Challenges in evaluating SARS-CoV-2 vaccines during the pandemic

Bahaa Abu-Raya, MD[1,2], Soren Gantt, MD, PhD, MPH[1,2], and Manish Sadarangani, BM BCh, DPhil[1,2]

[1] Vaccine Evaluation Center, BC Children's Hospital Research Institute, Vancouver, Canada

[2] Division of Infectious Diseases, Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada

Corresponding author:

Bahaa Abu-Raya, MD

Vaccine Evaluation Center, BC Children's Hospital Research Institute,

University of British Columbia

950 West 28th Avenue, Rm A5-174 V5Z 4H4

Email: baburaya@bcchr.ubc.ca

This is the post-print peer-reviewed version of the following article: Abu-Raya, B., Gantt, S., & Sadarangani, M. (2020). Challenges in evaluating SARS-CoV-2 vaccines during the COVID-19 pandemic. Canadian Medical Association Journal (CMAJ), 192(34), E982-E985. , which has been published in final form at https://doi.org/10.1503/cmaj.201237.

Key points:

- Challenges to the evaluation of SARS-CoV-2 candidate vaccines prior to approval or licensure during the ongoing pandemic include rapidly changing levels of exposure to the virus and population immunity, social distancing practices, and the possibility of antibody-dependent enhancement of disease.
- In order to measure vaccine efficacy accurately, researchers should account for these factors in sample size calculations and also carefully consider selection of trial endpoints.
- SARS-CoV-2 vaccines must also be evaluated in populations known to be at increased risk for severe COVID-19, such as older adults, people of African descent, and people with multiple comorbidities.
- Given the speed of SARS-CoV-2 vaccine development careful attention must be paid to post-licensure assessment of vaccines, including the risk of antibody-dependent enhancement of disease, which must be actively monitored closely over multiple years after vaccination.

Introduction:

Coronavirus disease 2019 (COVID-19) is a rapidly evolving pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In addition to minimizing risk of transmission by non-pharmacological measures, one or more effective vaccines would be invaluable to reduce the burden of COVID-19. Over 140 candidate SARS-CoV-2 vaccines are in development, and being assessed in pre-clinical studies and clinical trials (1). In general, for a vaccine to be approved or licensed by regulatory authorities, it must demonstrate both safety and high efficacy in the prevention of a specific disease in the relevant population(s). However, the COVID-19 pandemic poses specific logistic and scientific challenges with respect to the assessment of SARS-CoV-2 vaccine candidates. Evaluation of SARS-CoV-2 vaccine efficacy must consider population risk of exposure, susceptibility to the virus, current social distancing practices and geography. Moreover, SARS-CoV-2 vaccines also need to be evaluated in populations at greatest risk for severe COVID-19(2-4). We discuss challenges to the clinical evaluation of SARS-CoV-2 vaccines, as well as some potential solutions.

How are vaccines usually evaluated before licensure?

Vaccines considered for licensure are assessed initially for their safety profile and their ability to induce immune responses to vaccine antigen(s) in small phase 1 studies. Candidate vaccines that are safe and immunogenic may then advance to phase 2 studies, in which safety, immunogenicity, and sometimes preliminary efficacy, are assessed in larger cohorts. Vaccine efficacy is primarily evaluated in phase 3 studies, to determine the proportionate reduction in pre-defined infection rate or disease events among vaccinated subjects. Vaccine efficacy represents the best-case scenario

of protection derived from vaccination, and needs to be demonstrated in order for a vaccine against a novel pathogen to be licensed by regulatory authorities (2, 3). Ideally evaluation of efficacy is undertaken in well-controlled studies (e.g., double-blind, randomized, controlled clinical trials). Successful vaccines that have been shown to have high efficacy in clinical trials and are licensed for use in a population are continually assessed for their safety and effectiveness post-licensure and post-implementation (in phase 4 studies that evaluate how a vaccine reduces disease in a population in "real world" conditions).

What factors may affect the evaluation of SARS-CoV-2 candidate vaccines?

In general, individual host-related (e.g., age, genetic, and environmental exposures) and vaccine-related (e.g. antigen selection, adjuvants, formulation, delivery mode, waning of immunity over time) factors influence individuals' immune response to vaccines, and thus determine their efficacy. However, several other factors, some of which may be difficult to quantify, such as the level of transmission of the target pathogen (i.e., exposure) and the level of pre-existing immunity (i.e., susceptibility) in the population are also important to consider. Such factors are related and are different when a pathogen is endemic (that is, constantly and usually present within a given geographic area or population) *vs.* pandemic (that is, emerging and spreading worldwide), as with SARS-CoV-2. The baseline level of exposure of a population to a specific pathogen, the pathogen's seasonality and the level of population immunity are usually relatively predictable in endemic compared with pandemic states of infection. Table 1 summarizes the potential confounders unique to the COVID-19 pandemic that might affect the demonstration of efficacy of SARS-CoV-2 candidate vaccines.

Level of exposure and immunity to SARS-CoV-2

The dynamic and rapidly changing pattern of virus exposure and level of population immunity during the evolving pandemic are potentially important confounders in the assessment of efficacy of SARS-CoV-2 vaccines; this should be considered in sample size calculations for efficacy trials. For example, if a vaccine is trialed in a low-incidence population, or if immunity wanes significantly over time post-vaccination, a highly efficacious vaccine might not show statistically significant protection if the trial sample size is too small to demonstrate a significant reduction in occurrence of disease in vaccinated participants in such conditions. Thus, careful attention must be paid to trial sample size calculations and there may be a need to recruit more subjects in areas where the disease prevalence is very low. Moreover, levels of transmission of SARS-CoV-2 might vary between or within countries, and will change over time as the pandemic progresses, which must be considered when trialing the same vaccine in different geographical areas.

Population seropositivity, or baseline level of immunity might affect vaccine immunogenicity and/or population susceptibility to the target pathogen, which would influence the outcome of a vaccine trial. For example, a highly efficacious vaccine might not show benefit in settings with high seroprevalence as vaccination may not add substantially to the protection afforded by natural infection. While this might not be a problem very early in the pandemic while population seropositivity is still low (4), high baseline immunity could confound the results of vaccine trials as the pandemic progresses and seroprevalence increases, depending on the population. For example, the prevalence of anti-SARS-CoV-2 antibodies increased, from 3.1%, to 6.1%, to 9.7%, during three subsequent weeks in April, 2020 (5) in a population-

based sample in Geneva, Switzerland. Measurement of pre-existing immunity in efficacy trials is important, as is the inclusion, vaccination, and evaluation of seropositive participants.

Social distancing and other public health interventions

Social distancing has been shown to be effective in mitigating the transmission of SARS-CoV-2 (6-8). In settings where transmission is low due to social distancing measures the benefit of a highly efficacious vaccine might not be readily demonstrable. Study sample size calculations should account for this. Furthermore, public health interventions will likely vary as the pandemic progresses, which will challenge the ongoing assessment of vaccines. Flexibility in trial design may be necessary to achieve a sufficient number of endpoints to determine efficacy, depending on fluctuating transmission rates in different locations.

What potential vaccine-related harms may be anticipated?

Although the goal of a vaccine is to reduce the burden of COVID-19, SARS-CoV-2 vaccines may theoretically lead to antibody-dependent enhancement (ADE) (9). This phenomenon, which has been described with SARS-CoV-1 and other coronavirus vaccines in animal models (10), results from low-titre and/or poorly neutralizing antibody following vaccination that facilitates viral entry or replication in target cells, causing more severe disease from infection in vaccinated individuals. As shown with the CYD-TDV vaccine for dengue, vaccine-induced ADE can have enormous negative impacts on not only directly among vaccinated individuals, but on public trust and uptake of other vaccines (11, 12). ADE may only be observed following vaccination with specific COVID-19 vaccine adjuvants, platforms or products – not

all. Importantly, the effect of ADE on vaccinated subjects might not manifest early in the pandemic with lower infection rates in a vaccinated population, but may be more evident with larger numbers of COVID-19 cases in vaccinees, with waning vaccine responses in subsequent years, or with genotypic changes in the virus over time (e.g., antigenic drift) (13). We recommend that the risk of ADE be actively monitored closely over multiple years, in order to account for waning antibody titres and/or variation in circulating viral strains (Table 1).

Why is careful consideration of study population and trial endpoints important? SARS-CoV-2 vaccines, like other vaccines, are being first studied in populations of healthy adult volunteers. However, COVID-19 has been shown to affect the elderly, people of African descent, and people with multiple co-morbidities most severely (14). Thus, results from low-risk populations might not reflect benefits or risks in higher-risk populations. It is also possible that a vaccine might not provide sterilizing immunity (defined as immune status following vaccination that prevents virus infection of the host). This means that vaccinated individuals may still get the mild form of the disease. **[We infer that this means that vaccinated individuals may still get the disease but will get it in a milder form. If so, please clarify that here.]** Thus, it is possible that vaccination will have a substantially greater impact on preventing severe disease than on preventing milder symptoms or acquisition of infection. These issues should be considered when choosing the clinical endpoints for SARS-CoV-2 vaccine efficacy trials. For example, if the aim is to show that a vaccine is effective in reducing the severe forms and outcomes of COVID-19, endpoints such as hospitalization, intensive care unit admission, the need for respiratory support, and/or death could be considered as primary outcomes, although lower rates of more

severe events means such endpoints may be logistically challenging, depending on overall disease incidence rates.

It is also important that vaccines be tested in those populations at greatest risk for severe COVID-19, such as the elderly, health care workers, people of African descent, and those predisposing health problems (15). This is critical as it will inform policy makers about the population(s) that will benefit the most from vaccination and thus need to be prioritized for vaccination when a vaccine is available, but the demand outweighs the supply.

What are some other challenges to the development of SARS-CoV-2 vaccines?

Regulatory challenges

Development of vaccines for human use usually takes at least 10-15 years, from pre-clinical development to licensure. However, due to the urgent need for SARS-CoV-2 vaccines, the timeline for their development and approval will need to be shortened substantially, ideally to months rather than years. This might impose a substantial burden on regulatory agencies that will need to process all the usual work in a greatly reduced time frame.

Safety challenges

New technologies for vaccine delivery have been developed during the past decade (e.g., DNA or RNA vaccines); these technologies feature amongst the SARS-CoV-2 vaccines that have most rapidly progressed to clinical trials, despite their not having been used for any licensed vaccine to date (15). The safety of the SARS-CoV-2 candidate vaccines based on these new technologies must be especially carefully

assessed. This will require continuous assessment for both common and rare potential adverse effects in a large number of vaccine recipients, during clinical trials as well as during active post-marketing surveillance.

What are some particular organizational challenges and opportunities of SARS-CoV-2 vaccine trials?

Logistics of multiple vaccines in trials

Studying multiple vaccines at the same time in the same population might be a challenge if there is limited trial capacity. This might be overcome by using an adaptive study design allowing addition or removal of vaccines as data on safety, immunogenicity and efficacy accumulate. This approach is currently being employed in clinical trials assessing different pharmacological treatments for COVID-19 (e.g the Solidarity trial, launched by the World Health Association and partners (16)). Additionally, infrastructure is being developed to enable sites with experience of non-vaccine drug trials to be utilized, and for new trial sites to be rapidly set up, including appropriate focused training for research staff.

National and international collaborations

Establishing national and international consortia for COVID-19 vaccine trials will increase cooperation within and between countries' vaccine groups. For example, the Canadian Immunization Research Network is a national collaborative network of vaccine researchers that conduct collaborative research related to different aspects of vaccinology. In order to ensure equity in evaluating vaccines, individual study sites should be representative of the entire population in a specific country, and evaluation

of vaccines should be performed in high as well as low and middle-income countries. As a demand for efficacious vaccines will be high, setting parameters for equitable post-licensure distribution of vaccines across countries is also critical.

How should post-licensure assessment of vaccines be conducted?

Post-licensure assessment of the effectiveness of a vaccine that is being administered in the population is mainly assessed by retrospective case control analysis, ecologic or observational studies. Analyses of these studies should include populations with varying risk of exposure, pre-existing immunity (if known), geography, baseline characteristics (e.g., age, comorbidities). Time since vaccination can also be captured in these studies to assess the effectiveness of vaccination with SARS-CoV-2 vaccines over time after vaccination. This will help to determine whether there is waning immunity after vaccination.

Conclusion

We have discussed the unique challenges in evaluating SARS-CoV-2 vaccines during the ongoing pandemic. These arise from rapidly changing levels of virus exposure, the development of population immunity and the effects of local social distancing practices, as well as the speed with which vaccine candidates are being developed and tested, safety considerations of untested technologies, the need to consider which end points matter, and who is most affected and issues of equity in access to approved vaccines. In addition, as efficacy might be challenging to demonstrate in some populations, researchers should aim to fully dissect the protective immune response

(humoral and cellular immunity) to natural infection and after vaccination as establishing correlate(s) of protection would also inform vaccine development and evaluation.

Table 1: Population-related factors affecting evaluation of vaccine efficacy in endemic vs. pandemic states of infection, and those unique to COVID-19

Factors affecting demonstration of vaccine efficacy	Endemic state of infection	Pandemic state of infection	COVID-19 unique factors	Strategies
Baseline transmission of target pathogen in population (i.e., exposure) and its seasonality	Known	Rapidly changing; Seasonality unknown	Social distancing and other public health interventions	Flexible trial designs to ensure adequate numbers of endpoints (infections or hospitalizations); determination of potential confounding by non-vaccine prevention measures
Population level of pre-existing immunity to target pathogen (i.e., susceptibility)	Known	Rapidly changing	Paucity of sero-epidemiologic data; accuracy of serologic tests; unclear extent/duration of protection from natural immunity	Baseline serologic testing of participants in efficacy trials
Differential susceptibility of sub-populations to infection or disease	Known	Emerging	Numerous risk factors identified, but elderly at highest risk of severe disease; young children rarely have complications and may be less susceptible to infection; ADE?	Evaluation of vaccine efficacy and endpoints in the elderly and other high-risk groups; close monitoring and prolonged follow-up for possible ADE in all trials

Abbreviation: COVID-19: Coronavirus disease 2019; ADE: antibody-dependent enhancement

Conflict of Interest: BA has no conflict of interest to declare**.** BA is supported by the Canadian Health and Research Institute Vanier Canada Graduate scholarship. SG receives consulting fees related to vaccines from Moderna, Merck, GSK, and Curevo, and research funding for vaccine research from Merck, GSK, and VBI. SG is also a voting member of the Canadian National Advisory Committee on Immunization. MS is supported via salary awards from the BC Children's Hospital Foundation, the Canadian Child Health Clinician Scientist Program and the Michael Smith Foundation for Health Research. MS has been an investigator on projects funded by Pfizer, Merck, Seqirus, Sanofi-Pasteur, VBI Vaccines and GlaxoSmithKline. All funds have been paid to his institute, and he has not received any personal payments.

Contributors' statement: All of the authors contributed to the conception and design of the work. Bahaa Abu-Raya drafted the manuscript. All authors critically reviewed and revised the article, gave final approval of the final version to be published and agreed to be accountable for all aspects of the work.

References:

1. Draft landscape of COVID-19 candidate vaccines. https://www.who.int/who-documents-detail/draft-landscape of-covid-19-candidate-vaccines. Accessed 26 May, 2020. .
2. Clemens J, Brenner R, Rao M, Tafari N, Lowe C. Evaluating new vaccines for developing countries. Efficacy or effectiveness? JAMA. 1996;275(5):390-7.
3. Weinberg GA, Szilagyi PG. Vaccine epidemiology: efficacy, effectiveness, and the translational research roadmap. J Infect Dis. 2010;201(11):1607-10.
4. Sood N, Simon P, Ebner P, Eichner D, Reynolds J, Bendavid E, et al. Seroprevalence of SARS-CoV-2-Specific Antibodies Among Adults in Los Angeles County, California, on April 10-11, 2020. JAMA. 2020.
5. Silvia Stringhini , Ania Wisniak , Giovanni Piumatti , Andrew S Azman , Stephen A Lauer , Helene Baysson , David De Ridder , Dusan Petrovic , Stephanie Schrempft , KailingMarcus , Isabelle Arm-Vernez , Sabine Yerly , Olivia Keiser , Samia Hurst , Klara Posfay-Barbe , Didier Trono , Didier Pittet , Laurent Getaz , Francois Chappuis , Isabella Eckerle , Nicolas Vuilleumier , Benjamin Meyer , Antoine Flahault , Laurent Kaiser , Idris Guessous. Repeated seroprevalence of anti-SARS-CoV-2 IgG antibodies in a population-based sample from Geneva, Switzerland. medRxiv 2020.05.02.20088898; doi:https://doi.org/10.1101/2020.05.02.20088898..
6. Shoukat A, Wells CR, Langley JM, Singer BH, Galvani AP, Moghadas SM. Projecting demand for critical care beds during COVID-19 outbreaks in Canada. CMAJ. 2020;192(19):E489-E96.
7. Tuite AR, Fisman DN, Greer AL. Mathematical modelling of COVID-19 transmission and mitigation strategies in the population of Ontario, Canada. CMAJ. 2020;192(19):E497-E505.
8. Patrick K, Stanbrook MB, Laupacis A. Social distancing to combat COVID-19: We are all on the front line. CMAJ. 2020;192(19):E516-E7.
9. Hotez PJ, Corry DB, Bottazzi ME. COVID-19 vaccine design: the Janus face of immune enhancement. Nat Rev Immunol. 2020.
10. Tseng CT, Sbrana E, Iwata-Yoshikawa N, Newman PC, Garron T, Atmar RL, et al. Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. PLoS One. 2012;7(4):e35421.
11. Halstead SB. Critique of World Health Organization Recommendation of a Dengue Vaccine. J Infect Dis. 2016;214(12):1793-5.
12. BBC News Philippines gripped by dengue vaccine fears. BBC News, 3 February 2018. https://www.bbc.com/news/world-asia-42929255 . Accessed 26 May 2020. .
13. Korber B, Fischer WM, Gnanakaran S, Yoon H , Theiler J , Abfalterer W, Foley B , Giorgi EE , Bhattacharya T, Parker MD , Partridge DG , Evans CM , Freeman TM , de Silva TI , on behalf of the Sheffield COVID-19 Genomics Group , LaBranche CC , Montefiori DC . Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2

319 . bioRxiv 2020.04.29.069054; doi: https://doi.org/10.1101/2020.04.29.0690
320 54
321 14. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of
322 Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020.
323 15. Amanat F, Krammer F. SARS-CoV-2 Vaccines: Status Report. Immunity.
324 2020;52(4):583-9.
325 16. Cheng MP, Lee TC, Tan DHS, Murthy S. Generating randomized trial
326 evidence to optimize treatment in the COVID-19 pandemic. CMAJ.
327 2020;192(15):E405-E7.
328