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

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**Abstract**

*To be completed*

**Introduction**

Experiences during the COVID-19 pandemic have highlighted the crucial role of vaccinations in reducing disease burden, with over 15 million deaths averted due to vaccinations in the first year of the pandemic *(1)*. Availability of vaccines providing robust protection against severe disease has also enabled lifting of societal restrictions that, whilst efficacious at reducing transmission *(2)*, also carry significant socio-economic costs *(3)*. Indeed, recent work has shown the societal value of SARS-CoV-2 booster campaigns in Indonesia to be approximately $2,500 per dose (compared to <$30 for acquisition and administration), with much of this value arising from the reduced need for non-pharmaceutical interventions (NPIs) *(4)*.

The development and authorisation of highly efficacious vaccines against COVID-19 in under a year represents a significant achievement, given that traditional development pipelines typically take 10+ years *(5)*. Despite this accelerated timeline however, >1.5 million officially confirmed COVID-19 deaths occurred during this same time-period *(6)*. Moreover, actual access to doses following authorisation was characterised by significant inequity between the global north and global south, with the latter facing significant further delays to access *(7)* . This is despite the additional lives that equitable allocation strategies would have saved *(8–11)*. There is therefore a critical and currently unmet need for more rapid and globally equitable access to vaccines in the context of a future novel pathogen pandemic. SARS-CoV-2 is unlikely to be the last novel pathogen pandemic faced by the world over the next 100 years *(12)*. Both the frequency of pathogen spillover and the intensity of epidemics arising from this spillover are projected to increase in the future *(13, 14)*, with compound risks and increasing severe, frequent and complex emergencies requiring new approaches to preparedness *(15)*.

This has motivated significant interest in further shrinking vaccine development timelines. The Coalition for Epidemic Preparedness Innovations (CEPI) and others have announced initiatives to enable development, authorisation and manufacturing of vaccines against a novel pathogen within 100 days of pathogen identification *(16–18)*. Recent work has 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) *(19)*. However, analyses by CEPI indicate that existing approaches to vaccine development are unlikely to achieve development timelines less than 250 days *(20)*, highlighting the need for a paradigm shift in vaccine development to meet the 100 day target. A limitation of all these approaches however is their reactive nature. Pathogen-specific vaccine development is contingent on having detected, identified and sequenced the genome of the newly emergent novel pathogen. 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 control measures in the form of NPIs (and their associated socio-economic impact).

In this context, other research efforts have been focussed on alternative approaches to vaccine development that might facilitate more rapid availability. Of particular interest have been broad-spectrum vaccines providing broad and robust protection against a range of viruses belonging to the same family (e.g. coronaviruses) or sub-family (e.g. sarbecoviruses). Such vaccines could be manufactured and stockpiled ahead of a pandemic, enabling rapid access following pathogen detection. Previous work has identified potent pan sarbecovirus neutralising antibodies in previously infected humans *(21–23)*, suggesting that vaccines aiming to elicit broad-spectrum protection should be possible. A number of vaccines aimed at providing broad and robust protection to a range of coronaviruses are currently under development *(24)*. CEPI has to date awarded $230 million in grants to fund preclinical development of 13 broadly protective coronavirus vaccine candidates *(25)*. 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 wide range of different approaches, including mosaic nanoparticles containing spike receptor binding domains from a multiple sarbecoviruses *(26)*; approaches based on chimeric spike mRNA vaccines *(27)*; and vaccine antigens based on epitopes conserved across multiple coronaviruses *(28, 29)*.

Despite numerous candidates in preclinical development, our understanding of how best to operationalise broad-spectrum vaccines at a population-level remains limited, particularly around the most relevant use-cases and how to optimise their utilisation for maximum impact. Here, we extend a previously developed dynamical model of SARS-CoV-2 transmission used to explore the impact of vaccination *(1, 19)* and evaluate the potential impact of a broadly protective sarbecovirus vaccine (BPSV) during a hypothetical future SARS-CoV-X pandemic. Our work highlights substantial potential public-health impact arising from widespread availability and rapid access to a BPSV during a novel pathogen pandemic caused by a sarbecovirus. Critically however, we show that this impact is shaped by a diverse range of factors including intrinsic vaccine properties, health system capabilities, and features of the pandemic response. Realising the benefit of these tools will therefore require investment into diagnostics, surveillance and broader public-health response capabilities *(30, 31)*. In doing, we underscore the potential utility of broad-spectrum vaccines as tools to support future pandemic preparedness and identify funding priorities to help realise their potential impact.

**Results**

**A BPSV could support outbreak containment efforts via ring-vaccination but prospects for control are highly dependent on vaccine characteristics and pathogen properties.**

A stochastic branching-process framework was used to explore the potential for a BPSV to support containment of a hypothetical SARS-CoV-X outbreak via a ring vaccination- based approach (as has successfully been undertaken for control of Ebola outbreaks) *(32)* **(Fig 1A)**. Our analyses considered two “archetype” pathogens – one with properties similar to SARS-CoV-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). In both cases, we assumed the ring-vaccination campaign was able to identify 80% of contacts, that the BPSV has an efficacy of 75% against infection, and a logistical delay of 2 days between identification of an index case and ring-vaccination being completed.

Across both pathogen archetypes, the proportion of outbreaks successfully contained decreased as pathogen R0 increased, and increased as the assumed delay between vaccination and protection developing was shortened. For the pathogen with properties similar to SARS-CoV-1, a vaccine protection delay of 1 week or shorter was sufficient to completely contain the outbreak across all stochastic simulations up to R0 = 2. However, a vaccine protection delay of 2 weeks averted <1% outbreaks, across all values of R0 considered. For the pathogen similar to SARS-CoV-2, the only scenario in which availability of the BPSV improved containment prospects was when the protection delay was 2 days; and even then this impact did not persist when the R0 > 1.75. For this SARS-CoV-2-like pathogen, neither the 1 week nor 2 week protection delay scenarios increased containment prospects compared to a no vaccination scenario. The success of ring-vaccination strategies is predicated on individuals being successfully protected before they would otherwise be infected; this fraction of individuals decreases as the delay between vaccination and protection development increases, reducing prospects for control.

Prospects for control were highly sensitive to assumptions around vaccine characteristics and pathogen properties **(Fig 1D, 1E & 1F)**. When the mean generation time and the vaccine protection delay were assumed to be the same duration, the BPSV ring-vaccination did not lead to outbreak containment under any R0 scenario considered **(Fig 1D)**. By contrast, assuming the generation time was 3x the length of the vaccine protection delay (and therefore a larger fraction of ring-vaccinated individuals had successfully developed protection by the time they would otherwise have been infected) led to almost complete containment under all but the highest R0 scenarios considered. Increasing vaccine efficacy against infection similarly led to an increasing fraction of outbreaks being successfully controlled, especially for values of R0 less than 2, but failed to control outbreaks driven by more transmissible pathogens **(Fig 1E)**. As the assumed fraction of presymptomatic transmission increased (reflecting a higher proportion of transmission occurring before the trigger event for ring-vaccination, which is a symptomatic case), the proportion of outbreaks successfully controlled decreased **(Fig 1F)**.

**Vaccination of elderly populations with a BPSV following pathogen detection could significantly reduce mortality and limit need for NPIs.**

The results in **Figure 1** highlight some potential for outbreak containment via BPSV ring-vaccination, especially in contexts where the pathogen being considered has a comparatively low R0, low fraction of presymptomatic transmission and a long generation time (relative to the vaccine protection delay). However, it also highlighted contexts where prospects for control are limited. Indeed, ring-vaccination based strategies are unlikely to support containment in the context of a pandemic driven by a pathogen similar to SARS-CoV-2 (which has a high R0, short generation time and a comparatively high fraction of presymptomatic transmission *(33, 34)*). Motivated by this, we adapted a previously published dynamical model of SARS-CoV-2 transmission *(1)* to explore use-cases for the BPSV centred around 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).

In this hypothetical scenario, the BPSV has been manufactured and stockpiled ahead of the pandemic, enabling rapid deployment following pathogen detection. This is contrast to development of the pathogen-specific vaccine, which we assume to have a more favourable efficacy profile than the BPSV (75% efficacy against disease and 35% efficacy against infection for the BPSV, 95% and 55% for the disease-specific vaccine) but a development timeline of either 250 or 100 days (reflecting recent estimates from CEPI around realistic and ambitious vaccine development timelines *(16)* ). In our simulations, pathogen spillover is followed by a period of undetected circulation in the community. Hospitalisations with the infection lead to pathogen detection and identification. Following pathogen identification, development of the pathogen-specific vaccine starts, and after a short logistical delay, mass vaccination of the elderly population (here assumed to be those aged 65+) with the BPSV also begins. See **Fig 1A** fora graphical overview of this scenario. We considered the potential impact of this BPSV vaccination campaign on disease burden for a range of different scenarios reflecting differences in the stringency, duration and triggers for non-pharmaceutical interventions (NPIs) imposed to limit transmission **(Fig 2B)**.

Our results highlight the significant impact BPSV mass-vaccination could have on disease burden during a pandemic driven by a SARS-CoV-2-like pathogen. Assuming no NPIs are imposed in response to the pathogen leads to the most significant impact on mortality, from \_\_\_\_ deaths per 1,000 population without the BPSV to \_\_\_\_ deaths per 1,000 population with the BPSV assuming a disease-specific vaccine is available 250 days following pathogen identification; and \_\_\_\_ to \_\_\_\_ deaths per 1,000 population if the disease-specific vaccine is available after only 100 days **(Fig 2C, NPI Scenario 1).** Shorter disease-specific vaccine development timelines reduce the impact of the BPSV, especially in scenarios where the imposed NPIs are most stringent. Assuming a short period of stringent societal restrictions whilst the BPSV vaccination campaign occurs followed by a minimal set of NPIs afterwards **(Fig 2B, NPI Scenario 6)**, the BPSV achieves significant impact assuming the disease-specific vaccine is available after 250 days (with deaths reduced from \_\_\_\_ to \_\_\_\_ per 1,000 population, a \_\_\_\_% reduction). By contrast, its impact is more limited when the disease-specific vaccine is available after only 100 days, as the NPIs successfully limit community transmission and infection risk during this period. Importantly however, for the 250-day development timeline, availability of the BPSV limits mortality to levels below all but the most stringent NPI scenarios **(Fig 2B, NPI Scenario 9)** when the BPSV is absent, highlighting the crucial role that BPSV mass vaccination could have in both reducing disease burden and reducing the stringency and duration of NPIs required to prevent unacceptably high levels of mortality. The impact of the BPSV is most limited in scenarios assuming societal lockdown (limiting community transmission and population infection risk) for the entire period between pathogen detection and completion of the disease-specific vaccination campaign **(Fig 2C, NPI Scenario 9)**.

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

The results presented in **Figure 2** highlight the significant potential impact of a BPSV during a future hypothetical pandemic driven by a pathogen with properties similar to SARS-CoV-2. However, the magnitude of this impact is driven by assumptions around the NPIs introduced in response to the pathogen, which are highly uncertain. To examine this potential impact further and ground our analyses in empirically observed control measures, we carried out a series of analyses retrospectively exploring the potential impact of BPSV availability on COVID-19 mortality during the SARS-CoV-2 pandemic. Using previously published model fits calibrated to excess mortality data *(19)*, 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)**. Our results highlight the substantial impact that availability of a stockpiled BPSV could have had on COVID-19 mortality in these countries during the first year of the pandemic, globally averting approximately \_\_% of all COVID-19 deaths **(Fig 3B** and **Fig 3C)**. In Italy, availability of the BPSV could have substantially reduced the size of the country’s significant first wave, from 1360 daily deaths at its peak to only 810 deaths **(Fig 3D)** and total COVID-19 mortality over the first year from 124,500 to only an expected 49,700 deaths on average **(Fig 3D)**. A similar result was observed for our retrospective analysis of the epidemics in Iran **(Fig 3E)** and Bangladesh **(Fig 3F)**.

**The magnitude of BPSV impact is dependent on intrinsic properties as well as stockpile size and vaccination campaign speed.**

The presented results thus far have relied upon an assumed set of parameters for BPSV properties. Whilst a significant number of BPSV candidates are currently under development, the majority of these are at preclinical stages and therefore their potential properties remain deeply uncertain *(24)*. In order to account for this uncertainty, we carried out analyses exploring the potential impact of the BPSV during a hypothetical epidemic driven by a pathogen with epidemiological properties similar to SARS-CoV-2 whilst varying properties of the BPSV and the associated vaccination campaign, as well as features of the pathogen and NPI response to the epidemic.

Our results highlight a significant influence of BPSV efficacy against severe disease on disease mortality under all but the lowest R0 scenarios **(Fig 4A).** For low values of R0 (R0 = 1.5) and assuming a time-to-development for the disease-specific vaccine of 250 days, the impact of a BPSV is minimal under all NPI scenarios and disease efficacy values considered, with less than 1.5 deaths per 1,000 population averted even assuming a highly efficacious BPSV. Under these scenarios, development of the disease-specific vaccine is accomplished before significant spread of the pathogen through the population has occurred. For higher values of R0 however, increasing BPSV efficacy is associated with a linear increase in averted mortality. For R0 of 2.5 and assuming an intermediate level of implemented NPIs in response to the epidemic (the **“Moderate”** NPI scenario), deaths averted by the BPSV rise from 2.4 per 1,000 population when BPSV efficacy is 25% to 4.8 per 1,000 population when efficacy is 100%. Similar relationships are observed for the other NPI scenarios considered (the **“Minimal”** and **“Stringent”** NPI scenarios). We observed a less marked influence of efficacy against infection on BPSV impact – with deaths averted by the BPSV rising from \_\_\_\_\_ to only \_\_\_\_\_ per 1,000 population as efficacy against infection was varied between 10% and 100%, for an R0 of 2.5 and moderate NPI scenario. 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 increasesd with longer duration of elicited immunity **(Fig 4C)**, ranging from \_\_\_\_\_ to \_\_\_\_\_ deaths averted per 1,000 population (for the “Stringent” and “Minimal” NPI scenarios respectively) when average immunity duration is assumed to be 2 months, to \_\_\_\_\_ and \_\_\_\_\_ deaths per 1,000 population when average immunity is assumed to be 6 months.

The magnitude of disease mortality averted through availability of the BPSV increased linearly with the size of the stockpile (and the associated coverage of 65+ individuals with the BPSV therefore achieved) **(Fig 4D)**. Assuming an R0 of 2.5, 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 *(35)*, our analyses suggest availability of a BPSV could avert 3.1 deaths per 1,000 population compared to scenarios where the BPSV is not present. This represents \_\_% of total mortality due to the disease. The speed of the BPSV vaccination (and the associated duration of the vaccination campaign required to achieve coverage) also significantly shaped projected BPSV impact **(Fig 4E)**. In contrast to the results for the stockpile size, our analyses highlight a highly non-linear relationship between vaccination campaign speed and BPSV impact, that depended on the particular NPI scenario considered. For the moderate NPI scenario, \_\_\_\_\_ deaths per 1,000 are averted when the campaign can be completed in under 2 months, compared to only \_\_\_\_\_ deaths per 1,000 when the campaign is completed in 5 months. By contrast, under the stringent NPI scenario, there was no additional impact of the BPSV if the campaign was completed after 5 months.

These results assume that the epidemic starts with \_\_\_\_\_ seeding infections and the BPSV vaccination campaign is triggered after \_\_\_\_\_ hospitalisations have been observed by the surveillance system (see ***Supplementary Materials*** and **Figure SX and SY** for further results varying these parameters). Together these results highlight the importance of factors beyond intrinsic BPSV properties in shaping eventual population-level impact of the vaccine; and the crucial nature of factors relating to the vaccination campaign associated with the BPSV in realising its maximum impact.

**The magnitude of BPSV impact is dependent on stockpile size, vaccination speed and the time taken to develop disease-specific vaccine alternatives.**

We also explored how the potential impact of the BPSV is shaped by factors relating to the disease-specific vaccine that is developed at some delay following pathogen identification and genomic sequencing. Our results support a significant impact of the BPSV under a wide range of assumed timelines between pathogen identification and disease-specific vaccine development **(Fig 5A)**. BPSV impact is substantial in all but the shortest development timelines (<100 days). For a disease-specific vaccine development timeline of 250 days (matching timelines considered ambitious but achievable with current technologies *(18)*), availability of a BPSV averts significant mortality in the period before the disease-specific vaccine becomes available, ranging from \_\_\_\_\_ to \_\_\_\_\_ deaths depending on the exact NPI scenario considered and assuming a basic reproduction number of 2.5. BPSV impact remained high across all disease-specific vaccine development timelines for an R0 of 3.5. It had more limited impact in the R0 1.5 scenario, except under the longest vaccine development timelines considered (300-365 days).

The COVID-19 pandemic was characterised by significant vaccine inequity between the global north and global south, with countries in the global south receiving COVID-19 vaccines at a significant delay compared to global north countries, an inequity that had significant consequences for disease burden in these countries *(11)*. Analysis of vaccine distribution data on the time taken to achieve vaccination coverage of 1% of eligible population (as a proxy for timeliness off vaccine access) from Our World in Data *(36, 37)* highlights this **(Fig 5B)**. Relative to \_\_\_\_\_ (the first country to vaccinate 1% of their population), countries in Europe experienced a delay of only X days on average (median, interquartile range of \_\_\_\_\_ to \_\_\_\_\_ days). By contrast, countries in Africa successfully vaccinated 1% of their population on average \_\_\_\_\_ days (IQR \_\_\_\_\_ to \_\_\_\_\_ days) after \_\_\_\_\_. We next incorporated delays to access into the disease-specific vaccine development timeline (so that if delay to access was 100 days and the disease-specific vaccine development time was 250 days, a country would only get access to the disease-specific vaccine 350 days after development had been initiated). For a disease-specific vaccine development time of 250 days, our results highlight substantial impact of the BPSV across a range of different scenarios. For a moderate NPI scenario and R0 = 3.5, the BPSV averted significant mortality across all continent-average vaccine access delays considered **(Fig 5C)**. By contrast, 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 nation (\_\_\_\_\_ per 1,000 population) than the European delay scenario (\_\_\_\_\_ per 1,000 population). Appropriately allocated and stockpiled, BPSV availability therefore has the potential to mitigate disease burden arising from an inequitable global distribution of purchasing power and doses of the disease-specific vaccine following its development.

**Surveillance system sensitivity shapes BPSV impact in both source and secondary countries**

Initiation of the BPSV vaccination campaign and development of the disease-specific vaccine both depend on detection of the outbreak and identification of the novel pathogen. We therefore carried out a series of sensitivity analyses exploring the influence of surveillance sensitivity on BPSV impact. Using a stochastic branching-process based framework, we calculated the average time taken for daily incidence of hospitalisations to reach different thresholds required for successful “detection” (ranging from 1-25 hospitalisations), for different values of R0 **(Fig 6A)** and then integrated these detection times into our dynamical modelling framework. Assuming the disease-specific vaccine was developed in 100 days **(Fig 6B, top row)**, we observed different qualitative relationships between surveillance sensitivity and impact that varied with R0. Minimal BPSV impact was observed for R0 = 1.5 scenarios. By contrast, for R0 = 2.5, BPSV impact increased as the surveillance system became less sensitive (i.e. a higher daily incidence of hospitalisations was required to trigger pathogen detection and initiation of both the BPSV campaign and disease-specific vaccine development). For R0 = 3.5 however, the BPSV typically had significant impact on disease burden irrespective of surveillance system sensitivity. When the development time for the disease-specific vaccine was assumed to be 250 days, BPSV impact was high irrespective of surveillance system sensitivity for all scenarios except those where R0 = 1.5.

These analyses were restricted to understanding how surveillance system sensitivity shapes BPSV impact in the country where the novel pathogen outbreak initially occurs. They therefore assume that BPSV vaccination is initiated in response to pathogen identification following hospitalisations in local healthcare facilities. However, the SARS-CoV-2 pandemic was highlighted by extensive international and global spread, with the pathogen identified in Wuhan *(38)* and subsequent interventions implemented in response to this discovery, i.e. prior to reports of the first hospitalisations in other countries. We therefore carried out a set of analyses exploring how the timeliness of novel pathogen detection in the country where the pathogen initially emerges (hereafter referred to as the “source country”) might influence the impact of public health responses utilising the BPSV in other countries (hereafter referred to as “secondary countries”, where the epidemic arises due to importation of infections from the source country). We considered how surveillance capabilities and sensitivity in the source country shapes subsequent BPSV impact in secondary countries where the epidemic arises from importing infections, specifically how the BPSV impact is influenced by the number of days that pathogen detection (in the source country) is ahead of importation to this secondary country (**Fig 7A** and **Fig 7B)**.

Assuming the disease-specific vaccine is available in 220 days, the BPSV had significant impact under all 3 NPI scenarios considered for an R0 of 3.5 **(Fig 7C)**. When R0 was assumed to be 2.5, surveillance sensitivity and time to detection significantly shaped BPSV impact. Assuming a stringent NPI scenario **(Fig 7C, bottom central panel)**, sensitive surveillance in the source country (leading to earlier pathogen identification and disease-specific vaccine development relative to pathogen importation into the secondary country) led to reductions in BPSV impact (as the disease-specific vaccine could be developed before substantial community transmission had occurred in the secondary country). How realistic such timelines for detection are unclear however – with previous work suggesting that SARS-CoV-2 had likely been circulating for around a month before detection by clinical metagenomic sequencing *(39)*. By contrast, availability of the BPSV had a significant impact on disease burden in scenarios where pathogen detection in the source country occurred concurrently with pathogen importation into the secondary country. When disease-specific vaccine development was assumed to take 365 days rather than 220, BPSV impact was significant in all analysed scenarios **(Fig 7C, right-hand panel)**.

**Discussion**

Our work highlights that timely access to a BPSV could have a significant impact on both the disease burden and socio-economic impact of a future SARS-CoV-X pandemic. This impact is achieved under all but the shortest assumed development for a disease-specific alternative vaccine and the lowest considered R0 values; indeed, our work suggests that availability of a BPSV sufficient to vaccinate all individuals aged 65+ globally could have averted \_\_\_\_% of COVID-19 deaths during the first year of the SARS-CoV-2 pandemic. In addition to its effect on disease burden, we show that availability of the BPSV could lower mortality in non-stringent NPI scenarios to levels below that of scenarios characterised by far longer, wide-reaching and stringent NPIs. BPSV availability therefore not only enables reductions in the human cost of the pandemic to be mitigated, but also enables less stringent NPIs (and their associated socio-economic impact) to be implemented for the same disease burden.

Our work also highlights that BPSVs are unlikely to augment public-health responses focussed on containment (e.g. through ring-vaccination strategies). Our results show that the delay in development of protection following administration is the single biggest determinant of containment prospects with ring-vaccination strategies utilising the BPSV, with a negligible fraction of outbreaks contained when the delay in protection was longer than 7 days. Given that typical timelines for development of protection in SARS-CoV-2 vaccines were in the range of 7-14 days, it is unlikely that BPSVs will prove effective at containing another SARS-CoV-X pandemic. This is especially true if the generation time of the pathogen is more similar to SARS-CoV-2 (~6 days) than SARS-CoV-1 (~\_\_ days). It is in this context that other broad-spectrum medical countermeasures such as monoclonal antibodies (where protection arises almost immediately following administration) could represent crucial additions to the arsenal of tools available for pandemic containment and mitigation strategies *(40)*. Developing these tools should be possible. Previous work has identified potent pan-sarbecovirus neutralising antibodies in SARS-CoV-1 survivors receiving the BNT162b2 vaccine *(21, 41)*. Other work has demonstrated promising results around pan-sarbecovirus infection prophylaxis with anti-ACE2 monoclonal antibodies in mice models *(42)*. Whilst our work therefore highlights the potential of BPSV, we note the importance of efforts around the development of broad-spectrum medical countermeasures other than vaccines, such as monoclonal antibodies.

Although our work highlights the utility of a stockpiled BPSV across scenarios spanning a diverse array of pathogen properties, BPSV characteristics and use-cases, it also highlights critical factors modulating this impact. Achieving BPSV impact ultimately depends on ensuring timely vaccination relative to widespread community transmission. This is driven by how soon the pathogen is detected (a function of surveillance system sensitivity) and how rapidly the BPSV vaccination campaign can proceed (a function of health system capabilities). There has been significant heterogeneity worldwide in the rate at which SARS-CoV-2 vaccination campaigns have proceeded. Much of this has been arisen due to inequities in the availability of vaccine doses, but countries also differ in the degree and extent of health systems capabilities available to support rapid vaccine rollout, leading to wide between-country variation in vaccination rates in the case of SARS-CoV-2 campaigns *(43, 44)* – efforts focussed on strengthening health systems capabilities to rapidly roll our a stockpiled vaccine are therefore likely to be impactful. Improving equitable vaccine access will also be crucial – well-equipped health systems cannot distribute vaccines they do not have access to. Availability of COVID-19 vaccines was characterised by significant global disparities and inequity *(45)*, despite work showing that equitable access would be the most effective strategy for averting loss of life *(1, 11)*. There has been a significant focus on developing “rules of the road” (including equitable sharing of medical countermeasures *(46)*) for future epidemics and pandemics as part of a World Health Assembly initiative to developing a global accord on pandemic prevention, preparedness and response *(47)*, but much more must be done in order to ensure equitable access to life-saving medical countermeasures in future pandemics.

Our results also show that that investments into public-health surveillance capabilities (enabling more timely detection of novel pathogen outbreaks) will likely act to increase BPSV impact on disease burden. Novel pathogen surveillance capabilities are currently 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 *(31)*. Similarly, the sensitivity of genomic surveillance programmes is intimately shaped by diagnostic testing rates *(48)*, a pillar of public health that has often been exceptionally limited in resource-poor settings during the pandemic *(49)*. Previous work has highlighted that significant gains in SARS-CoV-2 genomic surveillance efficiency (as it relates to identification of novel variants) that could be achieved by targeting improvements to capabilities in settings where surveillance is most limited *(30)*. Previous work has highlighted the significant investment into public-health surveillance capabilities required to effectively and equitably strength global, national and local mechanisms for detecting infectious diseases (costing approximately $9.6 billion globally) *(50)*, but that such early warning systems for pandemics could be highly cost-saving *(51)*. Progress is possible – recent work evaluating implementation of the 7-1-7 target for detection, notification and response to public health threats in 5 countries has highlighted the feasibility of sensitive, timely surveillance across a diverse range of geographies *(52)*. Expansion of surveillance capabilities should also include routine surveillance for high or at-risk animal and human populations, taking a One-Health approach to enhance surveillance for cross-species viral transmission, especially in settings where large groups of potentially susceptible animals are kept in close-contact *(53)*, as well as human populations routinely coming into contact with wildlife species known to host pathogens with epidemic potential *(54)*. We note that these suggestions are distinct to programs of systematic viral discovery in wild animals, which potentially pose substantial biosecurity risks *(55)*.

A significant limitation of the results presented here relates to uncertainty in the epidemiological properties of the BPSV. Whilst a number of BPSV candidates are currently under development *(24)*, many of these candidates have thus far only demonstrated immunogenicity in mice, with comparatively few candidates having been evaluated in non-human primate studies *(26, 56)*. To date, no evaluations of immunogenicity have been carried out in humans. This is especially important given the wide diversity of coronaviruses that humans are now routinely exposed to (including SARS-CoV-2 but also seasonal coronaviruses such as HCoV-OC43 *(57)*) and previous research showing that past exposure shapes the breadth of neutralising antibody responses to sarbecovirus infection*(58)*. In order to mitigate this limitation, we have assumed conservative estimates of BPSV efficacy (35% efficacy against infection and 75% efficacy against severe disease) that are significantly lower than the estimates of efficacy achieved by initial mRNA vaccines against the ancestral SARS-CoV-2 lineage (e.g. >90% efficacy against symptomatic disease *(59)* and >50% efficacy against infection *(60)*). Additionally, we have conducted a comprehensive suite of sensitivity analyses varying key BPSV properties including efficacy against severe disease and the duration of elicited protective immunity. In both cases, our results highlight significant utility from a stockpiled and rapidly available BPSV, especially in contexts where timelines for development of disease-specific vaccines are similar (or longer) than that achieved with SARS-CoV-2. Whilst the eventual real-world properties of developed BPSVs will depend in part on the exact candidate and the pathogen these vaccines are deployed against, our results suggest that even with levels of efficacy significantly lower than disease-specific alternatives, the timely nature of BPSV availability and the ability to manufacture and stockpile them ahead of a pandemic means that they can still achieve significant public health impact. Future work refining estimates of efficacy as BPSV candidates enter clinical stages of evaluation is likely to prove instructive however and would reduce uncertainty around impact considerably.

Another significant limitation of this work is the absence of any evaluation of cost-effectiveness. Our work highlights the significant public-health impact that could be achieved through manufacturing and stockpiling of a BPSV, but evaluation of the economic viability of this strategy will require a comprehensive health economic evaluation. Currently, this is challenging, due to uncertainty around both the eventual properties of developed BPSVs as well as the cost of their acquisition, stockpiling and administration. Ring-vaccination strategies for Ebola have been suggested to potentially be cost-effective *(61)*, whilst a previous systematic review has highlighted COVID-19 vaccinations as consistently cost-effective or cost-saving *(62)*. Moreover, the COVID-19 pandemic had a near-unprecedented negative economic impact, including a contraction of economic activity in over 90% of countries *(3)* and an estimated 97 million more people living in poverty in 2020 alone *(63)*. Given this impact, it is therefore likely that integration of BPSVs into future pandemic preparedness strategies is likely to prove cost-effective. However, formal evaluation of their cost-effectiveness remains outstanding, as does comparative assessment of the cost-effectiveness of the different strategies for their utilisation (such as ring-vaccination, targeted vaccination of high-risk populations, mass vaccination campaigns etc) and the most cost-effective mechanisms for stockpiling (a globally centralised and coordinated stockpile or multiple geographically distributed stockpiles etc) and maintenance (taking into account vaccine expiration and stock turnover dynamics).

Despite these limitations however, our work highlights the significant population-level impact that could be achieved through manufacture and stockpiling of BPSVs to facilitate rapid access in the case of a hypothetical SARS-CoV-X pandemic. Such vaccines could provide an effective way of protecting the most at-risk groups during the period between novel pathogen identification and the development of efficacious disease-specific vaccines. 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 substantial investments into novel pathogen surveillance and capabilities for rapid distribution of vaccines if these broad-spectrum medical countermeasures are to most effectively form a part of future pandemic preparedness strategies.

A diagram of a graph

Description automatically generated with medium confidence

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

A stochastic branching-process-based approach was utilised to explore the potential for a BPSV to support outbreak containment efforts utilising ring vaccination strategies, and the vaccine properties most critical to prospects for control. **(A)** Schematic illustrating the framework and the different potential outcomes arising from ring-vaccination. In this framework, individuals with a symptomatic infection trigger ring-vaccination of their contacts. 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 (green); 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 (blue); 3) the individual is successfully vaccinated during the ring-vaccination campaign but infected before vaccine-derived protection arises (yellow); 4) the individual is infected before the ring-vaccination campaign can be carried out (orange); and 5) the individual is not identified by the ring-vaccination strategy and so is not vaccinated (assumed to be 20% of contacts). Individuals for whom protection has developed but who are infected anyway may have reduced transmissibility. Averted onwards infections are illustrated with grey dashed lines and circles. Note that individuals with an asymptomatic infection (here, assumed to be 15% of all infections) are assumed to be undetected by the health-system and so do not trigger ring-vaccination. Additionally, other measures such as case isolation (which would further support containment goals) are not considered here. **(B)** The percentageof outbreaks controlled via BPSV ring-vaccination (y-axis) and its dependency on the R0 of the pathogen being considered (x-axis), for a pathogen with SARS-CoV-1 characteristics (mean Tg = 12 days, no presymptomatic transmission). Black line indicates the scenario where the BPSV is absent (no ring-vaccination) and the coloured lines indicate different assumptions around how long it takes for protection to arise following vaccination with the BPSV. Results are the mean of 200 stochastic simulations for each value of R0 and vaccine protection delay considered. **(C)** As for **(B)** but for a pathogen with SARS-CoV-2 characteristics (mean Tg = 6.75 days, 35% presymptomatic transmission). **(D)** Sensitivity analysis exploring how the percentage of outbreaks contained through ring-vaccination varies with pathogen R0 (x-axis) and the ratio of the generation time (the average time between the index case becoming infected and that index case infecting a secondary case) to the delay in protection arising following vaccination. Tile colour indicates the percentage of outbreaks controlled via BPSV ring-vaccination. Orange rectangle indicates the value of the ratio held constant for other sensitivity analyses presented in this figure. **(E)** As for **(D)** but for R0 and vaccine efficacy against infection. **(F)** As for **(D)** but for R0 and the percentage of onwards transmission that occurs before symptoms arise in the index case.

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

A dynamical model of SARS-CoV-2 transmission previously used to explore the impact of vaccination *(1)* was adapted to include BPSV-based vaccination and explore use-cases centred around rapid mass-vaccination of priority groups following pathogen detection. **(A)** Illustrative figure highlighting the scenarios simulated using the model, and the comparative timing of key events within the scenario. In this hypothetical scenario, the BPSV has been manufactured and stockpiled ahead of pandemic, enabling rapid deployment following pathogen detection. This is contrast to development of the pathogen-specific vaccine, which we assume to have a more favourable efficacy profile than the BPSV (75% efficacy against disease and 35% efficacy against infection for the BPSV, 95% and 55% for the disease-specific vaccine) but which must first be developed and evaluated. In our simulations, pathogen spillover is followed by a period of undetected circulation in the community. Hospitalisations with the infection lead to pathogen detection and identification. Following pathogen identification, development of the pathogen-specific vaccine starts, and after a short logistical delay, mass vaccination of the elderly population (here assumed to be those aged 65+) with the BPSV also begins. **(B)** The different non-pharmaceutical intervention (NPI) scenarios imposed in response to the epidemic that are considered for the analyses presented here. These NPI Scenarios differ according to the 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)** The impact of BPSV availability on disease burden for each of the NPI scenarios considered, assuming the disease-specific vaccine is available either 100 days (top-panel) or 250 days (bottom-panel) following pathogen detection. In both panels, uncoloured crosses indicate scenario without the BPSV and points indicate scenarios where the BPSV was available, coloured according to the NPI scenario being considered. Main panel indicates the absolute number of deaths under each scenario, with inset panels indicating the deaths averted by the BPSV, again coloured by NPI scenario considered.

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**Figure 3: Retrospective evaluation of BPSV impact during the COVID-19 pandemic in selected countries.**

Using previously published model fits calibrated to excess mortality data *(19)*, a series of analyses were carried out to retrospectively assess the potential impact of BPSV availability on COVID-19 mortality during the SARS-CoV-2 pandemic. **(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. Shaded area indicates the deaths averted by the BPSV. **(C)** As for **(B)** but showing daily COVID-19 deaths. **(D)** The impact of BPSV availability on COVID-19 mortality in Italy during the first year of its COVID-19 epidemic. Grey line indicates the 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. Orange line indicates the expected mortality under the assumption of BPSV availability and a mass vaccination campaign of individuals aged 65+ during the first weeks of the epidemic. **(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 public-health impact on intrinsic properties and vaccination campaign dynamics**

The majority of BPSV candidates are currently in preclinical stages of development and their potential properties therefore remain deeply uncertain *(24)*. A series of sensitivity analyses were therefore carried out analyses exploring the sensitivity of BPSV impact on various parameters within the modelling framework. **(A)** Deaths averted by the BPSV (per 1,000 population) during a hypothetical SARS-CoV-X pandemic and how this varies with assumed BPSV efficacy against severe disease. Results are coloured according to the NPI scenario considered (pink = minimal NPIs, orange = moderate NPIs and blue = stringent NPIs) and the basic reproduction number assumed (paler colours for R0 of 1.5 and 3.5, darker colours for the central scenario of R0 = 2.5); grey ribbon encapsulates the range of values for the given R0 considered. Inset panels show the Rt profile for each of NPI scenarios. **(B)** For R0 = 2.5, the impact of BPSV efficacy against infection on the number of deaths averted per 1,000 population. Colours indicate the NPI scenario considered. **(C)** For R0 = 2.5, the impact of BPSV immunity duration on the number of deaths averted per 1,000 population. Colours indicate the NPI scenario considered. **(D)** For R0 = 2.5, the impact of BPSV stockpile size (and the associated coverage of the target population that can be achieved) on the number of deaths averted per 1,000 population. Colours indicate the NPI scenario considered. **(E)** For R0 = 2.5, the impact of the rate of vaccination during the BPSV campaign (and the associated time taken to vaccinate all eligible and willing individuals) on the number of deaths averted per 1,000 population. Colours indicate the NPI scenario considered.

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**Figure 5: The impact of BPSV vaccination campaign dynamics and disease-specific vaccine development timelines on BPSV impact.** Sensitivity analyses were carried out explore the effect of variation in the time-to-development of a disease-specific vaccine on BPSV impact. **(A)** Deaths averted by the BPSV per 1,000 population and the time taken to develop the disease-specific alternative vaccine. Lines are coloured according to the NPI scenario being considered, with pink indicating minimal NPIs, orange moderate and blue stringent NPIs. Simulation results for 3 different R0 scenarios are shown, with each set of scenarios for a particular R0 enclosed by the grey ribbon. **(B)** The delay (in days) between the first country in the world (\_\_\_\_\_) achieving 1% of their population vaccinated and other countries achieving this same milestone. Individual coloured points are specific countries, coloured by continent and with each boxplot summarising the distribution of delays for all countries belonging to a particular continent. **(C)** Impact of delays to BPSV access on deaths averted per 1,000 population. Scenarios shown are for R0 = 2.5 and bars are shaded according to continent, with the delay to disease-specific vaccine access derived for each continent from the results in **(B)**.

A graph of a person with a beard

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**Figure 6: Surveillance system sensitivity and BPSV impact.**

Initiation of both the BPSV vaccination campaign and development of the disease-specific vaccine depend on detection of the outbreak and identification of the novel pathogen; and so a series of sensitivity analyses were carried out exploring the influence of surveillance sensitivity on BPSV impact. **(A)** The average time taken to identify the novel pathogen outbreak based on the daily incidence of hospitalisations with the disease required for detection to occur. Results are based on 100 stochastic simulations of a branching-process based modelling framework, and coloured according to the value of R0 used in each set of simulations. **(B)** Deaths averted by BPSV (y-axis) plotted against the hospitalisation detection threshold. x-axis values describe the daily incidence threshold above which the pathogen is said to have been detected. BPSV impact is considered across a number of scenarios varying the basic reproduction number (R0, coloured lines), time to disease-specific vaccine development (facet rows) and the NPI scenario considered (facet columns).

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**Figure 7: BPSV impact is shaped by importation dynamics and the sensitivity of novel pathogen surveillance systems.**

The timeliness of initiated BPSV campaigns in non-source countries (hereafter referred to as “secondary countries” where epidemics are seeded via importations from the source country) is dependent on the sensitivity of infectious disease surveillance capabilities and how soon the novel pathogen can be detected following spillover. We carried out analyses exploring how the timeliness of novel pathogen detection in the country where the pathogen initially emerges influences the public health impact of the BPSV in both source and secondary countries; specifically, how the BPSV impact is influenced by the number of days that pathogen detection (in the source country) is ahead of importation to this secondary country. **(A)** Schematic timeline illustrating the distinction between source country and secondary countries. Here we illustrate two types of secondary countries – “early importers” where pathogen importation to the secondary country occurs before pathogen detection in the source country; and “late importers”, where pathogen importation occurs after detection in the source country. **(B)** As for **(A)** but with key events overlaid on top of representative incidence curves for each setting considered. **(C)** Deaths averted by BPSV (y-axis) plotted against the number of days that pathogen detection in the source country is ahead of pathogen importation (to the secondary country). Positive x-axis values (shaded in grey) indicate that pathogen importation into the secondary country occurs after pathogen detection in the source country. Negative x-axis values (shaded white) indicate pathogen importation into the secondary country occurs before detection in the primary country. BPSV impact is considered across a number of scenarios varying the basic reproduction number (R0, coloured lines), time to disease-specific vaccine development (facet columns) and the NPI scenario considered (facet rows).

**Materials & Methods**

***-Work in progress***

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**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>).