**Notes:**

**Submission Target: *Science Translational Medicine***

**Information:** Research Articles are original research papers that represent significant advances in translational research. They should be structured as follows: Title, Abstract, Introduction, Results, Discussion, Materials and Methods, References, Figures and Figure Legends, Tables and Table Legends, and Supplementary Materials. Research Articles **should be no more than 10,000 words in length (including main text, references and figure legends)** and may have up to **8 figures/tables**. Supplementary materials are permitted but should be limited to information that is not essential to the general understanding of the research presented in the main text. Shorter Research Articles with fewer figures will also be considered and may be published as Reports at the discretion of the editors. See <https://www.science.org/content/page/stm-instructions-research-articles-initial-submission> for more information. Key take homes are Abstract 125-250 words with an opening sentence that sets the question that you address and is comprehensible to the general reader, background content specific to this study, results, and a concluding sentence. It should be one paragraph only. Results section should be divided into subheadings. Structure should be ***Introduction, Results, Discussion, Materials & Methods.***

**Notes:**

I read through a bunch of papers on STM and collated word counts for different sections. Here’s an example of 4:

* Introduction: 691, 719, 1138, 695 words
* Results 5500, 3000, 1900, 3100 words
* Discussion 1350, 2231, 1300, 775 words
* Ratio of Results to Discussion Length: Average is 2.72x

**Based off this, will aim for the following word counts:**

* **Introduction: 800 words**
* **Results: 3000-3500 words**
* **Discussion: 1500 words**

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

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**One Sentence Summary:**

**Abstract**

**Relevant References (see also DCP work):**

* **Baker global change and infectious disease:** [**https://www.nature.com/articles/s41579-021-00639-z**](https://www.nature.com/articles/s41579-021-00639-z)
* **Carlson climate change spillover risk:** [**https://www.nature.com/articles/s41586%20-022-04788-w**](https://www.nature.com/articles/s41586%20-022-04788-w)
* **Plowright paper:** [**https://www.nature.com/articles/s41586-022-05506-2**](https://www.nature.com/articles/s41586-022-05506-2)
* **Linfa Pan-genus/family vaccines:** [**https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(23)00210-X#%20**](https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(23)00210-X#%20)
* **Greg 100 days mission:** [**https://papers.ssrn.com/sol3/papers.cfm?abstract\_id=4519550**](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4519550)**. Can also cite this:** [**https://www.medrxiv.org/content/10.1101/2023.06.16.23291442v2**](https://www.medrxiv.org/content/10.1101/2023.06.16.23291442v2)
* **OJ impact:** [**https://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2822%2900320-6/fulltext?fbclid=IwAR0gJmq-DBXq88rARWAkTmFKryt955Pa8KKieih\_8TQzDx4C8mLx\_Dsd3fs&mibextid=Zxz2cZ**](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2822%2900320-6/fulltext?fbclid=IwAR0gJmq-DBXq88rARWAkTmFKryt955Pa8KKieih_8TQzDx4C8mLx_Dsd3fs&mibextid=Zxz2cZ)
* **Broadly neutralising antibodies to sarbecoviruses:** [**https://www.science.org/doi/10.1126/sciadv.ade3470**](https://www.science.org/doi/10.1126/sciadv.ade3470)
* **Morani et al pandemic frequency:** [**https://www.pnas.org/doi/10.1073/pnas.2105482118?url\_ver=Z39.88-2003&rfr\_id=ori%3Arid%3Acrossref.org&rfr\_dat=cr\_pub++0pubmed**](https://www.pnas.org/doi/10.1073/pnas.2105482118?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed)
* **Vaccine accessibility increases and benefits:** [**https://www.nature.com/articles/s41467-023-37075-x**](https://www.nature.com/articles/s41467-023-37075-x)
* **100 day mission lancet piece:** [**https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01775-0/fulltext?trk=feed-detail\_main-feed-card\_feed-article-content#%20**](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01775-0/fulltext?trk=feed-detail_main-feed-card_feed-article-content#%20)
* **CEPI what will it take report (220 day ref):** [**https://cepi.net/news\_cepi/what-will-it-take-global-coalition-outlines-how-to-beat-the-next-disease-x-pandemic-in-100-days/**](https://cepi.net/news_cepi/what-will-it-take-global-coalition-outlines-how-to-beat-the-next-disease-x-pandemic-in-100-days/)
* **CEPI BPSV and similar:** [**https://cepi.net/news\_cepi/the-race-to-future-proof-coronavirus-vaccines/**](https://cepi.net/news_cepi/the-race-to-future-proof-coronavirus-vaccines/)
* **BPSV paper:** [**https://www.pnas.org/doi/abs/10.1073/pnas.2314392120**](https://www.pnas.org/doi/abs/10.1073/pnas.2314392120)
* **Another BPSV style:** [**https://www.nature.com/articles/s41551-023-01094-2**](https://www.nature.com/articles/s41551-023-01094-2)
* **New approaches to preparedness needed:** [**https://www.pnas.org/doi/10.1073/pnas.2106795118**](https://www.pnas.org/doi/10.1073/pnas.2106795118)

**Refs on vaccine equity I’ve found on my travels**

**Making the point that BPSV probably also potentially helpful in the face of continued erosion of efficacy due to antigenic variation**

* **Long term effectiveness of SARS-CoV-2 vaccines in face of antigenic variation:** [**https://www.nature.com/articles/s41467-023-39736-3#Sec2**](https://www.nature.com/articles/s41467-023-39736-3#Sec2)
* **Forecasting viral escape:** [**https://www.nature.com/articles/s41586-023-06617-0**](https://www.nature.com/articles/s41586-023-06617-0)
* **Population immunity predicts evolutionary trajectory of SARS-CoV-2:** [**https://www.cell.com/cell/fulltext/S0092-8674(23)01076-0**](https://www.cell.com/cell/fulltext/S0092-8674(23)01076-0)

**Making the point that maximising the impact of these tools requires timely detection and high quality surveillance, supported by good testing rates:**

* **Resolve to Save Lives 7:1:7** [**https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(23)00133-X/fulltext**](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(23)00133-X/fulltext)
* **Brooke Nichols and team:** [**https://www.nature.com/articles/s41588-022-01267-w**](https://www.nature.com/articles/s41588-022-01267-w)**,** [**https://www.medrxiv.org/content/10.1101/2023.11.01.23297901.abstract**](https://www.medrxiv.org/content/10.1101/2023.11.01.23297901.abstract)
* **Anderson’s Paper:** [**https://www.nature.com/articles/s41467-022-33713-y**](https://www.nature.com/articles/s41467-022-33713-y)
* **Economics of improving:** [**https://gh.bmj.com/content/6/9/e006597**](https://gh.bmj.com/content/6/9/e006597)

**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 global COVID-19 vaccinations in the first year of the pandemic *(1)*. Availability of efficacious vaccines providing robust protection against severe disease has also enabled lifting of extensive societal restrictions that, whilst efficacious at reducing transmission *(2)*, also carry significant socio-economic costs *(3)*. Indeed, recent work has emphasised the societal value of SARS-CoV-2 vaccination in Indonesia, where the societal value of booster campaigns was shown to be approximately $2,500 per dose (compared to <$30 per dose for the cost of acquisition and administration) *(4)*.

The development and authorisation of highly efficacious vaccines against COVID-19 in under year (326 days from release of the first SARS-CoV-2 genomic sequence to the authorisation of the first vaccine, BNT162B2) represents a significant achievement, given that traditional development pipelines typically take 10+ years *(5)*. Despite this accelerated timeline however, over 1.5 million officially confirmed COVID-19 deaths occurred during this same time-period *(6)*. Moreover, availability of efficacious vaccines following authorisation was characterised by significant inequity in the allocation and distribution of doses between the global north and global south *(7)*, despite the additional lives that such strategies would save, and benefits they would provide to the entire world *(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. And indeed, SARS-CoV-2 is unlikely to be the last novel pathogen pandemic faced by the world over the next 100 years. Recent research has estimated there to be a 38% chance of experiencing a pandemic similar to COVID-19 during a lifetime *(12)*. Both the frequency of pathogen spillover and the intensity of epidemics arising from this spillover are both 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 reducing timelines for vaccine development even further, with the Coalition for Epidemic Preparedness Innovations (CEPI) and others announcing 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 optimisation of existing innovations around vaccine development are unlikely to be able to reduce development timelines to less than 250 days *(20)*, highlighting the need for a paradigm shift in vaccine development in order to meet the 100 day target. A limitation of all of these approaches however is their reactive nature; given that pathogen-specific vaccine development is contingent on having detected, identified and subsequently sequence the novel pathogen that has emerged into the human population. This necessarily limits on 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 non-pharmaceutical interventions (and their associated socio-economic impact).

Altogether, these limitations around the speed with which pathogen-specific vaccines can be developed in the context of a novel pathogen pandemic has motivated significant in the interest of alternative approaches to vaccine development that might facilitate more rapid availability. Of particular interest has been vaccines that offer broad and robust protection against a range of viruses belonging to the same family, such as coronaviruses. Such vaccines could be manufactured and stockpiled ahead of a novel pathogen pandemic, enabling rapid access following pathogen detection. Previous work has identified potent pan sarbecovirus neutralising antibodies *(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)*. The Coalition for Epidemics Preparedness Innovations (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 and a smaller number in non-human primates. These candidates span a wide range of different approaches to vaccination development, ranging from mosaic nanoparticles containing spike receptor binding domains (RBDs) from a diverse range of sarbecoviruses *(26)*, approaches based on chimeric spike mRNA vaccines *(27)*, and vaccine antigens based on epitopes conserved across multiple coronaviruses *(28, 29)* amongst others.

Despite numerous potential candidates in preclinical development, our understanding of how best to operationalise broad-spectrum vaccines remains limited, particularly around the most relevant use-cases and how to optimise their utilisation for maximum population-level impact. Here, we extend a previously developed dynamical model of SARS-CoV-2 transmission previously used to explore the impact of vaccination *(1, 19)* and use this model to explore and evaluate the potential impact of a broadly protective sarbecovirus vaccine during a future SARS-CoV-X pandemic. Our work highlights substantial potential public-health impact arising from widespread availability and rapid access to a broadly protective sarbecovirus vaccine (BPSV) during a novel pathogen pandemic caused by a sarbecovirus, but also critically that this impact is shaped by a diverse range of factors including intrinsic vaccine properties, health system capabilities, and features of the pandemic response; and therefore that realising the benefit of these tools will 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-based approach was utilised to explore the potential for a BPSV to support outbreak containment efforts utilising ring vaccination strategies (as has successfully been undertaken for control of Ebola outbreaks) *(32)* **(Fig 1A)**, and the vaccine properties most critical to containment prospects. For the purposes of the analyses presented in **Fig 1B**, we assumed the ring-vaccination campaign was able to identify 80% of contacts, 15% of infections are asymptomatic, 35% of transmission is presymptomatic and a mean generation time of 6.75 days. We also assumed the BPSV has an efficacy of 75% against infection, and a delay of 2 days between identification of an index case and completion of the ring-vaccination campaign. Across the 100 simulations, the proportion of outbreaks successfully contained decreased as pathogen R0 increased, and increased as the assumed delay between vaccination and protection developing was shortened **(Fig 1B)**. For an R0 of 1.5, <3% of outbreaks were contained when the delay was 3 days or longer. By contrast, 61% of outbreaks were controlled the delay was assumed to be 2 days; and 100% of outbreaks contained when protection was assumed to arise instantaneously following receipt of the vaccine. 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. Our analyses alsohighlighted that prospects for control were highly sensitive to assumptions around vaccine characteristics and pathogen properties **(Fig 1C, 1D & 1E)**. When the mean generation time and the vaccine protection delay were assumed to be the same, the BPSV ring-vaccination did not lead to outbreak containment under any R0 scenario considered **(Fig 1C)**. 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 1D)**. 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 1E)**.

**Mass-vaccination of elderly populations with a BPSV following pathogen detection could significantly reduce mortality and support more rapid cessation of non-pharmaceutical interventions aimed at limiting transmission.**

The results in **Figure 1** highlight the prospects 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 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 220 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. Additionally, 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 220 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 220 days (with deaths reducing 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 220 day development timeline, availability of the BPSV limits mortality to levels below all but the most stringent 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. Indeed, the impact of the BPSV is 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 in Italy and Iran. These countries were chosen for the comparatively early epidemics they experienced, as well as the significant mortality sustained during the first year of the pandemic. 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. 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 3A)** and total COVID-19 mortality over the first year from 124,500 to only an expected 49,700 deaths on average **(Fig 3B)**. A similar result was observed for our retrospective analysis of Iran’s epidemic. Availability of the BPSV significantly reduced mortality, from over 900 COVID-19 deaths a day during the country’s largest wave of the first year to only approximately 580 deaths per day; and overall COVID-19 mortality during the first year reduced from 123,900 deaths to 53,400 deaths.

**Projected BPSV impact is shaped by an interplay of intrinsic vaccine characteristics, pathogen properties and imposed control measures.**

Currently, the previously presented results 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 hypothetical epidemics driven a SARS-CoV-X pathogen with epidemiological properties similar to SARS-CoV-2 whilst varying BPSV characteristics (specifically efficacy against severe disease and duration of elicited immunity), pathogen characteristics (R0) and characteristics of the disease-specific vaccine (the delay between pathogen identification and successful development of the vaccine). Our results highlight a significant impact of the BPSV 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 220 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 linear and substantial increases 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). BPSV impact similarly increases with longer duration of elicited immunity **(Fig 4B)**, 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. Our results also support a significant impact of the BPSV under a wide range of assumed timelines between pathogen identification and disease-specific vaccine development **(Fig 4C)**. BPSV impact is substantial in all but the shortest development timelines (<100 days). For a disease-specific vaccine development timeline of 220 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.

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

***[missing introductory couple of sentences]***

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 5A)**. Impact on mortality was highest under the scenarios with the highest R0 (R0 = 3.5) and decreased at lower R0 values. 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 the total disease mortality. 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 5B)**. In contrast to the results for the stockpile size, our analyses highlight a highly non-linear relationship between vaccination campaign speed and R0 in shaping BPSV impact. For the fastest moving epidemics with the highest R0 (R0 = 3.5), 4.88 deaths per 1,000 are averted when the campaign can be completed in under 2 months, compared to only 2.02 deaths per 1,000 when the campaign is completed in 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.

We also explored how the potential impact of BPSV availability is shaped by the delay to accessing the disease-specific vaccine following its successful development. 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 5C)**. 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 220 days, a country would only get access to the disease-specific vaccine 320 days after development had been initiated). For a disease-specific vaccine development time of 220 days, our results highlight substantial impact of the BPSV across a range of different scenarios. Under the highest R0 scenario (R0 = 3.5), the BPSV averted significant mortality under all NPI scenarios and delays to access considered. Interestingly, for R0 = 2.5 and stringent NPI scenarios, the impact of the BPSV was more limited in situations of rapid access similar to those experienced by the average European country during the SARS-CoV-2 pandemic **(Fig 5C, bottom panel, pink line)**, averting 2.2 deaths per 1,000 population on average. By contrast, 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, averting almost double the number of deaths per 1,000 population (4.1 per 1,000 population, **Fig 5C, bottom panel, yellow line**) compared to the European delay scenario. Appropriately allocated and stockpiled then, 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.

**BPSV impact is shaped extensively by health system strength and the sensitivity of infectious disease surveillance.**

The results presented here thus far 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 6A)**.

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 6B)**. When R0 was assumed to be 2.5, surveillance sensitivity and time to detection significantly shaped BPSV impact. Assuming a stringent NPI scenario **(Fig 6B, 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 6B, right-hand panel)**.

**Discussion (approx. 1500 words)**

* **Different use cases and factors influencing this. Limitations especially for containment and fast moving contexts – monoclonals and other broad-spectrum MCMs worth considering. Not considered here, but currently under development (point to Linfa’s work, Panoplia labs etc).**
* **NPI and death tradeoff and the BPSV enabling more open societies for the same disease burden impact.**
* **Key factors shaping impact – specifically pathogen properties, vaccine (campaign) properties and surveillance system strength. Highlights the importance of accompanying MCM development with health systems strengthening, to provide the early warning necessary to support the most effective utilisation of MCM tools.**
* **Something about equity**
* **~~Most BPSV candidates are in preclinical stages and so properties are very uncertain. Major limitation, but we get past this by carrying out a suite of sensitivity analyses, and additionally note that the results presented here are often conservative – e.g. we assume optimistic disease-specific development timelines, that such a vaccine can be successfully developed etc (if either of those optimistic assumptions aren’t met, BPSV development will be even more substantial).~~**
* **~~Further work needed on cost-effectiveness (especially given cost of maintaining stockpile etc), and how to most effectively globally stockpile (geographically distributed, centralised etc etc). Health economics approaches necessary here. Beyond the scope of this study but represents an instructive avenue for future research.~~**
* **Key factors shaping impact – specifically pathogen properties, vaccine (campaign) properties and surveillance system strength. Highlights the importance of accompanying MCM development with health systems strengthening, to provide the early warning necessary to support the most effective utilisation of MCM tools.**

Whilst our work highlights utility of a stockpiled BPSV across scenarios spanning a diverse array of pathogen properties, BPSV characteristics and use-cases, it also highlights critical factors shaping the impact of the BPSV.

Experiences during the COVID-19 pandemic have highlighted significant global disparities and inequities in surveillance capabilities, including genomic surveillance crucial to novel pathogen identification *(31)*

This should include routine surveillance for high or at-risk animal 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 *(40)*, as well as wildlife species known to host pathogens with epidemic potential and which routinely come into close contact with humans *(41)*. We note here that this latter suggestion is distinct to recent programs of viral discovery in wild animals, which potentially pose substantial biosecurity risks *(42)* and which lack a concrete theory of change linking discovery to reduced outbreak risk *(43)*.

Previous work has highlighted the significant investments 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) *(44)*, but that such early warning systems for pandemics could be highly cost-saving *(45)*

*-something about locally led, nationally and context specific and mosaic approaches, cite WHO paper-*

\_\_\_\_\_

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, 46)*. 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 *(47)*) and previous research showing that past exposure shapes the breadth of neutralising antibody responses to sarbecovirus infection*(48)*. In order to mitigate this limitation, we have assumed conservative estimates of BPSV efficacy against infection (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 *(49)* and >50% efficacy against infection *(50)*); 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 further refine estimates of potential population-level impact are likely to prove instructive.

Another significant limitation of the work is the absence of any evaluation of cost-effectiveness. Whilst our work highlights the significant public-health impact that could be achieved through manufacturing and stockpiling of a BPSV, full 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 previously been suggested to potentially be cost-effective *(51)*, whilst a previous systematic review has highlighted COVID-19 vaccinations as consistently cost-effective or cost-saving *(52)*. 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 *(53)*. 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, stockpile and utilisation of BPSVs to facilitate rapid access to protection 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 enable substantial economic gains through enabling less stringent NPIs to be imposed. 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.

* However, not suitable in all instances and so other broad-spectrum MCMs should also be considered ***[shall I add this?]***

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**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 the infection they would otherwise receive is successfully averted (blue); 2) the individual is successfully vaccinated during the ring-vaccination campaign but infected before vaccine-derived protection arises (yellow); 3) the individual is infected before the ring-vaccination campaign can be carried out (orange); and 4) 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. This is illustrated with grey dashed lines and circles representing individuals not infected due to reduced transmissibility of this secondary case. 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). 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 100 stochastic simulations for each value of R0 and vaccine protection delay considered. **(C)** 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. **(D)** As for **(C)** but for R0 and vaccine efficacy against infection. **(E)** As for **(C)** 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 220 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 COVID-19 epidemic of different countries. Black 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. **(B)** Cumulative COVID-19 mortality in Italy during the first year of the pandemic with the BPSV (orange bar) and without the BPSV (black bar). Error-bars indicate the 95% confidence interval for COVID-19 mortality across 100 draws from the posterior distribution of parameters arising from model fitting to COVID-19 death data. See ***Supplementary Methods*** for further information on model calibration process. **(C)** As for **(A)** but for Iran instead of Italy. **(D)** As for **(B)**, but for Iran instead of Italy.

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**Figure 4: Dependency of BPSV public-health impact on vaccine properties**

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 immunity duration on the number of deaths averted per 1,000 population. Colours indicate the NPI scenario considered. **(C)** For R0 = 2.5, the impact of the delay between pathogen identification and disease-specific vaccine development on the deaths averted per 1,000 population by the BPSV. 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.** Significant uncertainty remains at to the size of the BPSV stockpile that might be maintained in preparation for a SARS-CoV-X pandemic, as well as how rapidly a stockpiled BPSV could be rolled out and the time it would take to develop a disease-specific alternative vaccine. We therefore conducted a series of analyses exploring how these different factors shape the potential impact of BPSV availability on disease mortality during a SARS-CoV-X pandemic. **(A)** Deaths averted by BPSV and how this varies with stockpile size (and in turn, the proportion of eligible population able to be vaccinated with the BPSV during the initial vaccination campaign). Lines are coloured according to the R0 used for simulation purposes. **(B)** Deaths averted by BPSV and how this varies with the rate of vaccination during the BPSV campaign (i.e. the time taken to vaccinate all eligible individuals). Lines are coloured according to the R0 used for simulation purposes. **(C)** 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. **(D)** Impact of BPSV availability on disease mortality per 1,000 population and how it varies with R0 (coloured lines), delay to access disease-specific vaccine following its development (x-axis) and the NPI scenario assumed (different panels, with inset panels show the Rt profile for each of the different NPI scenarios). Vertical coloured lines indicate the continent-specific average delay to achieving 1% population vaccine coverage (relative to \_\_\_\_\_) – colours of these lines match the continent colours used in **(C)**.

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**Figure 6: BPSV impact is shaped by the sensitivity of novel pathogen surveillance systems.**

The timeliness of initiated BPSV campaigns (in both the “source country” where the novel pathogen emerges and “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)** 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**

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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>).