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

Charles Whittaker1, Gregory Barnsley1,2, Daniela Olivera Mesa1, *[****Alexandra?, Pete?, Linfa? Katharina? Rob? Folks from CEPI?]*** Oliver J Watson1 & Azra Ghani1

1MRC Centre for Global Infectious Disease Analysis, Department of Infectious Disease Epidemiology, Imperial College London, UK

2Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

3School of Population Health, University of New South Wales, Sydney, Australia

**One Sentence Summary:**

**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**

**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 (approx. 800 words)** [Note: I’m a little unclear currently how coronavirus specific the first couple of paragraphs of this should be]

* **Experiences with SARS-CoV-2 have highlighted the significant public health impact and utility of vaccinations during pandemics, but also the critical need for more rapid access to vaccines following pathogen emergence. Speak here about the unprecedented timelines of COVID-19 vaccine development, but the fact this still took a year. Highlight the renewed interest in developing vaccines even faster (such as CEPI’s 100 day mission – and cite Greg’s paper showing its potential impact but note the difficulty of achieving 100 days and even the uncertainty whether we will be able to at all); but even with substantial innovation, timelines might shrink even to only 220 days (cite CEPI report) – achieving anything more rapid will require sizeable paradigm shift in vaccine manufacturing and development. A limitation of all of these approaches and strategies for vaccine development is their reactive nature, contingent as they are on having detected, identified and sequenced the pathogen with pandemic potential that has emerged into the human population. This necessarily introduces limits on the timeliness of these strategies, which necessitates either substantial human toll or significant control measures in the form of NPIs and their associated negative economic impact.**
* **COVID-19 is unlikely the last pandemic to be experienced in our lifetimes. Epidemic intensity and frequency is increasing due to climate change, anthropogenic forces etc etc/.**
* **These limitations have therefore motivated significant interest in the development of alternative approaches to vaccine development that might facilitate more rapid responses. Of particular interest have been vaccines that offer broad and robust protection against a range of viruses belonging to the same family.**
* **A number of vaccine candidates are currently under development. Examples of these include \_\_\_\_, \_\_\_\_\_\_ and \_\_\_\_\_.**
* **--anf**
* **Something here about the molecular details and specifics**
* **Despite a significant number of potential vaccine candidates currently in development, our understanding of how best to operationalise this novel public health tool remains limited, especially around the most effective use cases for their utilisation.**
* **Here we utilise a modelling approach to explore….Our work highlights that….. In doing so, we underscore the potential utility of these tools and suggest ways to most effectively leverage them to support future pandemic preparedness strategies integrating broadly protective sarbecovirus vaccines.**

**Results (approx. 3000-3500 words)**

**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) *(1)* **(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/or 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 *(2, 3)*). Motivated by this, we also explored 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 *(4)* ). 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)**.

**Figure 3 title**

Our results highlighted significant impact during SARS-CoV-2 like pandemic. In order to explore this further, we did retrospective analysis looking at potential impact during actual pandemic, given actual levels of NPis (reflecting in Rt etc)

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 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.

A close-up of a graph

Description automatically generated

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

(as has been successfully deployed for diseases like Ebola [Ref]), and how prospects for containment depend on key BPSV properties, including vaccine efficacy against infection and the fraction of onwards transmission that occurs before symptoms develop in the index case (presymptomatic transmission)

**Discussion (approx. 1500 words)**

**Materials & Methods**

**References**

**Funding**

The investigation was funded by the Coalition for Epidemic Preparedness Innovations (CEPI). This work was supported by a Sir Henry Wellcome Postdoctoral Fellowship Ref 224190/Z/21/Z. This research was funded in whole, or in part, by the Wellcome Trust (Ref 224190/Z/21/Z). For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. The work is supported by the MRC Centre for Global Infectious Disease Analysis (reference MR/R015600/1) which is jointly funded by the UK Medical Research Council (MRC) and the UK Foreign, Commonwealth & Development Office (FCDO), under the MRC/FCDO Concordat agreement, the EDCTP2 programme supported by the European Union and Community Jameel. ABH is supported by an Australian National Health and Medical Research Council Investigator Grant.

**Author Contributions**

**Conceptualization:** CW, OJW & AG

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

**Investigation:** CW & AG

**Visualization:** CW, DOM & AG

**Funding acquisition:** OJW & AG

**Project administration:** AG

**Supervision:** AG

**Writing – original draft:** CW & AG

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

**Competing Interests**

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

**Data & Materials Availability**

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

1. A. M. Henao-Restrepo, A. Camacho, I. M. Longini, C. H. Watson, W. J. Edmunds, M. Egger, M. W. Carroll, N. E. Dean, I. Diatta, M. Doumbia, B. Draguez, S. Duraffour, G. Enwere, R. Grais, S. Gunther, P.-S. Gsell, S. Hossmann, S. V. Watle, M. K. Kondé, S. Kéïta, S. Kone, E. Kuisma, M. M. Levine, S. Mandal, T. Mauget, G. Norheim, X. Riveros, A. Soumah, S. Trelle, A. S. Vicari, J.-A. Røttingen, M.-P. Kieny, Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). *Lancet* **389**, 505–518 (2017).

2. E. Petersen, M. Koopmans, U. Go, D. H. Hamer, N. Petrosillo, F. Castelli, M. Storgaard, S. Al Khalili, L. Simonsen, Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. *Lancet Infect. Dis.* **20**, e238–e244 (2020).

3. D. Buitrago-Garcia, A. M. Ipekci, L. Heron, H. Imeri, L. Araujo-Chaveron, I. Arevalo-Rodriguez, A. Ciapponi, M. Cevik, A. Hauser, M. I. Alam, K. Meili, E. A. Meyerowitz, N. Prajapati, X. Qiu, A. Richterman, W. G. Robles-Rodriguez, S. Thapa, I. Zhelyazkov, G. Salanti, N. Low, Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: Update of a living systematic review and meta-analysis. *PLoS Med.* **19**, e1003987 (2022).

4. M. Saville, J. P. Cramer, M. Downham, A. Hacker, N. Lurie, L. Van der Veken, M. Whelan, R. Hatchett, Delivering pandemic vaccines in 100 days - what will it take? *N. Engl. J. Med.* **387**, e3 (2022).