**Quantifying the impact of a broadly protective sarbecovirus vaccine in a future SARS-X pandemic**

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**Abstract**

The COVID-19 pandemic has underscored the need for more timely access to vaccines during future pandemics. This has motivated interest in developing broad-spectrum vaccines providing protection against entire viral families, which could be stockpiled ahead of an outbreak and deployed rapidly following detection. We use a modelling approach to assess the utility of a broadly protective sarbecovirus vaccine (BPSV) during a hypothetical SARS-X outbreak, for strategies including ring-vaccination, spatial targeting and mass vaccination of high-risk populations. Our results show limited effectiveness of BPSV ring- or spatially-targeted vaccination strategies at containing a SARS-CoV-2-like virus but more impact against a SARS-1-like virus. We find a substantial potential BPSV impact on disease burden when given to high-risk populations ahead of a virus-specific vaccine (VSV) becoming available, even if the BPSV is less effective than the VSV. For a 250-day VSV development timeline, BPSV availability reduced disease deaths by 55% when no NPIs are imposed, and by 50% with stringent NPIs. Availability also enabled fewer and shorter NPIs to be imposed whilst limiting disease burden to that observed in the VSV-only scenario, though results were sensitive to vaccine properties (such as efficacy), health system capabilities (such as vaccination campaign speed) and the assumed timeline to VSV availability. A BPSV stockpile sufficient for 80% coverage of the world’s population aged 65+ could have averted 68% of COVID-19 deaths during the pandemic’s first year. Our work highlights significant potential impact of a BPSV, but achieving this impact also depends on investment into health systems to ensure rapid and equitable access during future SARS-X pandemics.

**Introduction**

Experiences with COVID-19 have highlighted the crucial role of vaccinations in reducing disease burden and mitigating socio-economic impact during pandemics. An estimated 14-20 million deaths were averted due to vaccinations in the first year of the pandemic *(1)*, with vaccine availability also enabling lifting of societal restrictions that carried significant socio-economic costs *(2)*. Development and authorisation of highly efficacious vaccines against COVID-19 in <1 year represents a significant achievement, given that traditional development pipelines typically take 10+ years *(3)*. Despite this accelerated timeline however, >1.5 million officially confirmed COVID-19 deaths occurred during this same time-period *(4)*. Moreover, access to doses following authorisation was characterised by significant inequity between the global north and global south, with the latter facing significant delays *(5)*. This is despite the additional lives that equitable allocation strategies could have saved *(6–9)*.

SARS-CoV-2 is unlikely to be the last novel pathogen pandemic faced by the world over the next 100 years *(10)*. Both the frequency of pathogen spillover, and the intensity of epidemics arising from this spillover, are projected to increase in the future *(11, 12)*. This has motivated significant interest in further reducing vaccine development timelines, including recent initiatives aiming to enable development, authorisation and manufacture of vaccines against a novel pathogen within 100 days of identification *(13–15)*. Recent work estimated that COVID-19 vaccine availability within this timeframe could have averted almost 10 million deaths, primarily in low-middle income countries (where vaccine availability was most delayed) *(16)*. However, other work has indicated that existing approaches to vaccine development are unlikely to achieve development timelines <250 days *(17)*. A further limitation of these approaches is their reactive nature, with pathogen-specific vaccine development dependent on having detected and sequenced the novel pathogen’s genome. This necessarily limits the timeliness of strategies centred around development of vaccines in response to an epidemic; a factor which in turn leads to either substantial human mortality or the necessity of significant (and costly) control measures in the form of non-pharmaceutical interventions (NPIs).

Research efforts have therefore focussed on alternative approaches to vaccine development that might facilitate more rapid availability. Of particular interest have been broad-spectrum vaccines providing protection against a range of viruses belonging to the same family or sub-family that could be manufactured and stockpiled ahead of a pandemic. Previous work has identified potent pan-sarbecovirus neutralising antibodies in previously infected humans *(18–20)*, suggesting that vaccines aiming to elicit broad-spectrum protection against sarbecoviruses should be possible. Several vaccines aimed at providing broad and robust protection to a range of coronaviruses are currently under development *(21, 22)*. Many of these have demonstrated an ability to induce broad neutralising antibodies in mice; several have demonstrated this in non-human primates. These candidates span a range of different approaches, including mosaic nanoparticles containing spike receptor binding domains from multiple sarbecoviruses *(23)*; approaches based on chimeric spike mRNA vaccines *(24)*; and vaccine antigens based on epitopes conserved across multiple coronaviruses *(25, 26)*.

Here, we use a mathematical modelling framework to evaluate the potential utility of a broadly protective sarbecovirus vaccine (BPSV) during a hypothetical future SARS-X pandemic. We explore several use cases including ring- and spatial-vaccination strategies for outbreak suppression, and widespread mass vaccination of vulnerable populations for disease burden mitigation. Our work highlights substantial potential public-health impact arising from widespread availability and rapid access to a BPSV during a novel sarbecovirus pandemic. However, we show that realising the maximum potential benefit of these novel tools will also require investment into diagnostics, surveillance and broader public-health response capabilities *(27, 28)*. In doing so, we underscore the potential utility of broad-spectrum vaccines as tools to support future pandemic preparedness.

**Results**

**Ring-vaccination with a BPSV could support outbreak containment efforts of a sarbecovirus similar to SARS-1 but not SARS-CoV-2**

We developed a stochastic branching-process framework to explore the potential for a BPSV to support containment of a hypothetical SARS-X outbreak via a ring vaccination approach (as successfully undertaken for Ebola outbreaks) *(29)* **(Fig 1A)**. We considered two “archetype” sarbecoviruses – one with properties similar to SARS-1 (**Fig 1B**, mean generation time 12 days, 0% presymptomatic transmission, 0% asymptomatic infections) and one similar to SARS-CoV-2 (**Fig 1C**, mean generation time 6.75 days, 35% presymptomatic transmission, 15% asymptomatic infections). In both cases, we assumed ring-vaccination identified 80% of contacts, a BPSV efficacy of 35% against infection, that breakthrough infections in vaccinated individuals have a 35% reduced infectiousness, and an (optimistic) delay of 2 days between identification of a symptomatic index case and their contacts receiving the vaccine. We also carried out detailed sensitivity analyses (see below and see **Supplementary Table 1** for list of sensitivity analyses carried out).

Across both pathogen archetypes, the proportion of outbreaks successfully contained decreased as R0 increased and increased as the assumed time between vaccination and protection developing (which we term *vaccine protection delay, VPD*) was shortened. For the “SARS-1-like-virus”, a protection delay of ≤1 week contained all outbreaks for R0≤1.5. However, a VPD of 2 weeks averted <1% outbreaks across all values of R0. For the “SARS-CoV-2-like-virus”, where a significant fraction of transmission occurs prior to symptoms, containment was only possible for VPD≤2 days and R0≤1.5. Prospects for control were sensitive to vaccine characteristics and pathogen properties **(Fig 1D, 1E & 1F)**. When the VPD equalled the mean generation time (Tg/VPD = 1, **Fig 1D**), BPSV ring-vaccination did not lead to containment **(Fig 1D)**. However, for longer generation times (Tg/VPD ≥3) almost complete containment was achieved in all but the highest R0 scenarios. Increasing vaccine efficacy against infection similarly led to an increasing fraction of outbreaks successfully contained for R0≤2 but failed for higher R0 **(Fig 1E)**. For viruses with higher levels presymptomatic transmission, containment was less likely **(Fig 1F)**.

**Spatially-targeted vaccination strategies using a BPSV must be accompanied by highly sensitive surveillance systems to be impactful**

We next extended the framework to explore the impact of spatially-targeted vaccination strategies utilising the BPSV and aimed at containment. We assumed that this would be triggered by detection of a cluster of hospitalised cases. Following detection (and an assumed operational delay of 2 days), all individuals within a certain spatial radius of the home address of the hospitalised case(s) are vaccinated **(Fig 1G)**. We utilise the same pathogen archetypes described above, with 95% of “SARS-1-like-virus” infections hospitalised and 5% “SARS-CoV-2-like-virus” infections hospitalised.

For “SARS-1-like-virus” with R0<2, spatially-targeted vaccination could contain outbreaks across all surveillance system sensitivities considered **(Fig 1H)**. However for “SARS-CoV-2-like-virus” **(Fig1I)**, containment with spatially-targeted vaccination with R0<2 only occurred in highly sensitive surveillance scenarios. We undertook sensitivity analyses examining how the proportion of simulated outbreaks contained varied as a function of R0 and i) the ratio of the vaccination campaign’s radius to the average distance separating infections **(Fig 1J)**; ii) BPSV efficacy **(Fig 1K)**; and iii) the number of hospitalisations required to trigger the vaccination campaign **(Fig 1L)**. Increased vaccination campaign radius, improved vaccine efficacy and increased surveillance sensitivity were all associated with an increased fraction of outbreaks being contained. However, none of the scenarios contained outbreaks with R0>2.

**Vaccination of high-risk populations with a BPSV during a SARS-X outbreak could significantly reduce mortality and limit need for NPIs.**

We next adapted a dynamical model of SARS-CoV-2 transmission *(22)* to explore the utility of a BPSV in providing rapid protection of high-risk groups to reduce disease burden during a hypothetical SARS-X outbreak. In this scenario, we assume that the BPSV has been manufactured and stockpiled ahead of the outbreak, enabling rapid deployment following virus detection (which triggers BPSV vaccination). We assume that virus-specific vaccine (VSV) development is also triggered at this time, but that there is a delay to this becoming available. To explore the relative benefits of a BPSV versus waiting for the VSV, we use a baseline scenario in which the BPSV has 75% efficacy against disease and 35% efficacy against infection whilst a future VSV has vaccine efficacy of 95% against disease and 55% against infection. For the VSV we explore a development timeline of either 250 or 100 days (based on recent estimates of realistic and ambitious vaccine development timelines *(13)*). We assume a R0 of 2.5, in-keeping with initial estimates of ancestral SARS-CoV-2 in Wuhan *(30)* (see **Figure S2** for results using different R0 values).

In our simulations, pathogen spillover is followed by a period of undetected circulation in the community. Hospitalisations due to the infection lead to pathogen detection and identification. Following pathogen identification, development of the VSV starts, and after an assumed delay of 7 days (to allow activation of stockpiles), mass vaccination of the at-risk population (assumed to be those aged 65+) with the BPSV begins. Vaccination switches to the VSV once it is available, with those that have received the BPSV boosted with the new vaccine. We illustrate impact with vaccination rates of 3.5% of the country’s population per week, such that the 65+ age-group is fully vaccinated within 4 weeks under a single dose regimen **(Fig 2A).** We considered a range of scenarios reflecting differences in the stringency, duration and triggers for NPIs **(Fig 2B)** with NPI days ranging from 0 (no intervention) to 80 for VSV development of 100 days, and 0-175 for VSV development of 250 days.

The BPSV has the greatest impact if no NPIs are implemented, reducing projected deaths per 1,000 population from 8.6 without the BPSV to 3.85 if the VSV is available in 250 days; and 8.6 to 3.9 it is available after 100 days **(Fig 2C, NPI Scenario 1).** If the VSV is developed and deployed more rapidly, the relative benefit of the BPSV is reduced. When NPIs are more stringent, the value of the BPSV is reduced but its impact depends on the time taken for the VSV to become available. For example, with a short period of stringent NPIs during the BPSV vaccination campaign followed by a minimal set of NPIs afterwards **(Fig 2C, NPI Scenario 6)**, the BPSV reduces deaths from 7.6 to 3.6 per 1,000 population, a 53% reduction if the VSV is available after 250 days, but its impact is more limited if the VSV is available after 100 days. More generally, for the 250-day development timeline, availability of the BPSV limits mortality to levels below all but the most stringent NPI scenarios **(Fig 2C, NPI Scenario 9)** when the BPSV is absent, enabling shorter and less stringent NPIs to be in-place for the same total disease. BPSV impact was high in R0=3 scenarios across all VSV development timelines considered, although impact was more limited in R0=1.5 scenarios. In these scenarios, BPSV impact was minimal except for the longest VSV development timeline (365 days)(**Fig S2).**

We also explored how availability of the BPSV might shape the duration and stringency of NPIs required to limit disease burden to the level observed in scenarios where only the VSV is available **(Fig 2D).** For a 250-day development timeline and NPI Scenario 6, availability of the BPSV reduced the number of NPI days required from 136 to 51 days to limit disease burden to that observed when only the VSV is available (a reduction of 63% of total NPI days) **(Fig 2D, lower panel)**. By contrast, for a 100-day development timeline and NPI Scenario 6, availability of the BPSV led to only 4 fewer NPI days, representing only 14% of total imposed NPI days **(Fig 2D, upper panel)**. In general, longer VSV development timelines necessitate more protracted and stringent NPIs to be implemented for the same accrued disease burden. It is in these contexts where availability of the BPSV most reduces the need for NPIs.

**Availability of a BPSV could have substantially reduced mortality during the COVID-19 pandemic.**

Given the impact that NPIs have on assessing the value of the BPSV, we explored the potential impact that a stockpiled BPSV could have had on COVID-19 mortality in the first year of the pandemic **(Fig 3A)** using previously published model fits calibrated to excess mortality data *(26)*. We assume that BPSV vaccination occurs after 14 days, targeting individuals aged 65+ with a BPSV stockpile sufficient to achieve 80% coverage of the eligible 65+ population. Our results indicate that such a stockpile available globally could have averted 68% of COVID-19 deaths **(Fig 3B** and **Fig 3C)**. A global stockpile is unrealistic but could be prioritised in places affected early in the pandemic. For example, in Italy, availability of the BPSV could have reduced mortality during the first wave from 1360 daily deaths at its peak to 810 deaths **(Fig 3D)** and total COVID-19 mortality over the first year from 124,500 to 49,700 deaths, a 60% reduction **(Fig 3D)**. Similar impacts were estimated for the epidemics in Iran **(Fig 3E)** and Bangladesh **(Fig 3F)**. Respective stockpile sizes required for these countries to vaccinate their eligible populations and achieve this impact would have been 14.1 million doses for Italy, 5.5 million doses for Iran and 8.6 doses for Bangladesh.

**BPSV impact depends on target product characteristics.**

The results presented thus far assume fixed illustrative BPSV properties. Whilst a significant number of BPSV candidates are currently under development, most are at preclinical stages and their potential properties remain uncertain *(28)*. We therefore undertook detailed sensitivity analyses to understand the impact of varying properties of the BPSV and the time taken to develop the more efficacious and disease-specific alternative, as well as features of the pathogen and NPI response to the epidemic (see **Supplementary Table 2** for list of scenarios and sensitivity analyses carried out). Our results show a significant influence of BPSV efficacy against severe disease on mortality under all but the lowest R0 scenarios **(Fig 4A).** For low values of R0 (R0 = 1.5, **Fig S2**) and assuming a time-to-development for the VSV of 250 days, the impact of a BPSV is minimal under all NPI scenarios and disease efficacy values considered, with < 1.5 deaths per 1,000 population averted. Under these scenarios, development of the VSV is accomplished before significant spread through the population. For higher values of R0, increasing BPSV efficacy is associated with a linear increase in averted mortality **(Fig 4A** and **Fig S2A)**. We observed a less marked influence of efficacy against infection on BPSV impact (**Fig 4B** and **Fig S2C**). This is because the BPSV campaign only targets a small fraction of the population (those aged 65+) and therefore the impact on onwards transmission is limited. BPSV impact increases with longer duration of elicited immunity **(Fig 4C** and **Fig S2B)**.

**BPSV impact is shaped by stockpile size, vaccination campaign speed and access equity.**

We additionally carried out analyses exploring how BPSV impact is affected by procurement and health systems factors shaping the speed and size of the vaccination campaign. Mortality averted by the BPSV increased linearly with the size of the stockpile (determining the associated coverage of 65+ individuals) **(Fig 4D** & **Fig S2D)**. Assuming an R0 of 2.5 and maintaining a stockpile sufficient to vaccinate 76% of eligible 65+ (in-keeping with estimates of primary SARS-CoV-2 vaccination series coverage of older adults as of December 2022 *(31)*), a BPSV could avert 3.1 deaths per 1,000 population. BPSV impact is positively correlated with the speed of the BPSV vaccination campaign **(Fig 4E)**. For the moderate NPI scenario, 3.8 deaths per 1,000 are averted when the campaign is completed in <2 months, versus 2.7 deaths per 1,000 for a 5 month campaign. However, under the stringent NPI scenario, there was no additional impact of the BPSV if the campaign took more than 5 months. This is because the VSV becomes available and therefore the benefit of the stockpiled BPSV is reduced. Vaccination campaign speed had even more influence on BPSV impact when the virus R0=3.5, and minimal impact when R0=1.5 **(Fig S2E).**

We also carried out analyses exploring the impact of delays to accessing the VSV. During the COVID-19 pandemic there was a significant delay to countries in the global south receiving vaccines *(28)*, as illustrated by the time taken to achieve vaccination coverage of 1% of eligible population (as a proxy for timeliness off vaccine access) *(32, 33)* **(Fig 4F)**. Relative to the first country to vaccinate 1% of their population), countries in Europe experienced a median delay of 32 days (IQR 27-39). By contrast, in took a median of 135 days (IQR 110-180) for countries in Africa. We incorporated these delays to access into the VSV development timeline. For a VSV development time of 250 days, a moderate NPI scenario and R0 = 3.5, the BPSV averted significant mortality across all continent-average vaccine access delays considered **(Fig 4G)**. However, in the R0 = 1.5 scenario, the BPSV had a substantially higher impact on disease burden when access was delayed to level similar to that experienced by the average African (1.75 deaths averted per 1,000 population) than the European delay scenario (0.18 deaths averted per 1,000 population).

**Surveillance system sensitivity and timeliness of virus detection initiation shapes BPSV impact**

Initiation of the BPSV vaccination campaign and development of the VSV depend on detection of the outbreak and identification of the novel virus. We therefore carried out a series of sensitivity analyses exploring the influence of surveillance sensitivity on BPSV impact. Assuming an R0 of 2.5, a moderate NPI scenario and that the VSV was developed in 100 days, we observed that BPSV impact was lowest when surveillance system sensitivity was high (i.e. a low hospitalisation threshold for response trigger), and highest when surveillance system sensitivity is low (i.e. a higher hospitalisation threshold for response trigger) **(Fig 5B left hand panel)**. In scenarios where surveillance system sensitivity is high, in tandem with its rapid development, the VSV can be distributed before significant epidemic progression and thus there is minimal additional impact of BPSV availability. In contrast, BPSV impact was high under all surveillance system sensitivity scenarios considered when the VSV development time was 250 days **(Fig 5B right hand panel)**. In this context, VSV development occurred after the epidemic and so there was significant benefit to availability of a BPSV and the protection it provided to eligible individuals.

**Timeliness of BPSV campaign initiation relative to the timing of pathogen importation influences impact**

The analyses presented thus far have been restricted to understanding BPSV impact in the country where the novel virus outbreak initially occurs. They therefore assume that BPSV vaccination is initiated in response to pathogen identification following hospitalisations in local healthcare facilities. However, both SARS-1 and SARS-CoV-2 pandemics exhibited early international spread. We therefore carried out a set of analyses exploring how the timeliness of novel pathogen detection in the country where the virus initially emerges (“source country”) might influence the impact of public health responses utilising the BPSV in other countries (“secondary countries”). Here, virus detection in the source country is assumed to trigger VSV development and BPSV vaccination in secondary countries. We vary the timing of importation relative to detection such that in some scenarios, importation into the secondary country occurs either before (“early importation”) or after (“late importation”) detection in the source country. In both, we assume BPSV vaccination starts when the virus is detected in the source country **(see Fig 5C for overview)**. Assuming the VSV is available 100 days after virus detection, the BPSV had limited impact in the late importation scenario because only limited community transmission occurs before the VSV becomes available **(Fig 5D, top row, orange lines)**. In contrast, the BPSV had significant impact in the early importation scenario, especially for high R0 (R0 = 2.5 and 3.5). Under these scenarios, significant community transmission and spread occurs before the VSV becomes available, thus the BPSV can protect high-risk populations **(Fig 5C, top row, green lines)**. For a VSV development time of 250 days, the BPSV had substantial public health impact under most scenarios considered.

**Discussion**

Our research demonstrates the significant impact that timely access to a BPSV could have in reducing both the disease burden and socio-economic impacts of future SARS-X pandemics. Notably, availability of a BPSV stockpile in the country where the new virus emerges could, with only limited NPIs, significantly lower mortality to below what could be achieved in the absence of a BPSV but with longer and more stringent NPIs. Such a vaccine therefore has the potential to simultaneously reduce disease burden and the wider economic costs associated with NPIs.

We identified several factors influencing this impact. These act at two levels; those intrinsic to properties of the BPSV (which affect the quality of protection it offers) and those that influence the number of individuals infected during the period between the BPSV vaccination campaign finishing and the VSV becoming available. It is during this period that the BPSV provides protection to individuals who would otherwise be infected. Faster development timelines for the VSV or low infection rates (due to stringent NPIs) can diminish the size of this counterfactual epidemic (i.e. what happens in the absence of a BPSV), reducing the population-level impact of the BPSV campaign. A higher transmissibility (R0), limited NPIs and/or longer VSV development times generally increase the size of the counterfactual epidemic, increasing the value proposition for a BPSV. The impact of the BPSV is then determined by the size of the maintained BPSV stockpile and the rate at which BPSVs can be delivered to the high-risk populations.

Despite this promise for disease burden reduction, our results indicate that BPSVs are unlikely to greatly enhance early containment, especially for highly transmissible viruses similar to SARS-CoV-2. A critical issue here is the VPD, with our results suggesting a negligible fraction of outbreaks contained via ring-vaccination when the VPD is of a similar timescale to the generation time of the virus. Given this, other broad-spectrum medical countermeasures such as monoclonal antibodies (where protection arises near-immediately) could represent crucial additions to the arsenal of tools available for outbreak containment *(34)*, *(35)*, as could tools eliciting more robust immunity against infection and onwards transmission, such as has been observed for vaccinations delivered intranasally *(36, 37)*. Our results suggest spatially targeted vaccination strategies are unlikely to contain a “SARS-CoV-2-like-virus” except when the spatial area covered by the campaign is large or hospital surveillance is highly sensitive. Novel pathogen surveillance capabilities are severely limited in many parts of the world. Experiences during the COVID-19 pandemic have highlighted significant global disparities in surveillance capabilities, including genomic surveillance crucial to novel pathogen identification *(34)*.

Whilst surveillance limitations may hinder BPSV use for containment, our results show that use of the BPSV for disease-burden mitigation is robust to these limitations. This arises because surveillance capabilities influence both the timing of the BPSV campaign and the initiation of VSV development. In low-sensitivity surveillance systems, which detect pathogens later, both BPSV distribution and VSV development are delayed – this shift in the timing of both events does not significantly change the counterfactually infected population protected by the BPSV. Conversely, in high-sensitivity systems, early pathogen detection facilitates prompt BPSV deployment and widespread population protection before significant community spread occurs. Previous work has highlighted the significant investment into public-health surveillance capabilities required to strengthen global, national and local mechanisms for detection (costing ~$9.6 billion globally) *(38)*. Tools (such as the BPSV) that are robust to the current limitations in novel pathogen surveillance capabilities worldwide *(39)* are therefore likely to prove useful.

Our results also highlight significant impact of a stockpiled BPSV when considering potential delays in VSV access. There was significant variation worldwide in the rate at which SARS-CoV-2 vaccination campaigns proceeded, much of this due to global disparities and inequity in the timeliness of COVID-19 vaccine availability *(40)*. This is despite work showing that equitable access would be the most effective strategy for averting loss of life *(36)*. Our results highlight that equitable and widespread availability of a BPSV would provide significant public-health benefit under all scenarios where we varied the timing of access to the disease-specific vaccine following its development. Crucially however, this is contingent on the BPSV itself being widely and equitably distributed. Equitable access to public health innovations and medical countermeasures has been a key focus of work looking to develop “rules of the road” for future pandemics *(41)*, as well a World Health Assembly initiative to develop a global pandemic accord *(42)*. However, much more must be done to ensure equitable access to life-saving medical countermeasures in future pandemics.

A significant limitation of the results presented here is uncertainty in the BPSV properties. Whilst multiple candidates are currently under development *(39)*, evaluation of immunogenicity to date have been limited to mice or non-human primates *(23, 43)*. No evaluations of immunogenicity have been carried out in humans. This is important given the wide diversity of coronaviruses that humans are routinely exposed to *(44)* and how past exposure shapes the breadth of neutralising antibody responses to sarbecovirus infection*(45)*. To mitigate this limitation, we assumed estimates of BPSV efficacy that are significantly lower than the estimates of efficacy achieved by initial mRNA vaccines against ancestral SARS-CoV-2 lineages *(46, 47)*. Additionally, we carried out analyses exploring how BPSV impact depends on vaccine properties such as disease efficacy and immunity duration. In both cases, our results show the BPSV has significant impact, especially in contexts where timelines for development of VSV are similar to that achieved with SARS-CoV-2. Whilst the eventual real-world properties of developed BPSVs are therefore highly uncertain, our results suggest that the timely nature of BPSV availability and the ability to stockpile them ahead of a pandemic means they can still achieve significant public health impact. This impact persists even when BPSV efficacy is significantly lower than disease-specific alternatives. A further limitation is that we do not account for potential existing cross-immunity to a new SARS-X virus. Previous work exploring neutralising antibody responses in SARS-1 survivors has shown strong cross-protection to both ancestral and variant SARS-CoV-2 virus *(20)*. Given the global prevalence of SARS-CoV-2, it is likely that any future SARS-X transmission may be mitigated in part by cross-immunity. However, the degree of impact remains highly uncertain. Thirdly, whilst our work highlights the significant public-health impact of a BPSV, a comprehensive evaluation of the viability of maintaining a stockpile is required. Whilst the outsized economic costs of the COVID-19 pandemic *(45, 46)* suggest that the maintenance of a BPSV stockpile would be highly cost-effective, the uncertainty in the rate and scale of a future outbreak alongside the value of investment needed requires further consideration.

Despite these limitations, our work highlights the significant population-level impact that could be achieved through development, manufacture and stockpiling of BPSVs to facilitate rapid access in the case of a hypothetical SARS-X emergence. Such vaccines could provide an effective way to protect high-risk groups during the period between novel pathogen identification and the development of efficacious VSVs. In doing so, BPSV utilisation has scope to both avert significant disease burden and substantial economic losses through relaxing the requirement for stringent NPIs to control transmission. However, our work also shows that realising the benefits of the BPSV is critically dependent on other feature of the health system, necessitating investments into health systems capabilities enabling rapid distribution of vaccines if these broad-spectrum medical countermeasures are to most effectively form a part of future pandemic preparedness strategies.

**Methods**

**Stochastic Branching Process Modelling Framework**

We extended a stochastic branching-process modelling framework initially developed to explore SARS-CoV-2 control through contact tracing *(48, 49)* to simulate different vaccination strategies focussed on outbreak containment (defined as a final outbreak size of <10,000 infected individuals). These were ring-vaccination (where detection of symptomatic cases triggers reactive vaccination of all contacts of that case, **Fig 1A**) and spatially targeted vaccination (where hospitalised cases trigger vaccination of all individuals in a defined geographic area, **Fig 1G**).

For both strategies, we calculate the proportion of outbreaks contained relative to a scenario in which the BPSV is not available whilst varying the pathogen epidemiological properties, the intrinsic properties of the BPSV, and features of the vaccination campaign response. The epidemiological properties that we vary are R0, generation time distribution, extent of pre-symptomatic transmission, proportion of asymptomatic infections and the probability of being hospitalised. We explore two pathogen “archetypes” – the first has properties similar to SARS- 1, with a long generation time, limited pre-symptomatic transmission, low proportion of asymptomatic infections and high disease severity. The second is SARS-CoV-2, with a shorter generation time, extensive pre-symptomatic transmission, more asymptomatic infection and low disease severity. For both archetypes, we vary the R0 across a range of values. Furthermore, we assume that past exposure to SARS-CoV-2 does not generate significant immunity to SARS-X. BPSV properties varied across model runs were efficacy against infection, relative infectiousness of breakthrough infections, and the assumed delay between vaccination and immunological protection developing.

In all instances, results are the proportion of outbreaks contained across 100 stochastic simulations, per parameter combination and vaccination strategy considered. Code to reproduce the results is available at <https://github.com/mrc-ide/diseaseX_modelling>. For further details of the model and parameterisation, see **Supplementary Information.**

**Dynamical Compartmental Modelling Framework**

We adapted a published compartmental model of SARS-CoV-2 transmission and vaccination *(47)* to explore the impact of BPSV availability on disease burden during a future hypothetical SARS-X pandemic. The original model is described in *(16, 50, 51)*, with details of the extensions added here described below and in the **Supplementary Information**. Briefly, we extended this modelling framework to enable simulation of two vaccines with distinct properties (the BPSV and the disease-specific vaccine). The BPSV, available immediately upon detection, is assumed to have an efficacy of 75% against disease and 35% against infection. The disease-specific vaccine, developed later, has a more favourable efficacy profile - 95% against severe disease and 55% against infection, with development timelines of either 100 or 250 days. We model two distinct forms of vaccine efficacy: efficacy against infection and efficacy against severe disease in breakthrough infections. Following spillover, pathogen detection occurs on the first day with ≥5 daily hospitalisations and leads to initiation of both the BPSV vaccination campaign and disease-specific vaccine development. The timing of detection was calculated using the stochastic branching-process framework. The BPSV is used to vaccinate individuals over the age of 65+ years. All age-groups except those under 15 are eligible to receive the disease-specific vaccine, with rollout of this vaccine (sufficient to achieve a coverage of 80% of the population) occurring in the oldest age-groups first.

**Hypothetical SARS-X Pandemic Scenario Modelling**

We assume an R0 of 2.5 and generation time of 6.7 days, aligned with estimates for the original Wuhan-1 strain, as well as a severity profile and age-specific IFR similar to SARS-CoV-2 *(52)*, adjusted to give an overall population-level IFR of 1%. We assume a demographic age-structure matching the age-distribution of the World Bank Upper Middle-Income Country with the median age and assume no healthcare constraints that limit the ability of hospitalised individuals to access medical care, noting that relaxing this assumption would increase our estimates of BPSV impact. We explore different scenarios varying the duration, stringency, and timing of imposed NPIs. These scenarios span three levels of NPI stringency: i) none, keeping R equal to R0; ii) minimal, reducing transmission by 25%; iii) stringent, reducing R to 0.9. Our analysis focuses on three scenarios: 1) minimal NPIs applied briefly after pathogen detection until the end of the BPSV campaign; 2) moderate NPIs lasting until the BPSV campaign's end, then relaxed until the completion of the disease-specific vaccine rollout; 3) stringent NPIs maintained throughout the BPSV campaign, then eased until the end of the disease-specific vaccine rollout. For each NPI scenario, an “NPI index” (representing a composite of the stringency of imposed NPIs and their duration) was calculated. Deaths averted per 1,000 population by the BPSV were estimated by comparing deaths in scenarios with both BPSV and the disease-specific vaccine to scenarios with only the disease-specific vaccine. PotentialNPI days averted by availability of the BPSV was calculated as follows: first, we constructed the Pareto frontier across explored NPI scenarios in the case where only the VSV was available. We then calculated the difference in composite NPI days between the scenario in which the BPSV is available and the composite NPI days for the point lying on the Pareto frontier leading to that same number of deaths in a scenario where only the VSV is available.

**Retrospective Evaluation of Potential Impact During SARS-CoV-2 Pandemic**

Using published Bayesian country-specific model fits to excess mortality data *(45, 46)* we explored the potential impact that a stockpiled BPSV could have had on COVID-19 mortality in the first year of the pandemic. We first sampled 100 draws from the previously estimated posterior distribution of Rt. To then estimate the impact of BPSV, we simulated a counterfactual scenario for each sampled Rt trajectory in which BPSV vaccines were introduced after 30 days, assuming all countries possess a BPSV stockpile to vaccinate 80% of their eligible elderly population. Deaths averted by the BPSV were calculated by subtracting the estimated COVID-19 deaths from the simulation with the BPSV from the simulation without the BPSV, with the median deaths averted per 1,000 population reported here. See **Supplementary Information** for further details.

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**Author Contributions**

**Conceptualization:** CW, GB, DOM, OJW & AG

**Methodology:** CW, GB, OJW & AG

**Investigation:** CW & AG

**Visualization:** CW, DOM & AG

**Funding acquisition:** OJW & AG

**Project administration:** AG

**Supervision:** AG

**Writing – original draft:** CW & AG

**Writing – review & editing:** CW, GB, DOM, OJW & AG

**Competing Interests**

The Coalition for Epidemic Preparedness Innovations (CEPI) funded the investigation into the impact of the 100 Days Mission. Authors maintained full freedom when designing the study and deciding on additional scenarios to explore. ACG has received personal consultancy fees from HSBC, GlaxoSmithKline, Sanofi and WHO related to COVID-19 epidemiology and from The Global Fund to Fight AIDS, Tuberculosis and Malaria for work unrelated to COVID-19. ACG was previously a non-remunerated member of a scientific advisory board for Moderna and is currently a non-remunerated member of the scientific advisory board for the Coalition for Epidemic Preparedness. OJW has received personal consultancy fees from WHO for work related to malaria. ABH has received personal consultancy fees from WHO for work related to COVID-19, and grant funding for COVID-19 work from WHO and NSW Ministry of Health, Australia. ABH is a member of the WHO Immunization and vaccines related implementation research advisory committee. 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. All other authors declare no competing interests.

**Data & Materials Availability**

The modelling framework, along with all relevant data and code required to reproduce the analyses presented here are freely available in Github repository (<https://github.com/mrc-ide/diseaseX_modelling>).

A collage of graphs and diagrams

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**Figure 1: Exploring the prospects for outbreak containment through utilisation of broadly protective sarbecovirus vaccines (BPSVs) in ring and spatially targeted vaccination strategies.**

A stochastic branching-process-based approach was used to explore the impact of a BPSV on outbreak containment efforts utilising ring or spatially targeted vaccination strategies, and the factors most critical to control. **(A)** Schematic illustrating the ring-vaccination framework. **(B)** %of outbreaks controlled via BPSV ring-vaccination (y-axis) and its dependence on R0 (x-axis), for “SARS-CoV-1-Like” virus. Black line indicates scenario without BPSV, coloured lines indicate different assumptions around vaccine protection delay (VPD). **(C)** As for **(B)** but for a “SARS-CoV-2-Like” virus. **(D)** Sensitivity analysis exploring how the % of outbreaks contained varies with R0 (x-axis) and the ratio of the generation time to the VPD (Tg/VPD). Orange rectangle indicates the value held constant for other sensitivity analyses. **(E)** As for **(D)** but for vaccine efficacy against infection. **(F)** As for **(D)** but % of presymptomatic transmission. **(G)** Schematic illustrating the spatially targeted vaccination framework. **(H)** %of outbreaks controlled (y-axis) and its dependence on R0 (x-axis), for “SARS-CoV-1-Like” virus. Black line indicates scenario without BPSV, coloured lines indicate different assumptions around the number of hospitalised cases required to trigger BPSV campaign. **(I)** As for **(H)** but for a “SARS-CoV-2-Like” virus. **(J)** % of outbreaks contained by R0 (x-axis) and the ratio of the vaccination campaign spatial radius to the average distance between infections. **(K)** As for **(J)** but for vaccine efficacy against infection. **(L)** As for **(J)** but for surveillance threshold.

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**Figure 2: The potential impact of BPSV mass-vaccination campaigns on disease burden during a future SARS-X pandemic.**

Dynamical modelling of BPSV mass-vaccination of priority groups (those aged 65+) following pathogen detection during a hypothetical SARS-X pandemic. **(A)** Illustrative figure of simulated scenarios and the timing of key events. **(B)** Time-varying reproduction number (Rt) profiles for thedifferent non-pharmaceutical intervention (NPI) scenarios imposed in response to the epidemic that are considered for the analyses presented here. These Scenarios differ by assumed stringency (either no measures, a minimal mandate reducing transmission by 25% or stringent measures reducing Rt to 0.9), duration (either until the BPSV campaign is completed or the disease specific vaccination campaign is completed) and the nature by which these NPIs are relaxed (either instantaneous or gradual). **(C)** BPSV impact on disease burden for each NPI scenario, assuming the VSV is available 100 days (top-panel) or 250 days (bottom-panel) following detection, for an R0 of 2.5. Uncoloured crosses indicate scenario without BPSV (VSV only); points indicate scenarios where BPSV is available, coloured according to NPI scenario. Inset panels shows deaths averted by the BPSV, coloured by NPI scenario. **(D)** BPSV impact on the need for NPIs for the same disease burden. For each NPI Scenario,the Pareto frontier was constructed for the VSV-only scenario, and used to calculate how many fewer NPI days can be imposed in BPSV scenario whilst still limiting limit disease burden to the level observed in the corresponding VSV-only scenario.

A close-up of a map

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Analyses using published model fits calibrated to excess mortality data *(46)* retrospectively assessed the potential impact of BPSV availability on COVID-19 mortality during the SARS-CoV-2 pandemic, under the assumption that all countries have access to a BPSV stockpile sufficient to vaccinate 80% of their eligible elderly population at a rate of 3.5% of the total population per week. **(A)** Modelled impact of the BPSV during the first year of the COVID-19 pandemic in different countries around the world. Country colour indicates the percentage of COVID-19 deaths occurring in the first year of the pandemic that could have been averted if a BPSV had been available. **(B)** Cumulative COVID-19 deaths during the first year of the pandemic without (grey) and with (orange) the BPSV. **(C)** As for **(B)** but for daily COVID-19 deaths. **(D)** BPSV impact on COVID-19 mortality in Italy during the first year of its COVID-19 epidemic. Grey line indicates model fit to empirically observed COVID-19 mortality data (light grey points) and ribbon indicates the 95% CI for COVID-19 mortality during the empirically observed epidemic. Coloured line indicates expected mortality under the assumption of BPSV availability and a mass vaccination campaign of individuals aged 65+ during the first weeks of the epidemic. Line colour reflects the percentage of deaths averted by the BPSV (matching the colour for that country in **(A)**). **(E)** As for **(D)** but for Iran instead of Italy. **(F)** As for **(D)**, but for Bangladesh instead of Italy.

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**Figure 4: Dependency of BPSV impact on intrinsic vaccine properties and vaccination campaign dynamics.**

Sensitivity analyses exploring the sensitivity of BPSV impact to intrinsic BPSV properties and factors governing the speed, availability and coverage of the BPSV vaccination campaign. **(A)** Deaths averted by the BPSV (per 1,000 population) and BPSV efficacy against severe disease. Results coloured according to NPI scenario considered (pink = minimal, orange = moderate, blue = stringent), for R0=2.5. Inset panels show Rt profile for each NPI scenario. Assumed virus-specific vaccine (VSV) development timeline was 250 days. **(B)** As for (A) but for BPSV efficacy against infection. **(C)** As for (A) but for BPSV immunity duration. **(D)** As for (A) but for BPSV stockpile size (and associated coverage of the target population that can be achieved). **(E)** As for **(A)**, but for the rate of vaccination during the BPSV campaign (and the associated time taken to vaccinate all eligible and willing individuals). **(F)** The delay (in days) between the first country in the world achieving 1% of their population vaccinated with COVID-19 vaccines and other countries achieving this same milestone. Individual coloured points are specific countries – data from Our World In Data. **(G)** Impact of delays to BPSV access on deaths averted per 1,000 population. Scenarios shown are for moderate NPIs and with continent-specific VSV access delays derived from (F).

A diagram of a graph

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**Figure 5: Surveillance system sensitivity, time-to-detection and BPSV impact.**

Sensitivity analyses exploring the influence of surveillance sensitivity and timing of detection on BPSV impact. **(A)** Epidemic time-series (dark grey line). Inset panel shows time-to-detection (x-axis) and versus hospitalisation detection threshold (daily hospitalisations required for initial virus detection to occur). Coloured points and arrows indicate timing of virus-specific vaccine (VSV) developed under timelines of 100 (blue) or 250 (pink) days. **(B)** Deaths averted by BPSV per 1,000 population according to hospitalisation detection threshold and VSV development timeline. **(C)** Timeline illustrating the distinction between source country (where the epidemic originates) and secondary countries (where epidemics are seeded via importations from the source country). Secondary countries include “early importers” (virus importation occurs before detection in source country); and “late importers” (virus importation occurs after detection in the source country). **(D)** Deaths averted by BPSV (y-axis) against the number of days that virus detection in the source country is ahead of or after pathogen importation (to the secondary country). Grey-shaded regions indicate virus importation occurs after detection in source country. White regions indicate virus importation occurs before detection in source country.

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**Supplementary Information**

1. **Supplementary Methods: Branching Process Framework**

**1.1 Overview of Stochastic Branching Process Modelling Framework**

We extended a stochastic branching-process modelling framework initially developed to simulate SARS-CoV-2 transmission and control through contact tracing *(48, 49)*, and use this framework to explore a number of different BPSV vaccination strategies. We explore this for two pathogen “archetypes” – the first pathogen archetype has properties similar to SARS-CoV-1, and is characterised by a long generation time, a limited degree of pre-symptomatic transmission, low proportion of asymptomatic infections and high disease severity. The second is SARS-CoV-2, characterised by a shorter generation time, high proportion pre-symptomatic transmission, moderate proportion of asymptomatic infections and low disease severity. For both pathogens, we vary the basic reproduction number across a range of values. Below, we describe this framework in general terms, and provide a table below describing the exact parameter values used to model different pathogens (either “SARS-CoV-1-Like Pathogen” or “SARS-CoV-2-Like Pathogen”) and vaccination strategies (either ring-vaccination or spatially targeted vaccination campaigns).

Within this framework, the total number of secondary infections produced by individual , is drawn from an offspring distribution as follows:

i.e. with the offspring distribution being a Poisson distribution with mean equal to the basic reproduction number of the pathogen, .

Each of these infections generated by individual , is then assigned a time of infection drawn from the generation time distribution , with this taking the form of:

(for “SARS-CoV-1-Like Pathogen”, average of 12 days)

(for “SARS-CoV-1-Like Pathogen”, average of 6.75 days)

Each infection has an independent probability of being asymptomatic. Symptomatic infections develop symptoms following an incubation period, which is drawn from the incubation period distribution , with this taking the form of:

(for “SARS-CoV-1-Like Pathogen”, average of 12 days)

(for “SARS-CoV-1-Like Pathogen”, average of 2.25 days)

We note here that the expectation of the ratio describes the average proportion of transmission that we expect to be presymptomatic i.e. the fraction of infections that are generated before the infector develops symptoms.

Each infection also has an independent probability of being hospitalised by the infection, with the time of hospitalisation relative to time of infection drawn from a time-to-hospitalisation distribution , with this taking the form of:

(for “SARS-CoV-1-Like Pathogen”, average of 12 days)

(for “SARS-CoV-1-Like Pathogen”, average of 12 days)

We used this framework to simulate the impact of two different vaccine-based containment strategies utilising the BPSV. These were ring-vaccination (where detection of symptomatic cases triggers reactive vaccination of all contacts of that case) and spatially targeted vaccination (where hospitalised cases trigger a vaccination campaign that seeks to vaccinate all individuals in a defined geographic area).

* 1. **Modelling Ring-Vaccination Campaigns**

Within the ring-vaccination framework, following identification of the pathogen (assumed here to occur 21 days following a pathogen spillover event with 5 individuals initially infected), detection of a new symptomatic infection triggers reactive vaccination of all their contacts, which occurs after a delay of 2 days, reflecting the time to identify, notify and administer vaccination to contacts. Vaccinated individuals go on to develop immunological protection following vaccination at a delay of days. During this vaccination campaign, a number of outcomes are possible for the contacts of index cases that would otherwise be infected:

1. The individual is successfully vaccinated during the ring-vaccination campaign, protection arises before they would otherwise be infected, and their infection is successfully averted.
2. The individual is successfully vaccinated during the ring-vaccination campaign, protection arises before they would otherwise be infected, but this protection fails to avert their infection.
3. The individual is successfully vaccinated during the ring-vaccination campaign but infected before vaccine-derived protection arises.
4. The individual is infected before the ring-vaccination campaign can be carried out.
5. The individual is not identified by the ring-vaccination strategy and so is not vaccinated (assumed here to be 20% of contacts).

For individuals who receive vaccination and develop robust protection before they would otherwise be infected, whether or not they are still infected despite vaccination is given by a drawn from a Bernoulli distribution with probability ), where is the BPSV efficacy against infection. In individuals for whom protection has developed but who are infected anyway, we assume that BPSV vaccination renders breakthrough infections less infectious and hence these individuals have reduced transmissibility. The total number of secondary infections produced by vaccinated individual , is drawn from the following modified offspring distribution:

where is the BPSV efficacy against onwards transmission in vaccinated individuals with breakthrough infections. We note here that individuals with an asymptomatic infection are assumed to be undetected by the health-system and so do not trigger ring-vaccination.

* 1. **Modelling Spatially-Targeted Vaccination Strategies**

To model the spatially targeted vaccination strategy, we modify the branching process such that each new infection is imbued with a set of geographical coordinates (their “home address”) {}. The coordinates of these newly generated infections depends on the coordinates of the infector and a spatial kernel, which is a distribution describing the probability of the home addresses of two directly linked infections being separated by a certain amount of distance. Together with a direction, these factors determine the “home address” of newly generated infections. Specifically, if individual is the infector with coordinates {}, then the coordinates of infection are generated using the following method:

* **Step 1:** Draw distance between infector and infectee from
* **Step 2:** Draw the direction of distance between infector and infectee from

Simple trigonometric identities can be used to calculate the new coordinates {} from an origin (here {}), a distance and a direction. In practice however, the exact spatial kernel will depend on specific features of the setting, population and pathogen being considered. We therefore considered a simplified case whereby instead of explicitly specifying a spatial kernel in absolute terms, we instead describe it relative to the radius of the spatial vaccination campaign that is implemented.

Within this framework, the spatially targeted vaccination campaign is triggered by hospitalised infections. Hospitalised infections accumulate until a certain threshold is reached , after which the pathogen is said to have been “detected”. Following detection (and an assumed operational delay of 2 days), all eligible individuals within a certain spatial radius of the home address of the case which triggered the detection are vaccinated. During this vaccination campaign, a number of outcomes are possible for individuals:

1. The individual is successfully vaccinated and protection arises before they would otherwise be infected.
2. The individual is successfully vaccinated before they would otherwise be infected but this protection fails to avert their infection
3. The individual is successfully vaccinated but infected before vaccine-derived protection arises.
4. the individual is infected before the vaccination campaign is carried out
5. The individual resides in an area outside the spatial radius of the vaccination campaign, is not vaccinated, and later becomes infected.
6. The individual chooses not to receive the vaccine (assumed here to be 20% of individuals).

Assumptions of BPSV properties and its impact on reduced transmissibility in breakthrough infections are the same as for the ring-vaccination strategy.

* 1. **Branching Process Vaccination Analyses**

For both strategies, we simulate the proportion of outbreaks contained (defined as a final size of <10,000 infected individuals) and explore the prospects for containment whilst varying:

* **Pathogen Epidemiological Properties:** including the basic reproduction number, generation time distribution, extent of pre-symptomatic transmission, proportion of asymptomatic infections and proportion of infections that are hospitalised.
* **Intrinsic BPSV Properties:** including vaccine efficacy against infection and against onwards transmission (i.e. the degree of reduced transmissibility in breakthrough infections) as well as the delay between vaccination and protection developing.
* **Vaccination Campaign-Related Factors:** including the spatial kernel (namely the size of the vaccination campaign radius relative to the average distance between infections) and surveillance system sensitivity (determining the number of hospitalised cases triggering the spatial vaccination campaign).

In all instances, presented results are based on the proportion of outbreaks successfully contained across 100 stochastic simulations per parameter combination and vaccination strategy considered; and these results are compared to scenarios in which the BPSV is not available (i.e. there is no vaccination). Models were implemented in the programming language R and code required to reproduce the simulations presented in this work is available at <https://github.com/mrc-ide/diseaseX_modelling>

**Table S1:** **Description of the key parameters varied during branching process analyses of ring and spatially targeted BPSV vaccination.** Central value describes the fixed value used during sensitivity analysis of other parameters; range describes the set of parameter values explored during the sensitivity analysis for that particular parameter.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Central Value** | **Sensitivity Analysis Range** | **Description** | **Notes** |
| **Pathogen Parameters** |  |  |  |  |
|  | Varied | 1.25 – 2.5 | Basic reproduction number, describing the average number of secondary infections generated by an index infection. |  |
|  | * 12 days “SC1-Like” * 6.75 days “SC2-Like” | See Notes on RHS | Generation time distribution, describing the distribution of infection times between index infections and secondary infections. | A series of sensitivity analyses were carried out varying for “SC2-Like Pathogen” pathogen whilst keeping the incubation period – which in turn affects the proportion of presymptomatic transmission occurring. Varied between 15% and 70% presymptomatic transmission. |
|  | * 12 days “SC1-Like” * 2.25 days “SC2-Like” | See Notes on RHS | Incubation period distribution, describing the distribution of times between infection and symptom onset in non-asymptomatic individuals. | Selected to give central values of 0% presymptomatic transmission for “SC1-Like” and 34% presymptomatic transmission for “SC2-Like”. |
| **BPSV Parameters** |  |  |  |  |
|  | 35% | 30%-90% | BPSV efficacy against onwards transmission i.e. the BPSV-mediated reduction in transmissibility in vaccinated individuals who become infected (breakthrough infections) | Efficacy against infection and efficacy against onwards transmission assumed to covary. Sensitivity analyses of efficacy involve varying these two parameters together. |
|  | 35% | 30%-90% | BPSV efficacy against infection |  |
|  | Varied | 0 days – 28 days | Delay (in days) between BPSV vaccination and protection developing | Time between receiving vaccination and immunological protection developing. We assume here that the BPSV is delivered as a single dose regimen. |
| **Other Parameters** |  |  |  |  |
|  | 25x | 1x – 100x | Spatial kernel distribution describing the distribution of distances between pairs of directly linked infections. | Expressed as the distance relative to the radius of the spatial vaccination campaign area. |
|  | 10 | 1 – 100 | The cumulative number of hospitalised infections required to trigger the spatial vaccination campaign. |  |

1. **Supplementary Methods: Dynamical Compartmental Modelling Framework**

**2.1 Overview of Modelling Framework**

We explored the potential utility of the BPSV in vaccination campaigns focussed on rapid mass-vaccination of priority groups following pathogen detection to support disease burden reduction and relaxation of societal restrictions imposed to control transmission (as has been the case with SARS-CoV-2 vaccination campaigns). To do this, we adapted a previously published dynamical model of SARS-CoV-2 transmission used to evaluate and explore the impact of SARS-CoV-2 transmission on COVID-19 mortality during the pandemic *(45)*.

Briefly, the model is an age-stratified SEIRS (susceptible-exposed-infectious-recovered-susceptible) model that explicitly models the progression of COVID-19 disease severity, the transition through various levels of healthcare, and the introduction of vaccination campaigns. In terms of modelling disease progression and differential disease severity, the modelling framework explicitly includes elements of the clinical pathway differentiating individuals by disease severity within clinical settings (e.g. those requiring a basic hospital bed and limited oxygen consumption, as well as those requiring a protracted ICU stay and mechanical ventilation). Transmission between age-groups depends on age-based contact matrices, assuming a constant transmission rate per contact. The model includes an explicit latent period between an individual becoming infected and subsequently becoming infectious, as well as age-dependent probabilities of hospitalisation and disease severity. The model’s vaccination pathway incorporates both a delay in the development of protection following vaccination, as well as the possibility of waning of vaccination protection. Both of these are assumed to follow an Erlang distribution with a shape of two and a mean duration controlled by a model parameter that can be altered to reflect different assumptions around waning. Susceptible, latent, or recovered individuals can be vaccinated. Importantly, because latent individuals can be vaccinated, it is possible for latent individuals to develop vaccine derived protection before realising their infection, though in practice the size of this group relative to susceptible or recovered individuals is small and the effect of this is minor. Complete details of the model are given in *(16, 50, 51)* and we focus below on the major elaborations and alterations made to adapt the model to simulate a future, hypothetical SARS-X pandemic and deployment of both a BPSV and (later) a disease-specific vaccine against the pathogen.

**2.1.1 Modelling BPSV and Disease-Specific Vaccine Distribution**

Following activation of BPSV stockpiles, all eligible individuals (here considered to be all those aged 65+) are vaccinated with the BPSV at a constant rate and to a level of coverage determined by the size of the BPSV stockpile relative to the size of the eligible population. We assume here that the BPSV is delivered as a single dose regimen but note that the model is flexibly able to accommodate a wide variety of delays in the development of protection through the delayed protection mechanisms described in the paragraph above. In all scenarios considered, the BPSV is only delivered to the 65+ population – individuals below this age do not receive it. Following introduction of the disease-specific vaccine, elderly individuals at the greatest risk (again, those aged 65+) are prioritised to receive the disease-specific vaccine – and both elderly individuals who received the BPSV and those who did not (e.g. because the size of the stockpile precluded it) are vaccinated. Following complete vaccination of the elderly high-risk groups with the disease-specific vaccine, the disease specific vaccination is then rolled out and distributed to all other age-groups > 15 years.

**2.1.2. Modelling BPSV and Disease-Specific Vaccination Effectiveness**

We model two distinct forms of vaccine efficacy: efficacy against infection and efficacy against severe disease (reducing risk of hospitalisation and death) in breakthrough infections (i.e. individuals who were vaccinated but where vaccination failed to prevent the infection occurring). We make the assumption that protection is partial, and that vaccine efficacy is the same for across all individuals considered. For those protected by both vaccine-derived and infection-derived immunity, we assume that the most protective effect is dominant – though note given the timeframes over which we simulate (typically no longer than 18 months), we expect minimal waning of immunity to have occurred.

**2.2 Hypothetical SARS-X Pandemic Scenario Construction & Baseline Parameterisation**

We use this modelling framework to explore the potential impact of BPSV availability on disease burden during a future hypothetical SARS-X pandemic. In this hypothetical scenario, the BPSV has been manufactured and stockpiled ahead of the pandemic, enabling rapid deployment following pathogen detection (which is the trigger for initiation of the BPSV vaccination campaign). We also explicitly model a pathogen-specific vaccine, which we assume to have a more favourable efficacy profile than the BPSV but that can only be developed following detection of the novel pathogen and sequencing of its genome. It is therefore only available after a significant delay. Our baseline scenario assumes the BPSV has 75% efficacy against disease and 35% efficacy against infection whilst a future disease-specific vaccine is assumed to have vaccine efficacy of 95% against disease and 55% against infection. In both instances, we assume there is minimal waning of vaccine-derived immunity over the timescale of the simulation period considered and we assume that it takes 7 days for development of immunological protection to occur following receipt of the vaccine. For the disease-specific vaccine we explore a development timeline of either 250 or 100 days (reflecting recent estimates from CEPI around realistic and ambitious vaccine development timelines *(13)* ). In our simulations, pathogen spillover is followed by a period of undetected circulation in the community. Hospitalisations due to the infection lead to pathogen detection and identification. We assumed detection occurred when daily incidence of hospitalised individuals reached 5 hospitalisations per day. The time for this to occur following spillover was calculated using the stochastic branching-process based framework described above.

Following pathogen identification, development of the pathogen-specific vaccine starts, and after an assumed delay of 7 days (reflecting delays around decision making and activation of stockpiles), mass vaccination of the elderly population (here assumed to be those aged 65+) with the BPSV begins. The size of the BPSV stockpile is assumed sufficient to vaccinate 80% of the elderly population, with health systems capabilities able to vaccinate the population at a rate of 3.5% of the population per week, leading to completion of BPSV vaccination campaign within 3 weeks. All age-groups except those under 15 are eligible to receive the disease-specific vaccine, with rollout of this vaccine (sufficient to achieve a coverage of 80% of the population) occurring in the oldest age-groups first. We assume an R0 of 2.5 and an average generation time of 6.7 days, in-keeping with estimates derived for the original Wuhan-1 strain, as well as a severity profile and age-specific IFR similar to that of SARS-CoV-2 *(52)*, adjusted to give an overall population-level IFR of 1%. We assume a demographic population age-structure matching the age-distribution of the World Bank Upper Middle-Income Country with the median age, and for the purposes of our scenarios assume no healthcare constraints that limit the ability of hospitalised individuals to access adequate medical care. We note that relaxing this assumption and imposing limited healthcare availability (and associated excess mortality risk arising from insufficient medical care) would only serve to increase our estimates of BPSV impact, and that previous analyses exploring the impact of COVID-19 vaccination on mortality have shown that direct protection was the main driver of deaths averted, with very few averted by the reduction in healthcare capacity required *(48)*.

We explore 9 different scenarios varying the duration, stringency and timing of non-pharmaceutical interventions imposed in response to identification of the novel pathogen (shown in **Figure 2B**). Three stringency levels are considered: i) no NPIs (and so R is equal to R0); ii) a minimal and limited set of NPIs reducing transmission by 25%; and iii) a stringent set of NPIs sufficient to reduce R to 0.9. Whilst **Figure 2** considers 9 scenarios spanning a wide range of possible NPI responses, we use three central NPI scenarios for the rest of the analyses presented here. These are 1) “minimal NPI scenario” which assumes a short imposition of limited NPIs between pathogen identification and completion of the BPSV campaign; a 2) “moderate NPI scenario” involving imposition of the limited NPIs in response to pathogen identification. These then last in full until the end of BPSV campaign, whereafter they are gradually released and relaxed, and lift completely upon completion of the disease-specific vaccination campaign; and a 3) “stringent NPI scenario” which sees stringent NPIs implemented until the BPSV campaign is complete, followed by imposition of more limited NPIs which gradually lift until the disease-specific vaccination campaign is complete. We additionally carried out a series of sensitivity analyses varying a number of the model parameters described above. In all cases, we varied model parameters in a univariate manner whilst keeping all other parameter estimates identical to the baseline parameters described above. A detailed description of the exact parameters varied, and the parameter ranges used are described in **Table 1** and in the **Supplementary Table 2**.

For all scenarios, we calculated the deaths averted due to BPSV vaccination by subtracting the estimated SARS-X deaths from the simulation with both BPSV and disease-specific vaccines from the estimated number of SARS-X deaths under a scenario where only the disease-specific vaccine is available and report the number of deaths averted per 1,000 population. To calculate the NPI index featured in **Figure 2 of the main text** we construct a composite measure that considers both the duration and stringency of NPIs imposed in response to the hypothetical pandemic. This composite measure was calculated first by calculating the relative stringency of each set of NPIs, defined as the % reduction in the R0 by the NPIs (with a higher % reduction reflecting more stringent and costly NPIs). We then multiplied this stringency by the number of days spent under those NPIs to construct an index considering both stringency and duration of NPIs.

**2.3 Retrospective Evaluation of Potential Impact During SARS-CoV-2 Pandemic**

Using previously published model fits calibrated within a Bayesian framework to excess mortality data (known to be a more complete measure of pandemic mortality, especially in LMIC settings with less robust vital registration) *(50)*, we explored the potential impact that a stockpiled BPSV could have had on COVID-19 mortality in the first year of the pandemic. We used the resulting model fits to estimate the time-varying reproductive number, Rt, and its associated uncertainty by sampling 100 draws from the estimated posterior distribution of Rt from these previous fits. To estimate the impact of BPSV, we simulated a counterfactual scenario for each sampled Rt trajectory in which BPSV vaccines were introduced after X days, under the assumption that all countries have access to a BPSV stockpile sufficient to vaccinate 80% of their eligible elderly population (here assumed to be those aged 65+) at a rate of 3.5% of the total population per week, and under the strong assumption that availability of the BPSV would not have altered the NPIs imposed in response to SARS-CoV-2 (and hence alterations to Rt due to NPIs would be the same across both scenarios). We then calculated the deaths averted as a result of BPSV vaccination by subtracting the estimated COVID-19 deaths from the simulation with BPSV vaccines included from the estimated COVID-19 deaths from the simulation with only the real-world vaccination campaign included and reported the median deaths averted per 1,000 population.

**Table S2:** **Description of model parameters varied in dynamical compartmental modelling of mass-vaccination of high-risk populations with BPSV.** Central value describes the fixed value used during sensitivity analysis of other parameters; range describes the set of parameter values explored during the sensitivity analysis for that particular parameter. Parameter estimates were selected to replicate the approximate epidemiological properties of SARS-CoV-2, and complete set of model parameters used can be found in *(16, 50, 51)* and <https://github.com/mrc-ide/diseaseX_modelling>.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Central Value** | **Sensitivity Analysis Range** | **Notes** |
| **Epidemiological & Pathogen Parameters** |  |  |  |
| Basic reproduction number (R0) | 2.5 | 1.5 – 3.5 |  |
| NPI Scenarios | 3 NPI scenarios | 9 NPI scenarios considered, ranging in stringency and duration **(Fig 2B & Fig 2C)** | In all cases, minimal mandate controls are assumed to reduce transmissibility by 25%, and stringent measures assumed to bring Rt to 0.9.  3 central NPI scenarios are:  **Minimal NPIs:** 25% reduction in Rt during BPSV campaign. No NPIs thereafter.  **Moderate NPIs:** 25% reduction in Rt during BPSV campaign. Slow cessation of NPIs that finishes when disease-specific vaccination campaign completes.  **Stringent NPIs:** 75% reduction in Rt during BPSV campaign. Slow cessation of NPIs that finishes when disease-specific vaccination campaign completes. |
| Surveillance System Sensitivity | Daily incidence of 5 hospitalisations to trigger pathogen detection | Daily incidence of 1-50 hospitalisations to trigger pathogen detection |  |
| **Target Product Characteristics & Vaccine Development-Related Parameters** |  |  |  |
| BPSV disease efficacy | 75% | 10-100% **(Fig 4A)** | BPSV efficacy against severe disease in breakthrough infections (i.e. where BPSV efficacy against infection fails to prevent the infection). Central value for BPSV assumed lower than disease-specific vaccine efficacy against severe-disease (95%) |
| BPSV efficacy against infection | 35% | 10% - 100% **(Fig 4B)** | BPSV efficacy against being infected. Central value for BPSV assumed lower than disease-specific vaccine efficacy against infection (55%) |
| Duration of BPSV-induced immunity | 365 days | 30-180 days **(Fig 4C)** | 365 days selected to reflect the assumption of minimal waning over the period between BPSV vaccination and introduction of the disease-specific vaccine 250 days later. Central value assumes minimal waning over the 100–250 day period between BPSV vaccination starting and the disease-specific alternative vaccine becoming available. |
| **Operational, Vaccination Campaign & Access-Related Parameters** |  |  |  |
| Time to develop the disease-specific vaccine | 250 days | 100 – 365 days **(Fig 2C and Fig 4D)** | Time to develop the disease specific vaccine following pathogen identification and genomic sequencing. 100 days and 250 days selected as central scenarios **(in Fig 2C)** and the full range explored in a sensitivity analyses in **Fig 4D.** Selected based on CEPI report of optimistic and realistic scenarios for improvements to vaccine development timelines *(17)* |
| Size of BPSV stockpile | 80% | 10-80% **(Fig 5A)** | Describes the size of the BPSV stockpile and the associated level of BPSV coverage able to be achieved in the 65+ year old population eligible to receive the vaccine. |
| Speed of BPSV vaccination campaign | 3.5% of population per week | 0.5% - 4.5% of population per week **(Fig 5B)** | Central scenario corresponds to taking 4 weeks to vaccine entire 65+ years age-group. Range corresponds to taking 20 – 170 days. Central value based on estimates derived from COVID-19 vaccination data from Our World In Data *(53)* |
| Delay to Accessing Disease-Specific Vaccine | 0 days | 5 days – 180 days | Assume local vaccine manufacturing capabilities in place for central value. Sensitivity analysis range derived from COVID-19 vaccination data from Our World In Data *(53)* |

A screenshot of a graph

Description automatically generated

**Figure S1: The influence of NPIs, R0 and VSV development timelines on BPSV impact during a SARS-X pandemic.**

**(A)** Time-varying reproduction number (Rt) profiles for thedifferent non-pharmaceutical intervention (NPI) scenarios imposed in response to the epidemic that are considered for the analyses presented here. These Scenarios differ by assumed stringency (either no measures, a minimal mandate reducing transmission by 25% or stringent measures reducing Rt to 0.9), duration (either until the BPSV campaign is completed or the disease specific vaccination campaign is completed) and the nature by which these NPIs are relaxed (either instantaneous or gradual). **(B)** BPSV impact on disease burden for each NPI scenario, assuming the VSV is available 100 days (top-row), 250 days (middle row) or 365 days (bottom row) following detection, for an R0 of 1.5 (left hand column) or 3.5 (right hand column). Uncoloured crosses indicate scenario without BPSV (VSV only); points indicate scenarios where BPSV is available, coloured according to NPI scenario. **(C)** Deaths averted by the BPSV, coloured by NPI scenario and stratified by each unique VSV and R0 scenario considered here.

A graph of different colored lines

Description automatically generated with medium confidence

**Figure S2: Dependency of BPSV impact on intrinsic vaccine properties, vaccination campaign dynamics and virus properties.**

Sensitivity analyses exploring the sensitivity of BPSV impact to intrinsic BPSV properties and factors governing the speed, availability and coverage of the BPSV vaccination campaign, as well as the basic reproduction number of the virus. **(A)** Deaths averted by the BPSV (per 1,000 population) and BPSV efficacy against severe disease. Results coloured according to NPI scenario considered (pink = minimal, orange = moderate, blue = stringent), for R0=1.5 (top row) and R0=3.5 (bottom row). **(B)** As for (A) but for BPSV efficacy against infection. **(C)** As for (A) but for BPSV immunity duration. **(D)** As for (A) but for BPSV stockpile size (and associated coverage of the target population that can be achieved). **(E)** As for **(A)**, but for the rate of vaccination during the BPSV campaign (and the associated time taken to vaccinate all eligible and willing individuals).