CGD Note
DEC 2020

# The COVID-19 Vaccine:
## Do We Know Enough to End the Pandemic?

*Rima Shretta, Ricardo Aguas, Kalipso Chalkidou, Hiral Shah, Francis Ruiz, and Lisa J White*

## SUMMARY

- Preliminary efficacy results from three vaccine candidates currently in Phase 3 trials have shown an efficacy of more than 90% against the development of symptomatic COVID-19. While these results are promising, all vaccines are in relatively early stages of testing.
- It is unclear how heterogeneity of immune responses will influence how different age groups mount induced immune responses. Lower immune responses in target populations and a lack of effectiveness of the vaccine to reduce mortality will hamper its utility in curbing the pandemic.
- There is limited understanding of which immunity factors are good correlates of protection against infection and disease, and ongoing vaccine trials have had an extremely short follow-up period to date.
- Many of the anticipated challenges associated with global-scale vaccination campaigns are related to logistics, most of which have yet to be resolved.
- A comprehensive and transparent roadmap is urgently needed, to determine how limited doses of the first vaccines to be licensed will be distributed, together with which groups will initially be prioritized.

## INTRODUCTION

The SARS-COV-2/COVID-19 pandemic has created an unprecedented public health challenge, spurring a global race to develop and distribute viable vaccines. A vaccine that creates broad immunity against the SARS-COV-2 virus is the only effective means to control the pandemic. There are currently more than 200 vaccine candidates, of which thirteen are undergoing Phase 3 clinical trials [1]. By mid-2021, there will likely be multiple licensed vaccines. Although there is an urgent need for these vaccines to be made available, several critical features of any COVID-19 vaccine must be considered to ensure optimal delivery and impact.

## VACCINE EFFICACY

To understand the potential of any vaccine, its efficacy and duration of protection is critical. The US Food and Drug Administration (FDA) defines success as preventing at least 50% of vaccinated individuals from developing symptomatic COVID-19; the European Medicines Agency (EMA) has not set a minimum standard, although it will conduct rolling analyses following licensure [2]. Preliminary results from three vaccines, being developed by Pfizer, Moderna and AstraZeneca, indicate efficacies of more than 90% at 14 days after the second dose [3, 4]. While promising, these findings are based on small sample sizes across the intervention and control arms. The true efficacy may change as the trial progresses and when larger sample sizes are analyzed.

Of critical importance is the type of protection conferred. The primary endpoint of four vaccine candidates undergoing Phase 3 trials (developed by Pfizer, AstraZeneca, Moderna and Janssen) is symptomatic COVID-19 of any severity [5]. None are designed to detect reductions in hospital admissions, admission to intensive care or death. In addition, older people and those with preexisting conditions who are at highest risk of severe COVID-19 disease typically have lower immune responses to vaccinations; a failure to measure clinical outcomes in these groups will compromise the vaccine's effectiveness for reducing mortality at a population level [6]. Although preliminary results released by Pfizer indicate efficacies of >94% in trial participants aged >65 years, the duration of protection and the variance in different populations is unclear. Unless the endpoints and timelines of the studies are modified, the vaccines may have limited utility among those needing protection the most [7].

Data to estimate vaccine effectiveness against infection are important to estimate potential impacts on transmission and longer-term strategies. However, prevention of infection is not a criterion for success for any of the vaccines for which protocols are currently available. A vaccine with 90% efficacy will require 54%–72% of the population to be vaccinated to confer herd immunity.

## IMMUNITY

As with natural infection, the immune system must detect and respond to the vaccine, and deliver an antigen that the immune system can easily detect and mount an effective and lasting response. Such an adaptive immune response can be characterized by the quantity and 'quality' of two types of lymphocytes: B cells and T cells. The former produce antibodies playing a critical role in the recognition of specific antigens. Vaccines aimed at preventing infection should maximize the production of neutralizing antibodies. While all ongoing trials are investigating the quantities of neutralizing antibodies produced at specific time points following vaccination, only one appears to have infection as a primary endpoint [8]. Experience with vaccine candidates for other coronavirus diseases has also raised concerns about potentially augmenting respiratory disease via antibody-dependent enhancement (ADE), where sub-neutralizing antibodies do not completely neutralize viral particles but instead cause their enhanced uptake. ADE can cause adverse effects and is a concern for COVID-19 vaccines [9].

Ideally, vaccines would provide long-term antibody responses, abrogating the need for repeated booster doses. Neutralizing antibodies are produced for 5 to 7 months following SARS-CoV-2 infection [10], similar to seasonal coronaviruses. However, cases of reinfection with COVID-19 have been reported [11], raising concerns about the prospects for long-term protection. Unfortunately, given the length of the trials, the duration of protection conferred by the vaccine candidates will be difficult to assess.

SARS-CoV-2-specific T cells are detectable in antibody-seronegative individuals with a history of asymptomatic or mild COVID-19, suggesting that previous exposure (possibly also to related coronaviruses) may prevent recurrent episodes of severe COVID-19 [12]. Observational studies suggest a significant number of people not exposed to SARS-CoV-2 exhibit cross-reactive T-cell responses to the virus [13]. While these do not prevent infection, they elicit a faster immune response and reduced risk of severe illness [14]. Heterogeneity of host immune responses is also likely to affect vaccine-induced responses; vaccinated individuals recently exposed to a different coronavirus strain might acquire stronger, longer lasting protective immunity. Conversely, older and/or immunocompromised individuals may respond poorly to a vaccine, with less efficient or more short-lived immune protection.

Along with minimizing infection and disease, vaccines can prevent people who later get infected with the virus from infecting someone else. The transmission of SARS-CoV-2 appears to be related to nasal shedding, which is mediated by mucosal immunity [15]; a vaccine that does not address nasal mucosal immunity may have limited impact on viral transmission. The effect of vaccine candidates on those previously infected also remains to be assessed.

## MANUFACTURING AND DELIVERY

Most COVID-19 vaccine candidates incorporate a protein or genetic material from the virus. Each candidate has different manufacturing requirements and may require novel processes.

At a herd immunity threshold of 70%, assuming two doses are required, manufacturers would need to produce >10 billion doses for the global population. Production considerations include, inter alia, the type of vaccine and its administration, size and location of initial target populations, number of doses needed, and storage requirements. Several countries have signed advance market commitments with manufacturers, to secure doses once available. However, the contract terms are confidential and details around procurement and delivery unclear.

Vaccine production is part of a complex system – to work, vaccines must reach the population. Vaccine supply chains involve numerous factors that must be carefully coordinated. Many vaccines are highly sensitive to temperature and must be stored accordingly. Two vaccine candidates require storage at between -75°C and -20°C [3, 4], a logistical and cost challenge. It is crucial to understand existing supply chains for immunization programmes, historical vaccine distribution strategies, anticipated capacity, and an assessment of the ability to receive, store and distribute large quantities of vaccine. Evaluating a country's ability to provide cold-chain storage and relevant supplies, such as personal protective equipment, will be necessary. Optimizing supply chains through integration or other means will be essential to ensure delivery of COVID-19 vaccines. Other aspects of programmatic feasibility (e.g. available delivery platforms, human resource requirements, feasibility of identifying/accessing target populations), vaccine acceptance and demand (e.g. knowledge, attitudes and behaviours of vaccine recipients, caregivers and providers) will also be needed.

FDA Emergency Use Authorization allows fast-track registration of a vaccine. If such authorization is granted, a manufacturer can 'unblind' a trial and begin vaccinating individuals in the control arm. Other vaccines in development would risk switching to 'non-inferiority trials' to show that theirs are not less effective than the first approved vaccine, creating a de facto monopoly. Participants from other trials may also choose to get vaccinated with an vaccine.

## PRIORITIZATION

Any vaccine delivery strategy must prioritize those at higher risk of infection before it is made available more widely. Planning documents call for health care workers, public safety personnel, and vulnerable populations to receive the first vaccine batches [16]. However, the need to vaccinate the most vulnerable could ultimately undermine its purpose. The breadth of vaccine alternatives suggests some will be superior in efficacy, safety or ease of delivery. If the first vaccine to be licensed is given to those at higher risk, we could be dictating that these high-risk groups will not receive a subsequently released, potentially safer or more cost-effective vaccine [6]. The type of protection will also influence which groups are prioritized. A vaccine that prevents progression to severe disease requires high-risk groups to be prioritized over health workers, who can still carry and transmit the virus. Conversely, infection-blocking vaccines could potentially be delivered to high-contact groups to provide indirect protection to non-vaccinated individuals. This will, however, risk adverse events in those at least risk from the disease. These groups will also need to be identified and vaccinated at very high coverage rates. Such a strategy would be ethical only if the vaccine had negligible efficacy in risk groups, given their elevated risk of severe disease.

Prioritization should also be based on cost-effectiveness throughout the value chain, as part of a strategy to optimize the policy mix in particular settings. Consideration of the economic costs of strategies is critical given the potential cost and limited availability, particularly of first-generation vaccines.

The COVID-19 vaccine Global Access Facility (COVAX) aims is to secure vaccine doses and allocate them equitably in lower income countries. However, the facility is currently under-resourced. Decisions about how priority groups will be identified must be clearly and transparently.

## CONCLUSION

Vaccine roll-out programmes must include increased monitoring, including regular testing of vaccinees to look for asymptomatic infections. A large-scale, Phase 4 monitoring trial of vaccine safety and efficacy will be critical to fill knowledge gaps.

*On 2nd December, 2020, the UK government accepted the recommendation from the Medicines and Healthcare products Regulatory Agency (MHRA) to grant emergency authorization of the Pfizer-BioNTech's Covid-19 vaccine. About 800,000 doses of the vaccine are expected to be in place for the start of the immunization program with elderly people in care homes and medical workers being prioritized on Tuesday 8th December. Emergency use approval is under consideration by the US FDA.*

### Author Contributions

RS and LJW conceived the paper. RS wrote the first draft of the paper. All authors revised subsequent drafts and agree with the final version.


### Acknowledgements

This work was supported by the COVID-19 Research Response Fund, managed by the Medical Sciences Division, University of Oxford. LJW is supported by the Li Ka Shing Foundation. The authors declare no competing interests. Thank you to Y-Ling Chi for the review and Adam Bodley for editorial support.

## REFERENCES


1. Milken Institute. Covid19 Tracker. 2020; Available from: https://covid-19tracker.milkeninstitute.org/.

2. Guarascio, F., EU watchdog won't set minimum efficacy levels for potential COVID-19 vaccines. 2020, Reuters: Brussels.

3. Pfizer, Pfizer and Biontech announce vaccine candidate against COVID-19 achieved success in first interim analysis from phase 3 study. 2020, Pfizer: New York.

4. Gallagher, J., Moderna: Covid vaccine shows nearly 95% protection. 2020, BBC: London.

5. Haseltine, W. Covid-19 Vaccine Protocols Reveal That Trials Are Designed To Succeed. 2020 September 23, 2020; Available from: https://www.forbes.com/sites/williamhaseltine/2020/09/23/covid-19-vaccine-protocols-reveal-that-trials-are-designed-to-succeed/?sh=1e6e5dc85247.

6. Chen, Y., et al., A comprehensive, longitudinal analysis of humoral responses specific to four recombinant antigens of SARS-CoV-2 in severe and non-severe COVID-19 patients. PLoS Pathog, 2020. 16(9): p. e1008796.

7. BBC Covid vaccine: Pfizer says '94% effective in over-65s'. 2020.

8. Ramasamy, M.N., et al., Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. The Lancet.

9. Buchbinder, S.P., et al., Use of adenovirus type-5 vectored vaccines: a cautionary tale. The Lancet.

10. Ripperger, T.J., et al., Orthogonal SARS-CoV-2 Serological Assays Enable Surveillance of Low Prevalence Communities and Reveal Durable Humoral Immunity. Immunity, 2020.

11. Iwasaki, A., What reinfections mean for COVID-19. Lancet Infect Dis, 2020.

12. Sekine, T., et al., Robust T Cell Immunity in Convalescent Individuals with Asymptomatic or Mild COVID-19. Cell, 2020. 183(1): p. 158-168.e14.

13. Altmann, D.M. and R.J. Boyton, SARS-CoV-2 T cell immunity: Specificity, function, durability, and role in protection. Science Immunology, 2020. 5(49): p. eabd6160.

14. Grifoni, A., et al., Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. Cell, 2020. 181(7): p. 1489-1501.e15.

15. Begum, J., et al., Challenges and prospects of COVID-19 vaccine development based on the progress made in SARS and MERS vaccine development. Transboundary and Emerging Diseases, 2020.

16. Huang, C., et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 2020. 395(10223): p. 497-506.


**WWW.CGDEV.ORG**



**RIMA SHRETTA** Nuffield Department of Medicine, University of Oxford.

**RICARDO AGUAS** Nuffield Department of Medicine, University of Oxford and Mahidol Oxford Tropical Medicine Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University.

**KALIPSO CHALKIDOU** Center for Global Development and Global Health Development Group, Imperial College London.

**HIRAL SHAH** Center for Global Development.

**FRANCIS RUIZ** Global Health Development Group, Imperial College London.

**LISA J WHITE** Big Data Institute, Li Ka Shing Centre for Health Information and Discovery and Nuffield Department of Medicine, University of Oxford.