response compared to BAU for the ten scenarios considered, in the event that a SARS-X pandemic occurs in year 15. Each scenario combines different types of cost, accumulating annual costs over 15 years and one pandemic cost, discounted to the year 2025. Points show medians and lines interquartile ranges. The break-even line shows scenarios (on or below the line) that would break even at year 15 in the event of a pandemic. Negative numbers imply a saving of the respective investment scenarios compared to BAU.

(Figure 1).

For annual costs of 370mn (or 1.1bn) USD, additional capacity of 700mn (or 2bn) doses per year was reserved, leading to savings in procurement costs of up to 34 (or 110) billion USD in real terms in outbreak response (Figure 2). Potential savings due to lower procurement costs far exceeded those of other response and preparedness costs in real terms; the second-largest cost – delivery – was not impacted directly by the investments modelled. Across all scenarios, they represented between 55% and 69% (procurement) and 31% and 45% (delivery) of all response costs (Table C.10).

The saving from reserved capacity could exceed the costs associated with maintaining the reservation in inter-pandemic periods (Figure 3), depending on the number and timing of pandemics. Specifically, given our assumptions that the reservation costs 0.53 USD per dose per year,⁴ reserved doses would cost 6.18 USD,¹³ and unreserved doses would cost 18.94 USD,¹⁴ purchasing doses via reserved capacity would be cost saving in real terms in the event that SARS-X pandemics precipitating an international response occur with a frequency of at least once every 24 years. Conversely, with discounting, the present-value cost of the larger reservation would exceed the whole response cost if the next pandemic arrives in more than 61–85 years (Figure C.7).

In terms of pandemic impact, we estimated Δ LIR of small additional capacity reservations (700mn doses; S02) and large additional reservations (2bn doses; S03) to be 0.0039–0.011% and 0.0069–0.019% of global GDP per year, respectively. These gains came from accelerated access to doses, in part from reserved capacity converting earlier and faster to produce SSV doses, and in part due to equal distribution of reserved doses.

R&D into strain-specific vaccines

We modelled investments into R&D that decreased the time taken for the SSV to become available from 365 days under BAU to 200 days (S04–S06) and 100 days (S07–S09), costing 3.2–3.3 and 7.6–8.6 billion USD, respectively (Table 2). Response costs appear higher with a shorter time to SSV (e.g. in Figure 3, compare S04 and S07 with BAU). This is an artefact of discounting, due to procurement and delivery costs occurring sooner under faster SSV timelines. In real terms, response costs were lower with R&D investments due to shortened

clinical phases in reactive development (Table C.10).

The associated impacts were 0.016–0.044% (S04) and 0.028–0.077% (S07) of global GDP per year, respectively. Increases in Δ LIR in scenarios combining capacity reservations and R&D exceeded the sums of their parts: 700mn reservations yielded ranges of 0.024–0.066% for 200 days (S05) and 0.04–0.11% for 100 days (S08). With 2bn doses per year reserved, Δ LIR for S06 was 0.028–0.076% per year, and 0.046–0.13% for S09, the highest among all scenarios we considered.

Greater equality of access and distribution

S10 was defined to have the same preparedness costs as BAU but to be more equal in the allocation of doses between income levels, distributing doses proportionally to population, and LLMIC administration rates were increased from 2% to 4% per week (which was still lower than the rate in UMIC and HIC of 7%). Due to the combination of discounting and deferring HIC deliveries, which are more expensive, to later years, at which point they were more heavily discounted, response costs appeared reduced (Figure 3), although in absolute terms they differed only due to the weekly production schedule creating more doses than required in BAU (Table C.10). Δ LIR was 0.0076–0.021% per year (Table 2).

S10 was the only scenario to redistribute doses and benefits to LLMIC (see Figure 1 for the dose distribution, and Figure C.12 for the consequences in terms of pandemic outcomes). In BAU, preferential allocation of doses to HIC resulted in HIC having more doses than they were able to deliver at the beginning of the roll-out while others had none (up to 560 million; see Table C.7). Greater equality in distribution and delivery in S10 meant that doses did not lie idle, and coverage was greater overall as well as being more equal (Table C.8, Figure C.6). At no additional cost, changing the distribution alone was sufficient to bring benefits globally (Table 2).

Visual comparison of all scenarios

To contextualise the relationships between preparedness and response costs, we show costs in the event of a pandemic after 15 years in Figure 3. 15 years was the longest duration for advance R&D among our scenarios; it is a conservative assumption for the full cycle of R&D

necessary to enable reactive development of SSVs in 100 days. This is the most favourable light in which to present this investment: the outbreak occurs when R&D has concluded successfully, and no future preparedness costs are accumulated beyond the 15 years considered. The figure shows which scenarios could be cost-saving in this situation. The BPSV of S01 added costs; capacity reservations could be cost saving; accelerating the time to SSV appears to increase response costs and greater equality appears to decrease them, although examination of Table C.10 shows these to be exclusively (for time to SSV) or mostly (for equality) an artefact of discounting. Comparison of Figures 2 and 3 reveals that uncertainty in these results is primarily due to discounting.

To aid comparison of costs and impacts across all scenarios, we accumulate their values over a fifty-year time horizon, presented in Figure 4. We count the costs of upfront investments, assuming R&D has completed successfully. Annual costs accumulate over the period, as do annualised Δ LIR. Response costs are added to Δ LIR and are weighted by the expected number of outbreaks triggering a response using the same probability as in the Δ LIR computation (0.18–0.49 events expected), and all costs are discounted over time relative to Δ LIR, to reflect costs decreasing with respect to GDP. Thus, the longer the time horizon chosen, the more favourable investments look: costs per year decrease (relative to rising GDP), and the upfront cost becomes a smaller portion of all costs. Meanwhile, benefits accumulate almost linearly with time.

Impacts shown on the x axis are several orders of magnitude greater than those on the y axis. For context, 1% of GDP in 2025 is approximately 1.1 trillion USD, and 30 billion USD is less than 0.03% of GDP in 2025. Uncertainty in preparedness costs was driven by the rate of discounting. In contrast, the uncertainty in impacts was driven by uncertainty about the number and severity of SARS-X pandemics in the time horizon. Note that this uncertainty was independent of investments, meaning that differences between scenario positions along the x axis are indicative of differences in impact, even though they overlap. For example, on a case-by-case basis, SSV availability in 100 days (S07) should always be advantageous over 200 days (S04).

S02, S03 and S10 show modest impacts for no R&D investments. S02 and S03 indicate an approximately linear relationship: increases in annual spending corresponded to proportionate

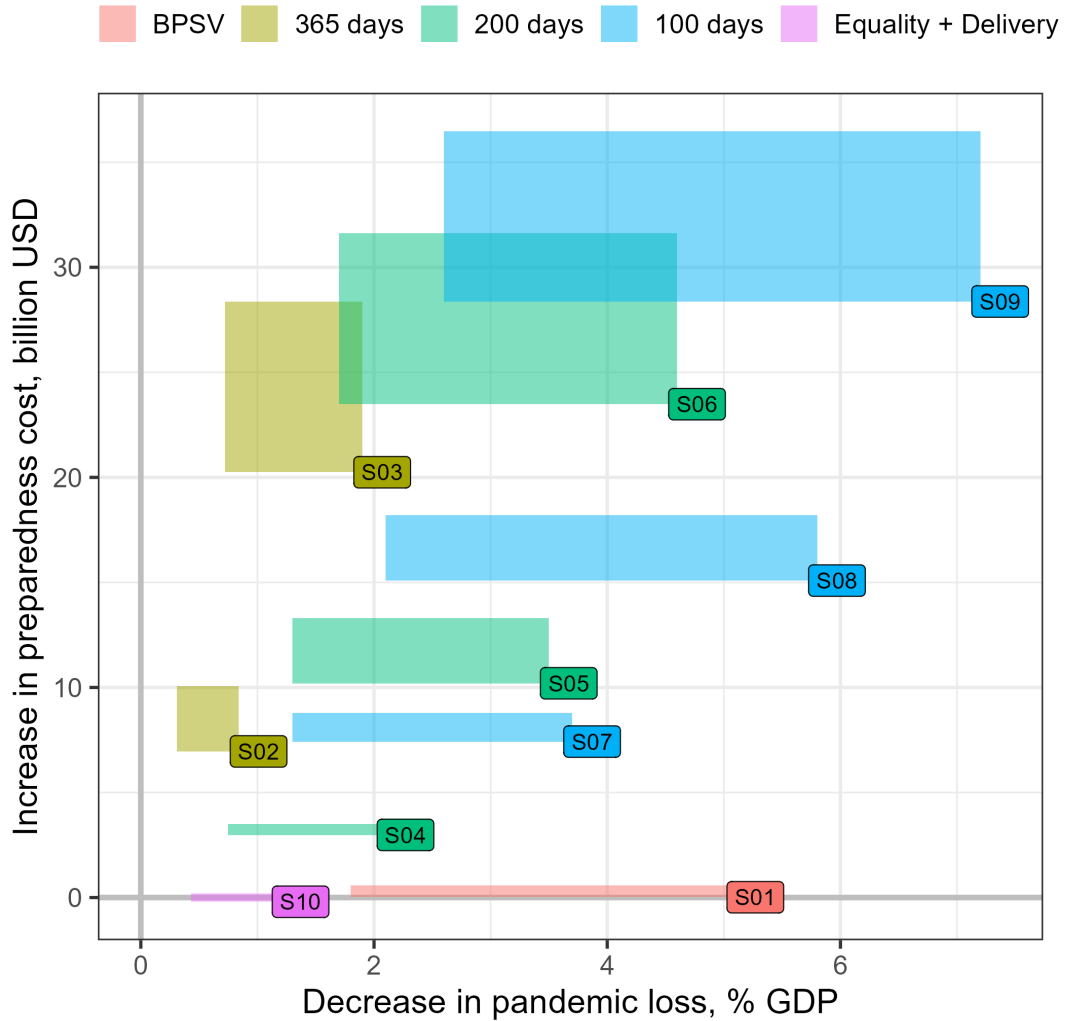


Figure 4: **Costs and impacts (interquartile ranges) accumulated over 50 years, relative to BAU.** The increase in preparedness cost, in billion USD (2025 prices) vs. the decrease in pandemic loss, shown as a % of GDP. Values are summed over a fifty-year time horizon that begins after all preparedness R&D activities have been completed, and discounted to the start of the time horizon assuming the discount rate is equal to GDP growth. Preparedness cost is the sum of two components: (1) One-off investments into preparedness (cumulative R&D costs); and (2) Annual maintenance costs (holding the BPSV investigational reserve and SSV capacity reservations; summed over the time horizon). Pandemic loss is the sum of two components, summed over the time horizon: (1) Δ LIR; and (2) Response costs per pandemic (multiplied by the expected number of pandemic events; note that our response costs do not include production winddown or potential savings in the case of multiple pandemic responses; this is a model limitation).

increases in pandemic losses averted. A linearity can also be detected in R&D only, in S04 and S07.

The R&D scenarios show larger impacts with proportionately greater uncertainty. All these scenarios had substantial reductions in time to achieve high SSV coverage (see Table C.8). Gains accumulated as capacity reservations were added to SSV R&D investment showing, again, that the joint impacts were more than the sum of their parts. BPSVs in particular had considerable impact with very little upfront cost (S01).

Across scenarios, three consistent patterns emerge: (i) reducing time to SSV availability yielded the largest reductions in expected pandemic losses; (ii) combining R&D investments with manufacturing capacity reservations produced greater impacts than either intervention alone; and (iii) improving global distribution equality generated measurable benefits without increasing preparedness costs.

Discussion

We aimed to model the costs and impacts of investments into vaccine technologies towards BPSVs and accelerated availability of SSVs considering the threat of future SARS-X pandemics. We drew on COVID-19 data and expert elicitation to model costs, and epidemiological data pertaining to past pandemics to model impacts, using an economy-structured epidemiological model to capture the effects of vaccines and associate economic outcomes. Costs and impacts were estimated by comparison with a BAU counterfactual, in which SSVs became available after 365 days, there were no BPSVs, and there was global inequality in vaccine distribution, reserved manufacturing capacity only for HIC, and slow administration of vaccines in LLMIC (Table 1).

Our counterfactual annualised death toll for SARS-X was 0.023–0.063 per thousand, which is around 190,000 to 520,000 for the current world population. This can be compared with Madhav et al.,¹² who estimated an average annual sarbecovirus death toll of around 890,000. Our counterfactual economic losses are comparable with those of Glennerster et al.,⁹ who estimated annualised global pandemic costs to be 0.35 to 2.1% of GDP in optimistic and pessimistic scenarios, respectively, vs. our counterfactual annualised LIR of 0.39–1.1% of global GDP.

Our approach yielded an estimate of the recurrence time for a pandemic with the severity of COVID-19 (3.5 deaths per thousand¹⁵) of 67–110 years, i.e. we would expect to observe a pandemic with severity equal to or greater than that of COVID-19 once every 67–110 years (IQR). This is less than the 120–140-year recurrence time estimated by Marani et al.,¹⁰ and more than the 33–50 year period estimated by Madhav et al.¹² (both ranges are 95% confidence intervals).

We found that preparedness investments into R&D and manufacturing capacity reservations reduced response costs in the event of a pandemic for most scenarios. BAU response costs were estimated to be up to 600–660bn USD in real terms, and savings that can be achieved with capacity reservations of 2bn doses were estimated to be up to 110bn USD, or 17–18% of response costs. This was at a cost of 1.3bn USD per year, compared to 270mn for BAU (Table C.10).

We estimated the Δ LIR of decreasing the time to SSV availability from 365 to 200 and

to 100 days to be 0.016–0.044 and 0.028–0.077% of global GDP per year respectively (S04 and S07, Table 2), and the respective upfront costs to be 3.2–3.3 and 7.6–8.6bn USD. For context, global GDP in 2025 was 113.8 trillion USD.¹⁶ Capacity reservations augmented gains in Δ LIR when combined with SSV R&D. The most expensive scenario, S09, combining advance investment that achieved SSV availability in 100 days with a 2bn-dose reservation, had Δ LIR of 0.046–0.13% of global GDP per year, and a cost difference compared to BAU of 7.6–8.6bn USD upfront and 1.1bn USD per year to maintain the reservation.

BPSVs had high impact at lower cost due in part to anticipated spillover effects. It had Δ LIR of 0.038–0.11% for additional costs of 210–370mn USD upfront, 0.17mn USD annually, and 19–23bn USD in pandemic response. There are several conditions that underpin these results. We modelled 14 candidates entering the development pipeline,³ and we assumed that the Phase 3 clinical trials required to license one of those candidates would conclude successfully in 18 weeks (i.e. that it would meet the target efficacy), and that these trials would be independent of subsequent SSV trials. In the impact model, BPSVs were delivered to people aged 65 and older due to the higher infection–fatality ratios among older age groups for the pathogens we considered, and were distributed proportional to eligible populations, which had a large impact on LLMIC in particular, where the delay to SSVs was longest under BAU. The key spillover effect we assumed was contingent on SSVs and BPSVs having a shared platform, meaning that prior conversion to BPSV production expedited SSV production by 18 weeks. We assumed in turn that BPSV production would not impact SSV production in any negative way.

We explored a scenario that addressed inequality in SSV distribution compared to BAU (S10). We increased the administration rate in LLMIC from 2% to 4% and specified that vaccine doses from unreserved capacity were allocated in proportion to global population. This distribution yielded a Δ LIR IQR of 0.0076–0.021% per year, and saved response costs when later years were discounted relative to earlier ones (Table 2). These results demonstrated that global outcomes could be improved without additional investments. By increasing equality of distribution across countries, the volume of doses lying idle was automatically limited (Table C.7). We achieved the same effect in other scenarios (S02, S03, S05, S06, S08, S09) through capacity reservations whose contracts specifically require produced doses to be distributed

equally, i.e. proportional to population.

In evaluating our work we discuss its most salient limitations. The losses averted with investments were modelled as the difference in loss under ideal response, or ΔLIR . These were approximated at a global level by aggregating epidemic-level health, economic and educational losses, which were simulated using an existing economy-structured epidemiological model.¹¹ To estimate the ΔLIR of each investment, we calculated the difference in losses when, in each epidemic, the policy option that most reduced the aggregate societal loss was chosen, and the surrounding conditions were favourable, such as high vaccine uptake. In so doing, our modelled pandemic impacts might be too low, and thus we might have underestimated the potential impacts of vaccine technologies. The epidemiological model we used was parametrised using data from a limited number of countries, with a bias towards HIC (see Table B.6). We did not model pandemics as singular events. Instead, we simulated isolated epidemics in synthetic countries, sampling constitutive parameters with replacement, and used a second step to aggregate outcomes in place of a single connected model (see Section B.2 for details).

Another key limitation stemming from the epidemiological model is that contact rates in work-related settings came from surveys conducted in four European countries,¹⁷ and are unlikely to apply to countries with different social and economic structures, particularly LLMIC and UMIC. The economic projections from the country-level epidemic model derived from a simple assumption that sectoral gross value added decreases linearly with labour supply. We assumed that sector-specific impacts observed during the COVID-19 pandemic in three countries could be interpreted and operationalised as mandated closure policies stratified by sector. In this way, we re-purposed COVID-era data in order to make speculative projections, assuming disease and economy would be similarly linked. Without a dynamic economic model, we were not able to model the economy itself. Without modelling agents interacting with the economy, we were not able to capture economic impacts of behavioural changes.

We sampled epidemiological parameters for pathogens using collated data¹¹ and used historical data to calibrate pandemic probabilities.¹⁰ Following the precedent of others,^{10,9} we assumed past outbreaks to be informative of future outbreaks. While there are very many reasons that historic outbreak data would not be relevant for projecting future outbreaks, we currently lack theoretical and empirical insights indicating what these trends might be. We

thus resampled data to generate different projections, yielding an IQR of expected deaths per year due to SARS-X pandemics that was appropriately wide, at 0.023–0.063 deaths per thousand people. In extrapolating this value forward in time, we implicitly assumed no secular trends, through which the timings of future pandemics would modify the magnitudes and distributions of impacts.

We acknowledge that there are different ways of measuring health and economic losses, and we may have underestimated the losses. Specifically, we did not count health costs beyond lives lost, the costs to mental health of stay-at-home orders, or the costs of displaced healthcare. We did not count the costs of increased inequalities, unemployment, or poverty. We included the cost of missed education only as a long-term economic loss. We omitted costs associated with epidemic mitigation measures such as testing, contact tracing, and healthcare, as well as broader preparedness systems investments, e.g. surveillance, regulatory systems, and broader ecosystem readiness. We did not model factors such as demand or competition impacting the prices of doses, and we assumed that prices would remain the same over time. Therefore, the degree to which future costs were discounted and the timing of future outbreaks together determined which costs dominated.

The losses of pandemics are felt by all countries in the world, and investments into preparedness have global benefits that go beyond the countries that incur the costs. In this regard, the losses and investments associated with pandemics are comparable to those associated with climate change and antimicrobial resistance (AMR). Some of the modelling challenges are similar, too. In modelling global climate and economic impacts, the Network for Greening the Financial System (NGFS) defined two axes, transition risks and physical damage risks, giving four quadrants (e.g. “disorderly”, with high transition risks and low physical risks), to facilitate scenario design. Scenarios were evaluated assuming the same conditions apply everywhere. Our work follows similar principles: our choice to model “ideal responses” positions us as “orderly” on the policy axis, though we do not attempt to characterise a “disorderly” scenario in which some responses are chaotic, inappropriate or disorganised (see Figure B.1).

The NGFS estimated counterfactual losses from acute physical risks by 2050 as 8% of global GDP per year.¹⁸ The best scenario they considered (Net Zero 2050) had losses of 4% at a cost of $\sim 1\%$ of GDP. In contrast, our counterfactual LIR has an IQR of 0.39–1.1% per year

of global GDP which, although it includes health costs, is an order of magnitude smaller.

Our counterfactual IQR of 0.023–0.063 deaths per thousand (190,000 to 520,000 deaths per year for a world population of eight billion) is close to estimates from World Health Organization¹⁹ of health impacts of climate change at 250,000 additional deaths per year for the years 2030–2050.¹⁹ A more recent estimate is considerably higher at 0.73 per thousand for the end of the century, reducing to 0.11 with mitigation.²⁰

To take another example, AMR has been predicted to cause around 0.2 deaths per 1,000 people per year up to 2050.²¹ Investments worth 63 billion USD (0.06% of 2025 GDP) into treatments and innovation are expected to have combined economic and health benefits worth 0.87% of GDP per year by 2050.²² The upfront cost and the modelled benefits are both an order of magnitude greater than those we have considered. In our case, the modelled benefits are smaller as a fraction of the counterfactual loss, up to only 12–15% (Table C.16).

These comparisons contextualise the scale of SARS-X pandemic losses and preparedness investments relative to other global threats that require consideration of long time horizons, costly interventions, and multinational coordination. SARS-X is one of many pathogens that threaten our health and economies. While we cannot generalize the results of SARS-X to other pathogens, we expect that investments in preparedness for SARS-X will have positive spillover effects for other pathogens. Future work should consider preparedness investment impacts for other pathogens and viral families, whose risk presentations and modelling considerations will differ. SARS-X also merits revisiting with a chaotic, or disorderly, response frame. Across these analyses, via different mechanisms and interventions, investments in the order of billions of USD are associated with modelled outcomes corresponding to trillions of USD. That such preparedness, mitigation and adaptation efforts remain under-resourced points to a role for coordination of sustained and directed innovation towards public value creation.²³

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Methods

To evaluate the potentially broad societal benefits of vaccination, we developed a framework to quantify the costs and benefits of preparedness and response investments against pandemic threats by linking costing and health and economic impact models. Here, we describe the methodology. Mathematical details are given in the supplementary material, and code to reproduce the results can be accessed at Johnson et al..²⁴

The ‘What-If’ approach provides a detailed analysis of a SARS-X pandemic and its effects across synthetic countries, assessing the costs and impacts of ten scenarios of preparedness and related response options, plus one business-as-usual (BAU) scenario. This approach combines two models: 1) a costing model to estimate the costs associated with different scenarios of vaccine advance preparedness investment and surge response and 2) an exceedance-probability approach to approximate impacts for pandemic coronavirus threats. The impacts of investments are the losses that are averted compared to BAU with its limited advance investments. These investments include R&D for strain-specific vaccines (SSVs) developed after the emergence of the SARS-X virus, R&D for broadly protective sarbecovirus vaccines (BPSVs) developed and held in an investigational reserve before the emergence of the SARS-X virus, and capacity reservations made in advance of the emergence of the SARS-X virus, to secure access to manufacturing capacity for a future pandemic. “Sarbecovirus” is an abbreviation of SARS *Betacoronavirus*. SARS stands for severe acute respiratory syndrome, and *Betacoronavirus* is the name of the genus. SARSr-CoV (SARS-related coronavirus, also known as SARS-CoV and *Betacoronavirus pandemicum*) is the name given to the species belonging to the Sarbecovirus subgenus. SARS-CoV strains have previously caused outbreaks and pandemics: SARS-CoV-1 in 2003 and SARS-CoV-2 in 2020. We refer to a future strain with pandemic potential as SARS-X.

Investments achieve a decrease in the time to the availability of SSVs via several routes: 1) shorter R&D process, 2) faster conversion of manufacturing capacity for general vaccines into SSVs, 3) greater vaccine manufacturing capacity reservations, which increases the rate of production, decreasing the time taken to secure SSVs for all countries. We specify that vaccine doses produced from reserved capacity are distributed proportional to eligible populations. These investments therefore achieve a more equal distribution of doses between countries.

Pandemic impacts of investments are approximated by modelling their health and economic effects in synthetic epidemics. These are mapped to pandemic impacts by aggregation, and the health impacts are used to inform the likelihood of pandemic arrival, and thus the joint distribution of disease outbreaks and their severity is accounted for in estimating the yearly average. The framework's outcomes are losses averted in monetary terms, which correspond to the marginal value of lives saved, economic output loss averted, and human capital loss averted, alongside the costs of preparedness investments and response required to successfully deliver these gains at speed and scale. Vaccine administration over time is calculated in the costing model based on specific delivery assumptions, and the results are used in the epidemiological model. This provides the linkage between investment level costs and impact calculations.

Modelling costs of advance vaccine investments

The costing model was developed to estimate costs associated with pre-pandemic investments and surge financing needs for a vaccine response to a SARS-X pandemic. This model aims to capture global pandemic spending for a vaccine response by focusing on three types of cost: R&D, procurement, and delivery. This separation allows the model to track cost inputs and cash flows, incorporate uncertainty for several cost assumptions, and further delineate costs into categories that include upfront preparedness costs, ongoing investments, and response spending (Table 3). Equations, parameter values and distributions, and data sources are given in Appendix A.

The model's outputs include the distribution of global costs required to develop, purchase, and deliver a vaccine in response to a SARS-X pandemic and the associated vaccine delivery profiles (a time series detailing doses per day per country). Upfront preparedness costs accumulate over a number of pre-specified years, and annual costs recur each year. Response costs accumulate after pandemic arrival over the time required to vaccinate the population with a BPSV (if available), an SSV primary series, and SSV booster doses. Uncertainty in costs is captured via a Monte Carlo simulation, incorporating a distribution of values for R&D cost and duration, vaccine cost of goods sold (COGS), delivery costs, and discount rate. The Monte Carlo model runs using @Risk software, which relies on Akaike information criterion for selecting the distribution curves of input variables.

Table 3: **Spending categories captured in the costing model.** Response spending comprises only spending related to the vaccination response, including the SSV and BPSV vaccine R&D, procurement, and delivery. It excludes spending for other pandemic response interventions, such as medical treatments, or test-and-trace.

Output	Cost type	Timing	Costs involved
Upfront preparedness	One time	Start of model until R&D completion	BPSV R&D phases 0 to 2
		Start of model until SSV is R&D-ready	SSV enabling costs
Ongoing investment	Annual upkeep	From end of Phase 2	BPSV procurement
		From start until pandemic occurrence	Capacity reservation fee
Response spending	One time	Pandemic occurrence until vaccination completion	BPSV R&D Phase 3 SSV R&D BPSV & SSV procurement BPSV & SSV delivery

Cost estimates incorporate vaccine development probabilities, costs per R&D phase, advanced capacity reservation assumptions (volume of doses included, fees, and time for facility transition), global capacity, pandemic duration, and delivery costs by World Bank income group. Data inputs, investment scenarios, and assumptions were defined through a literature review, industry expert interviews, CEPI databases, and Linksbridge SPC databases. Data sources and values used are given in Table A.5 in Supplementary Methods for the cost model.

R&D costs

R&D costs modelled include the costs for proactive development of the BPSV before the next pandemic, Phase 3 reactive costs for the BPSV, and reactive development of the SSV after the emergence of SARS-X. R&D costs are calculated by multiplying the weighted average cost of R&D per individual vaccine candidate (i.e., the average total R&D costs per candidate from the preclinical phase through licensure) by the size of the entire development pipeline. The weighted average cost combines R&D costs per clinical trial phase with estimates of the probability of success for each phase. The risk-adjusted R&D cost per candidate is calculated as the sum of the costs of each phase multiplied by the likelihood of phase occurrence, i.e. the probability of success for previous phases. This approach ensures the weighted average cost of each phase accounts for the probability that the previous phase occurred and was successful.

Rather than assuming each candidate incurs reported R&D costs for every clinical trial phase through licensure, this approach discounts the costs for future phases based on the likelihood that some candidates fail somewhere in the pipeline and incur no further costs. While a few successful candidates incur R&D costs for every phase in the pipeline, the average cost per phase per candidate is lower because other candidates dropped out at earlier phases.

The BPSV pipeline is based on the number of vaccine candidates required to secure one successful BPSV in the event of an outbreak. In scenarios with a BPSV, the vaccine is held in an investigational reserve through Phase 2 until the pandemic arrives. It then proceeds through Phase 3 in a similar timeframe as observed during the COVID-19 pandemic (18 weeks). To model reduced costs from a faster Phase 3 timeline, costs from previous trials are calculated at a cost-per-week rate and applied to the assumed 18-week trial. For the SSV pipeline, the model calculates the required number of candidates needed to reach a 90% certainty threshold of achieving at least five vaccine authorisations. This number is based on estimates of the probability of technical and regulatory success from expert surveys (see table A.5). Costs-per-week rates for all clinical trial phases are applied to the expedited SSV R&D timelines as presented in Table 4.

Table 4: Assumed time taken for clinical trials. With R&D starting one week after pathogen sequencing, the 365-day timeline concludes after 52 weeks, which is 364 days. The 200-day timeline concludes after 28 weeks, which is 196 days. The 100-day timeline concludes after 14 weeks, which is 98 days.

Time to SSV authorisation (days)	Preclinical (weeks)	Phases 1 & 2 (merged, weeks)	Phase 3 (weeks)
365	14	19	18
200	5	7	15
100	5	0	8

Enabling activities, including investments in biological standards, centralised laboratory networks, surveillance networks, preclinical models, and regulatory synchronisation, are scientific endeavours that support the accelerated development of safe and effective vaccines. They are required to achieve faster reactive SSV R&D but are not explicitly calculated in the costing model. The model assumes a \$700M annual cost for these investments based on the CEPI 2.0 budget.⁸ Furthermore, it assumes that five years of such investments reduce the SSV R&D

636 timeline to 200 days, while 15 years are needed to achieve 100 days.

637 **Procurement costs**

638 Procurement costs include those for buying vaccines before (BPSV investigational reserve)
639 and during (BPSV and SSV) the SARS-X pandemic. In investment scenario S01, with BPSVs
640 available prior to a pandemic, procurement and replenishment costs begin upon completion of
641 Phase 2. Once a pandemic arrives, procurement costs depend on the number of BPSV and SSV
642 doses required for global vaccine coverage. Based on 2025 demographics, approximately 949mn
643 doses of BPSV are required to vaccinate 80% of the global 65+ population, and approximately
644 22bn doses of SSV cover 80% of the 15+ population for a two-dose primary series and two
645 single-dose annual boosters.²⁵

646 Procurement costs depend on the type of vaccine procured (BPSV vs. SSV) and the
647 agreement under which they are produced. For BPSV, procurement costs are estimated at
648 \$6.18 per dose based on COVID-19 vaccine COGS data.¹³

649 For SSVs produced under an advance capacity reservation, the annual cost for reserving
650 manufacturing capacity is based on a European Union–Pfizer deal valued at \$0.53 per dose
651 per year for 325 million doses.⁴ This cost is incurred annually and covers facility transition
652 readiness, personnel training, and procuring fill/finish materials. For reserved doses, SSV
653 procurement costs the same as BPSV (\$6.18 per dose).

654 For SSV doses produced under unreserved capacity, i.e. reactive private market capacity
655 outside advance capacity reservation, the assumed procurement cost is \$18.94 per dose, based
656 on COVID-19 vaccine prices.¹⁴ This price captures the cost of facility transition, surging
657 capacity in existing facilities, and building new facilities to meet global vaccine demand.

658 **Delivery costs**

659 Delivery costs consist of those associated with vaccine delivery after pandemic arrival. We
660 assume that delivery costs vary by rollout phase. We define vaccination campaign phases
661 with distinct delivery costs per dose based on COVID-19 data and the Immunization Delivery
662 Cost Catalogue.²⁶ We define three different phases in terms of percent coverage of the total
663 population, by country: 0–10% coverage (start up), 11–30% (ramp up), 31–80% (at scale).

Costs differ by country income level (see Table A.5). The costs per dose cover spending for labour, syringes and safety boxes, social mobilisation, cold chain storage, training, planning, monitoring, personal protective equipment, transportation, technical assistance, and waste management.

The vaccine delivery costs, summarised in Table A.5, were set based on a literature review of COVID-19 delivery costs covering global and country-based estimates. Data gathered to estimate these costs in this literature review are summarised in Table A.2. Global values for Advanced Market Commitment (AMC) countries in COVAX and all low- and middle-income countries estimated delivery costs per dose of \$1.66 and \$0.73, respectively.^{27,28} Country-specific estimates were found for LIC, LMIC, and UMIC with each income group reporting cost per dose ranges of \$0.50–\$4.55, \$0.29–\$4.28, and \$3.84–\$19, respectively. Human resource costs were the main drivers behind these delivery rates,^{29,30} with local salary levels likely accounting for the differences across individual countries. For global estimates across World Bank income groups, the AMC and UNICEF estimates were used to assume the LIC delivery cost of \$1.5 per dose.^{27,28} For LMIC and UMIC, unit cost comparisons across income groups were used to scale up the \$1.5 per dose estimate for LIC. These comparisons, relating outpatient costs and health worker salaries between LIC, LMIC, and UMIC, reported unit cost increases of between 2-3x in LMIC and 5-7x in UMIC.³¹ The “start up” cost for LMIC (\$4.5 per dose) was calculated by applying a 3x unit cost increase to the \$1.5 per dose LIC estimate. For UMIC, a 6x unit cost increase was applied to the LIC value to return a \$9 per dose estimate. For HIC, reimbursement data from the U.S. and United Kingdom were used as a proxy for delivery rates for all HIC due to the absence of available delivery cost data. Thus, delivery costs were based on reimbursement guidance for vaccine providers from the U.S. Centers for Medicare & Medicaid Services³² and the United Kingdom.³³

The delivery costs for LMIC and UMIC decreased by 33% as the vaccination campaign progressed from the “start up” phase to the “ramp up” phase and from the “ramp up” phase to the “at scale” phase. This decrease in unit cost was observed in multiple studies across three countries and was attributed to economies of scale as dose volumes increased along with increased vaccination efficiency.^{34,29,35} For LIC, their unit costs decreased by 33% like LMIC and UMIC as the campaign progressed from the “start-up” phase to the “ramp-up” phase.

However, LIC vaccination campaigns in the COVID-19 pandemic reached a maximum coverage of about 28% and did not reach the “at scale” phase. In modelling delivery, we therefore assumed additional costs were required to address demand challenges, increasing unit costs from \$1 per dose in the “ramp up” phase to \$2 per dose in the “at scale” phase.

Operational manufacturing and response

SSV and BPSV supply are modelled by producing doses sourced from advance capacity reservations and from the private market. The production volumes for each of these supply mechanisms are interconnected and based on the following assumptions:

- The potential annual global vaccine manufacturing capacity is 9bn doses, and this capacity is deployed in the response to a SARS-X pandemic. This volume assumes all global facilities, which are currently producing 6.6bn doses/year,¹⁴ increase the number of production cycles from 2/day to 3/day to run 24 hours/day.
- This capacity can be reserved in advance of pandemic outbreaks via advance capacity reservation agreements.
- Advance capacity reservations allow manufacturing facilities to transition and scale production of SSV doses faster because facilities are paid to maintain a high level of transition preparedness and produce vaccines on the same platform as the approved SSV.
- Additional advance capacity reservation agreements guarantee an equal distribution to all country income groups as part of their terms and conditions (an exception is made for the 500mn doses available for all scenarios for HIC distribution, representing existing advance capacity reservations (see Section A.1.3)).
- Private manufacturing will respond to meet any additional gap in SSV demand above the volume covered by advance capacity reservations.
- Private SSV manufacturing will occur in all existing vaccine production facilities not under a reserved capacity agreement.
- Additional production capacity of 6bn doses will be built in response to a global pandemic to reach a global annual production volume of 15bn doses, similar to the 2021 production during COVID-19 response.¹⁴
- In BAU and scenarios S01, S02, S03, S04 and S07, private manufacturers prioritise

delivering SSV doses to HIC, like during the COVID-19 response. Once HIC have received sufficient doses to vaccinate eligible populations, doses are reallocated to UMIC. Private manufacturers provide population-proportional distribution to all income groups (like the advanced capacity reservations) in the other scenarios (S05, S06, S08, S09, S10).

- HIC receive SSV doses faster than other income groups due to existing advance capacity reservations and preferential delivery from private manufacturers.

Vaccines are distributed to countries immediately at the time of production, but vaccine delivery is constrained based on the following assumptions:

- The BPSV follows a single-dose regimen.
- The SSV follows a two-dose regimen with four weeks between doses.
- Individuals are not considered vaccinated until they have received the second dose.
- A single booster dose is given 1 year after receiving the full SSV primary series, and a second booster dose is given 1 year after the first booster dose.
- Countries are limited by health system capacity in their maximum achievable delivery rate.
- Administration rates are set by a country group based on COVID-19 responses, and LLMIC capacity increases with increased preparedness.

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When countries receive an excess supply of vaccines, delivery is constrained by the health system administration rate. In particular, due to their preferential access, HIC receive vaccines quicker than they can administer doses. These doses sit idle, held by HIC before use, rather than being free for administration by other income groups.

Modelling pandemic outcomes

In an ideal world, we would run simulations for all countries together using country-specific data and interconnected epidemic and economic models. However, interconnected models are beyond our current capabilities. Concerning the aim of modelling all countries independently, we have few countries with complete datasets, with a strong bias in missingness by income level. We therefore create a suite of random synthetic countries by resampling the country data we have, stratifying by country income level. Economics costs are modelled at a country level by inclusion of mandated economic closures that impact both economic and epidemiological outcomes. These are associated to pandemic outcomes through aggregation, and an assumption that pandemic severity in terms of deaths is correlated between countries. Severity is also used to estimate pandemic exceedance probability. Our overall methodology is summarised in Box 2 and explained in detail in Appendix B.

Synthetic countries

We generate synthetic countries by sampling economic, population and response input parameters (see Johnson et al.²⁴ for details). Using the World Bank income-classification categories, we define:

- Low- and lower-middle-income countries (LLMIC), using inputs from low-income countries (LIC) and lower-middle-income countries (LMIC)
- Upper-middle-income countries (UMIC), using inputs from UMIC
- High-income countries (HIC), using inputs from HIC

Randomly generating countries allows us to include uncertainty in many parameters. We sample from specified distributions, or sample with replacement from a discrete set of candidate options, where the candidate options are the values belonging to countries in the income group.

An economy-structured epidemiological country model Epidemic outcomes are generated using an economy-structured country-level epidemiological model, Daedalus. We use a version similar to that presented in Doohan et al.;¹¹ see Johnson et al.²⁴ for more details. The model encodes relationships between demographic, epidemic and economic variables, and projects health, economic and educational impacts of epidemics in a country. The model

Box 2: Methodology for estimating the Δ LIR of advance vaccine investments

1. Create candidate epidemics
 - (a) Draw parameter values for 2,048 pathogens based on historic pandemics
 - (b) Create one synthetic country per income level per pathogen
 - (c) Simulate epidemic. Evaluate *societal losses* associated with each epidemic:
 - i. for each of the investment scenarios and BAU
 - ii. for each of four sector-closure policy (within each scenario), resulting in four candidates each for 11 scenarios, three income levels and 2,048 epidemics
2. Create epidemic library
 - (a) Keep the epidemic with the loss-minimising sector-closure policy from each set of four in the epidemic library
 - (b) Calculate differences in societal losses between investment scenarios and BAU to obtain the difference in loss under ideal response by investment scenarios in synthetic countries
3. Aggregate epidemics to pandemics
 - (a) Resample epidemics from the library to construct pandemic outcomes for epidemics correlated across countries
 - (b) Use the number of deaths in the BAU scenario to estimate each pandemic's probability to occur¹⁰
 - (c) Calculate the expectation, or annualised Δ LIR, for each investment scenario across pandemics of any severity, as well as values restricted to pandemics that have a once-in-thirty-years occurrence, up to those with a once-in-one-hundred-years occurrence

encodes reactive mitigation via closures of non-essential economic and educational activity, which impacts both economic output (measured by GDP) and spread of infection. This allows us to capture the reduced need for closures as the population gets vaccinated.

Daedalus is a deterministic compartmental epidemiological model that consists of seven disease states (susceptible, exposed, asymptomatic infectious, symptomatic infectious, hospitalised, recovered, and deceased), in triplicate to represent vaccination states unvaccinated, vaccinated with a BPSV, and vaccinated with an SSV. The population is stratified into four age groups: pre-school children, school-age children, working-age adults, and retirement-age adults. Working-age adults are further stratified into 46 groups: 45 economic sectors, plus one non-working group.^a

^aAs far as possible, parameters, assumptions and modelling approaches are aligned with Whittaker et al..⁷

For this work, we assume the epidemiological features of SARS-X to resemble respiratory pandemics observed in the past. We simulate 2,048 pathogens by sampling from a parameter space constructed using profiles of pathogens that have previously caused respiratory pandemics.¹¹ This allows us to establish plausible ranges for the values of important parameters such as the infection–fatality ratio. We restrict the basic reproduction number (R_0) to be between 1.5 and 3.5.⁷

The model includes four generic sector-closure policies that might be adopted once a respiratory pandemic emerges, as defined by Doohan et al..¹¹ The policies represent possible choices that range from very stringent to laissez faire, and are based on observations from COVID-19.

We generate distributions over epidemic outcomes for each income group. These samples can be interpreted as representing 2,048 hypothetical SARS-X epidemics occurring in 2,048 synthetic countries of each of three country archetypes, given by three income-classification categories (LLMIC, UMIC, HIC) whose characteristics are randomly taken and combined from all countries falling into the respective income category.

Societal losses For each epidemic, three outcomes are projected:

1. Deaths: Life-years lost;
2. GDP: Short-term economic loss from economic closures and disruptions to demand and labour supply;
3. Education: long-term economic loss from closures of educational institutions.

We estimate cumulative losses for each of the three outcomes over the epidemic period. In our simulations, the epidemic period for a synthetic country begins with either the importation event or the international response time if it occurs before. The epidemic period ends within a year of the target vaccination coverage being reached.

The death toll is translated into years of life lost (YLL), which takes into account the remaining life expectancy of each person who dies. YLL are valued using the value of a statistical life (VSL).³⁶ We derive the value of one life year from the VSL using remaining life expectancy over the population.³⁷

GDP loss is estimated as the total GDP – the sum of gross value added (GVA) across all sectors and over time, scaled by how open they are – subtracted from the value of GDP when

all sectors are completely open over the whole projection horizon, as given by pre-pandemic values. The economy is stratified into 45 sectors following UN Economic and Social Affairs³⁸ definitions. GVA per sector is assumed to depend linearly on its workforce, and its workforce can only decrease relative to its pre-pandemic maximum as a consequence of any of: mandated closures of businesses by sector; sickness and deaths of workers; and loss of international tourism.

Education loss takes into account the extent to which schools are closed, as well as the effectiveness of remote learning in the country. Education loss is valued by estimating life-long earning losses, following Psacharopoulos et al..³⁹

Taken together, these form the societal loss associated with the epidemic in a synthetic country, which can be expressed as a percentage of pre-pandemic annual GDP. We evaluate total societal losses under the four sector-closure policies for each epidemic in turn. We do not attempt to predict what policies countries will choose in order to estimate what the real costs or benefits will be. Instead, for each modelled epidemic, we choose the loss-minimising option from the four policies. The difference in losses between each scenario and BAU then informs ΔLIR .^b The chosen epidemics constitute an “epidemic library” of 2,048 epidemics per investment scenario and country type.

Synthetic pandemics

We approximate pandemic outcomes by combining epidemic outcomes (total societal losses) from the epidemic library. We expect severity to be correlated across countries in a pandemic. This would mean that a severe pandemic is relatively severe in all countries, although we would expect variation across countries, i.e. we would not expect the very worst outcomes to be observed in all countries. We emulate this correlation by resampling from the epidemic library to construct new sets of epidemics that are correlated, summing sets of 200 countries to obtain “global” outcomes associated with pandemics (see section B.2 for details).

We estimate ΔLIR as the difference in LIR between a scenario and BAU. The likelihood and severity of future pandemics has an important impact on ΔLIR , with ΔLIR being higher

^bWe test the policies without prejudice: we do not make any assumptions about their plausibility or appeal to policymakers. In this work, our aim is to estimate ΔLIR , which we formulate with reference to loss-minimising sector closures. Thus, we always choose only one of the four options considered: that which minimises losses.

the more likely it is for severe pandemics to occur. We use exceedance probabilities (EP) to characterise pandemic probability, following Marani et al., Glennerster et al., Madhav et al.^{10,9,12} In this work, we define the EP to be the probability that a certain severity (here measured by the number of deaths per thousand population) will be exceeded in the event of an outbreak, which we apply to the BAU (or counterfactual) pandemic. We estimate the EP using a generalised Pareto distribution that is parametrised to describe the severity profile of historical outbreaks recorded in Marani et al.^{10c}, which we resample with replacement to capture model uncertainty (see section B.3 for details).

We present the expected values of ΔLIR , obtained by summing over severity with weights given by exceedance probabilities. The expectations of ΔLIR can be interpreted as annualised values. In addition, we present illustrative results: what ΔLIR would be in the cases of a SARS-X whose severity corresponds to a “once in thirty years” pandemic up to a “once in one hundred years” pandemic (that is, pandemics with a severity we would expect to witness with probability 1/30 and 1/100 in any given year, and where the pandemic is caused by a SARS-X pathogen). We report these ΔLIR both in terms of % of counterfactual pandemic losses, and in terms of % of global GDP. As we do not model secular trends or any other changes over time, the ΔLIR grows at the same rate as GDP. We therefore report results as a percentage of contemporaneous GDP.

Data availability

All data used are publicly available and cited where referenced in the text, with the exception of cost data for clinical trials, which come from Gouglas et al.⁴⁰ and are not publicly available.

Acknowledgements

PD, RJ, GNG, CM, MM, GF and KDH acknowledge funding from Community Jameel and from the MRC Centre for Global Infectious Disease Analysis (reference: MR/X020258/1), funded by the UK Medical Research Council (MRC). This UK-funded award is carried out

^cThis approach was used by Marani et al.¹⁰ to calculate outbreak EP as a function of intensity, where the unit of interest was “intensity” (defined as deaths per thousand population per year) rather than “severity” (deaths per thousand population).

in the frame of the Global Health EDCTP3 Joint Undertaking. PD, RJ, MM, GF and KDH also acknowledge funding from Kenneth C. Griffin. RJ and KDH acknowledge funding from the World Health Organization. AAT, PW, and DW acknowledge funding from the Coalition for Epidemic Preparedness Innovations (CEPI). CM acknowledges the Schmidt Sciences for research funding (grant code: 6-22-63345). GF is also supported by the Jan Wallanders and Tom Hedelius Foundation and the Tore Browaldh Foundation (grant no.: P19-0110). KDH is also funded by the National Institute for Health and Care Research (NIHR) Health Protection Research Unit in Modelling and Health Economics, a partnership between the UK Health Security Agency, Imperial College London and LSHTM (grant code: NIHR200908), and by the NIHR Health Protection Research Unit in Health Analytics and Modelling, a partnership between the UK Health Security Agency, Imperial College London and LSHTM. CW was supported by a Sir Henry Wellcome Postdoctoral Fellowship Ref 224190/Z/21/Z.

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Author contributions

RJ, PW, AAT, AS and KDH conceptualised the study. RJ, PW, AAT and DW were responsible for data acquisition and validation. RJ and PW were responsible for software. RJ and PW were responsible for formal analysis and visualisation. RJ, PW, AAT, AS and KDH were responsible for data interpretation. RJ and KDH were responsible for writing the initial draft. RJ, PW, AAT, AS, PD, CM, GNG, GM, CW, MM, GF and KDH were responsible for writing and editing. AAT and KDH were responsible for supervision. KDH was responsible for funding acquisition and project administration.

Competing interests

PD, RJ and KDH declare receipt of personal fees from WHO for consultancies on integrated epidemiological–economic modelling and pandemic vulnerabilities, respectively. GF declares receipt of personal fees from WHO and Imperial College London for consultancies. KDH declares receipt of personal fees from WHO, Pfizer, GSK and Munich Re for work unrelated to

892 this study, payments for expert testimony from Infected Blood Inquiry (UK) and stocks from
893 Astra Zeneca. CW has received personal consultancy fees from SecureBio for work relating
894 to novel pathogen surveillance and from Blueprint Biosecurity for work relating to pandemic
895 preparedness.

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