

VIEWPOINT

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Multimedia

COVID-19 in 2021—Continuing Uncertainty

More than a year has passed since the first confirmed case of SARS-CoV-2 infection in the US was reported on January 20, 2020. What followed was an unprecedented year with nearly 30 million documented infections and more than 500 000 excess deaths in the US due to SARS-CoV-2. Alongside this devastation is the successful development and deployment of multiple safe and effective vaccines.¹

To date, almost 80 million doses of vaccine have been administered in the US with some experts suggesting that the extent of disease, including the number of deaths, will continue to decline between now and summer. Yet moving to the next phase of the pandemic remains a challenge; clinicians and patients have many questions that may not have clear answers. This Viewpoint summarizes the current best evidence to some of these complex questions.

Which Vaccine Is Best and How Should They Be Deployed? Currently, 2 mRNA vaccines (created by Pfizer-BioNTech and Moderna) and 1 adenovirus-vectored vaccine (Janssen/Johnson & Johnson) have received Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA). These vaccines have proven to be safe and highly effective in preventing severe COVID-19 and death and likely also prevent transmission.¹

The Janssen vaccine is the first adenovirus-vectored vaccine to be evaluated and to receive EUA by the FDA. This vaccine uses a cold virus (Ad26) engineered to carry the genetic code of the SARS-CoV-2 spike protein. As a single-dose vaccine, it offers practical advantages in terms of deployment and scale-up. However, comparing the different vaccines is more difficult with respect to efficacy. The 2 mRNA vaccines have similar efficacy of approximately 95% for the prevention of symptomatic COVID-19 and nearly 100% efficacy in preventing death from COVID-19 after 2 doses.¹ However, neither of these vaccines were tested when more recently identified SARS-CoV-2 variants like B.1.1.7 and B.1.135 were the predominant ones in circulation. The Janssen vaccine was 66% protective against moderate to severe COVID-19 although this varied by geographic location: 72% protective in the US while only 57% protective in South Africa, reflecting the various variants in each country.² However, the vaccine was 85% protective against severe disease and 100% protective against hospitalization and death from COVID-19 without geographic differences.²

At present, given the differences between the 3 vaccines, which vaccine should individuals receive? Initially the answer is that they should receive whichever vaccine is available when they become eligible. However, as supplies become less of a limitation, it may be that for groups with higher risk of severe disease and complications (eg, older adults, immunocompromised people), the mRNA vaccines would provide an advan-

tage, whereas for younger populations, and those who have difficulty returning for a second injection, the Janssen single-dose vaccine may be preferable.

Do Vaccines Protect Against Infection and Prevent Transmission? Having COVID-19 vaccines that prevent infection and transmission will be critical to stopping the pandemic, but there is not yet clear evidence that this occurs. Protection against transmission may be difficult to prove because a decline in infections may be due to multiple factors. Preliminary data from phase 3 trials suggest some reduction in asymptomatic infection after vaccination. Early results from Israel suggest a decline in infections and symptomatic disease after vaccination.³ It would be unusual if the vaccines did not prevent infection, but the extent of protection is unknown.

What Is the Best Way to Address Vaccine Hesitancy? Vaccine hesitancy refers to delay in acceptance or refusal of vaccination despite availability of vaccine services. Several factors contribute to the hesitance including the compulsory nature of vaccines, their coincidental temporal relationship with adverse health outcomes, unfamiliarity with vaccine-preventable diseases, and lack of trust in corporations and government public health agencies.⁴ In a survey of 1676 US adults conducted in December 2020, approximately 27% of the public remained vaccine hesitant, saying they *probably* or *definitely* would not get a COVID-19 vaccine even if it were available for free and deemed safe by scientists.⁵ Vaccine hesitancy was highest among those who identified as Republicans (42%), those aged 30 to 49 years (36%), and rural residents (35%). Importantly, 35% of Black adults said they definitely or probably would not get vaccinated.

Addressing vaccine hesitancy starts with explaining the technology (mRNA or adenovirus vector), addressing safety concerns (eg, mRNA does not affect a person's genetics), and countering misinformation and conspiracy theories. However, foremost, it requires cultivating trust within the community and recognizing that for Black people in the US in particular, hesitancy may be rooted in a long history of mistreatment and disrespect by the health care system.

What Is Safe for People to Do Once Fully Vaccinated? The Centers for Disease Control and Prevention (CDC) has indicated that 14 days after receiving the second dose of a COVID-19 vaccine, and for a period of 3 months, fully vaccinated people no longer need to quarantine after being exposed to someone with COVID-19.⁶ While it is likely safe to socialize with others who are fully vaccinated, vaccinated individuals should continue to wear a face mask and to follow other public health guidance, such as maintaining social distancing, or meeting outdoors or in a room with good ventilation. For now, large indoor gatherings and crowds should be avoided.

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Are the Current Vaccines Effective Against New Variants? As long as SARS-CoV-2 continues to spread, mutations will occur and new variants will emerge. Among the dominant variants currently in circulation, data suggest that the mRNA-1273 vaccine (Moderna) effectively neutralizes the B.1.1.7 (emerging in the UK) variant but that there is a decrease of neutralization ability to the B.1.351 variant (emerging in South Africa).⁷ The data from clinical trials are more limited but in the Novavax phase 3 trial conducted in the UK where the B.1.1.7 variant had become dominant, the vaccine was 89% effective while in South Africa, where there was a predominance of the B.1.351 variant, the efficacy was 60%.⁸ Data from Israel suggest that the BNT 162b2 (Pfizer-BioNTech) vaccine is effective at the population level in a country where the B.1.1.7 variant is now predominant.³

How Long Can People Wait Between Doses? Can Vaccines Be Mixed and Matched? Given that the current supply of vaccines remains limited, some have suggested delaying the second vaccination to provide at least 1 dose to a larger number of people. The UK government decided to delay the second dose of the Pfizer-BioNTech vaccine until 12 weeks after the first dose instead of following the recommended dosing interval of 21 days.⁹ The CDC has indicated that the second immunization can be administered up to 42 days, or 6 weeks, after the initial inoculation.⁶ Concern has been raised that lengthening the time between vaccines will leave individuals with longer periods of time with only partial protection and might contribute to the emergence of additional variants.⁷

As additional vaccines are expected to become available soon, should people get the second dose with the same vaccine they got their first or can they “mix and match”? There are currently no data to either support or not support doing this. The CDC has discouraged people from mixing vaccines unless there are “exceptional situations.” It is possible that mixing vaccines could boost protection against COVID-19 and several studies are underway to examine various combinations. Until those results are available, the recommendation remains to get a second vaccination with the same vaccine as the first dose.

What Happens if Individuals Receive Only 1 Dose? The clinical trials of both Pfizer and Moderna vaccines were performed with 2 inoculations separated by either 21 or 28 days. In persons who have already had COVID-19, a single vaccine dose produces a robust antibody response akin to a second dose.¹⁰ However, currently there

is not a recommendation for a single dose for those with prior infection, and the recommendation to complete the vaccination series is primarily due to concern for the emergence of variants.

In a small study that evaluated the immune response to the first vaccine dose in persons with a prior history of COVID-19 the investigators found high levels of antibodies comparable to those seen in persons with no history of COVID-19 after 2 doses. These results raise the possibility that 1 dose might be sufficient for those previously infected with SARS-CoV-2 who have already generated antibodies against the virus. While this is certainly intriguing, the implementation may be challenging as antibody levels would have to be checked prior to vaccination. Until more data are available, everyone who receives the available mRNA vaccines should receive 2 doses.

How Long Will Immunity Last? Like most vaccines, the COVID-19 vaccines have multiple mechanisms for preventing infection. The first involves the production of antibodies; the second involves the induction of responses in memory T cells. While it is unclear how long immunity after vaccination will last, follow-up booster shots may be required given growing evidence of viral evolution and new variants.

Will COVID-19 Become Endemic? It is likely that in the next few months COVID-19 will be eliminated from some countries but will continue in others. Long-term SARS-CoV-2 may become endemic or seasonal with outbreaks during winter months.

Conclusions

The world has transformed in the past year and some aspects of life may remain changed forever. COVID-19 may reoccur seasonally, like other respiratory viruses, most notably influenza. In addition, a substantial number of patients with post-COVID syndromes will experience various degrees of disabilities and symptoms for years. Infection risk aside, it will be essential for public health agencies and society to develop ways to safely continue essential activities, including in-person learning in the K-12 and higher education space. Social gatherings, sporting events, and other community activities will undoubtedly resume but some restrictions will continue depending on evidence of community spread, the proportion of individuals vaccinated, and other factors that will need to be monitored regularly as individuals, institutions, and governments all perform calculations to balance competing risks.

ARTICLE INFORMATION

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REFERENCES

1. Creech CB, Walker SC, Samuels RJ. SARS-CoV-2 vaccines. *JAMA*. Published online February 26, 2021.
2. US FDA Vaccines and Related Biological Products Advisory Committee February 26, 2021 meeting announcement. <https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-february-26-2021-meeting-announcement>
3. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med*. Published online February 24, 2021. doi:10.1056/NEJMoa2101765
4. Salmon DA, Dudley MZ, Glanz JM, Omer SB. Vaccine hesitancy: causes, consequences, and a call to action. *Am J Prev Med*. 2015;49(6)(suppl 4):S391-S398. doi:10.1016/j.amepre.2015.06.009
5. Hamel L, Kirzinger A, Muñana C, Brodie M. KFF COVID-19 vaccine monitor: December 2020. Accessed February 25, 2021. <https://www.kff.org/coronavirus-covid-19/report/kff-covid-19-vaccine-monitor-december-2020/>
6. CDC. Interim clinical considerations for use of mRNA COVID-19 vaccines currently authorized in the United States. Accessed February 24, 2021. <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html>
7. Moore JP, Offit PA. SARS-CoV-2 vaccines and the growing threat of viral variants. *JAMA*. Published online January 28, 2021. doi:10.1001/jama.2021.1114
8. Novavax COVID-19 vaccine demonstrates 89.3% efficacy in U.K. phase 3 trial. January 28, 2021. <https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3>
9. Iacobucci G, Mahase E. Covid-19 vaccination: what's the evidence for extending the dosing interval? *BMJ*. 2021;372(n18):n18. doi:10.1136/bmj.n18
10. Krammer F, Srivastava K, the PARIS team, Simon V. Robust spike antibody responses and increased reactogenicity in seropositive individuals after a single dose of SARS-CoV-2 mRNA vaccine. *medRxiv*. Preprint published online February 1, 2021. doi:10.1101/2021.01.29.21250653