Real-Time Learning Network Vaccines FAQ

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Featured FAQs

Q: What is the rationale and evidence for administering COVID-19 vaccine boosters?

Booster doses of COVID-19 vaccines are one potential strategy to address the issue of waning immunity. The role of booster doses in this context relies on several assumptions, for which there is emerging supportive evidence:

Immune responses to SARS-CoV-2 vaccines have waned.

> Evidence:
> There is now extensive evidence that COVID-19 vaccine-induced antibodies decrease over time. One study compared the kinetics of humoral and cellular responses between recipients of the Pfizer-BioNTech, Moderna and Johnson & Johnson/Janssen COVID-19 vaccines. In this study, the mRNA COVID-19 vaccines elicited robust neutralizing antibody responses shortly after vaccination that then decayed significantly over 8 months (Collier, October 2021).
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> In another prospective 6-month longitudinal immunogenicity study of nearly 5,000 health care workers aged 18 years and older at Sheba Medical Center in Israel who received two doses of the Pfizer-BioNTech COVID-19 vaccine, anti–SARS-CoV-2 spike antibody titers reached their peak between days 4 and 30 after the second dose of vaccine, then consistently declined over the entire study period, ultimately decreasing by a factor of 18.3 after 6 months. Neutralizing antibodies also decreased, but the rate of decline slowed after 3 months (Levin, October 2021).
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> Limitations:
> Declines in antibody concentrations may not correlate with a decrement in memory responses, which may be more relevant for protection against severe disease. In a longitudinal study of humoral and cell-mediated immune responses to SARS-CoV-2 following mRNA COVID-19 vaccination (mostly the Pfizer-BioNTech COVID-19 vaccine), although anti-spike antibodies waned over 6 months, memory B- and T-cell responses were durable over the same time period (Goel, October 2021).
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> Furthermore, decrements in antibody responses demonstrate an imperfect correlation with waning clinical protection. As an example, in longitudinal immunogenicity and efficacy analyses of data from the Phase 1-3 clinical trials of the Pfizer-BioNTech COVID-19 vaccine, neutralizing antibody titers against wildtype SARS-CoV-2 decreased 6- to 13-fold over the 8 months after the second dose of vaccine (Falsey, September 2021). Vaccine efficacy against symptomatic infection did decrease from 96% to 84% but remained >96% against severe COVID-19 (Thomas, September 2021).

Waning immunity is (or is predicted to be) a significant driver of breakthrough infections, and in particular, severe cases.

> Evidence:
> There is accumulating evidence that neutralizing antibody concentrations correlate with the risk for symptomatic SARS-CoV-2 infection. For example, in a prospective cohort study of vaccinated health care workers in Israel, investigators identified 39 episodes of breakthrough infection for

which preinfection neutralizing antibody concentrations were available. When compared with matched individuals who did not experience breakthrough infection, those who experienced breakthrough had lower concentrations of neutralizing antibodies (Bergwerk, July 2021). One study incorporated the observed kinetics of antibody decay following SARS-CoV-2 vaccines to model COVID-19 vaccine effectiveness over time and predicted a decline in vaccine effectiveness by 6 months (Khoury, July 2021). Multiple population-based vaccine effectiveness studies have since shown that mRNA COVID-19 vaccine effectiveness against symptomatic infection decreases with increasing time since vaccination, including in the U.S. (Self, September 2021; Fowlkes, August 2021; Tartof, October 2021), UK (Pouwels, October 2021; Public Health England report, September 2021) and Israel (Mizrahi, November 2021; Goldberg, October 2021). In addition, in a 6-month follow-up study of participants in the multinational Phase 2/3 trial of the Pfizer-BioNTech COVID-19 vaccine, before the emergence of the Delta variant, vaccine efficacy against infection had decreased to 84% by 6 months (Thomas, September 2021).

Limitations:
In all these studies, vaccine effectiveness against severe disease has remained high (>90%), even in the context of widespread circulation of the Delta variant. Additionally, the follow-up period for most of these studies also coincided with a relaxation of control measures (e.g., masking, social distancing, etc.) which may differentially impact the likelihood of exposure among vaccinated and unvaccinated individuals, and there may have been other important baseline differences between the groups who were vaccinated at different times that influenced their likelihood of infection.

Booster doses meaningfully augment immune responses (quantitatively or qualitatively) against SARS-CoV-2 (and relevant variants).

Data for augmented immune responses following booster doses come from a small number of studies. In a substudy of the Phase I clinical trial of the Pfizer-BioNTech COVID-19 vaccine, 23 participants received a booster dose of the vaccine at approximately 8 months after completion of the primary series. One month after the booster dose, neutralizing antibody titers against both wildtype virus and the Beta (B.1.351) and Delta (B.1.617.2) variants had increased to levels higher than at one month after the primary series (Falsey, September 2021).

These and other data were also presented for review by the Vaccines and Related Biological Products Advisory Committee in response to Pfizer's biologics license application supplement seeking approval for a booster dose of its COVID-19 vaccine. A press release from Moderna described a study of 344 participants enrolled in a Phase 2 study of the Moderna COVID-19 vaccine who received a 50 μg booster dose at 6 months following completion of the primary series. In this press release, neutralizing antibody titers following the booster dose were reported to exceed those described in the Phase 3 trial. Additionally, the booster dose elicited robust antibody responses against SARS-CoV-2 variants of concern, including Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2).

Finally, an interim analysis of a multicenter trial conducted at 10 sites in the U.S. reported immune responses following heterologous and homologous booster doses among >400 participants who had previously been vaccinated with either two doses of an mRNA COVID-19

vaccine or one dose of the Johnson & Johnson/Janssen COVID-19 vaccine (at least 12 weeks earlier). In this study, a booster dose with any product augmented antibody concentrations, but heterologous boosts ("mixed" regimens) elicited a more robust response than homologous boosts ("matched" regimens) (Atmar, October 2021 – preprint, not peer-reviewed).

Limitations:
The durability of these augmented immune responses is unknown. In a longitudinal study of immune responses to SARS-CoV-2 following mRNA COVID-19 vaccination (mostly the Pfizer-BioNTech COVID-19 vaccine), the investigators separately analyzed the kinetics of the immune response in individuals with and without prior SARS-CoV-2 infection. For those with prior infection, the primary vaccine series may be considered a "booster." In this group, antibody, memory B-cell and T-cell responses were augmented by vaccination but had declined nearly back to baseline by 6 months (Goel, October 2021).

These augmented immune responses translate into increased vaccine effectiveness against SARS-CoV-2 infection and severe disease.

Evidence:
Only one published study has evaluated the clinical effectiveness of a COVID-19 vaccine booster dose. In a retrospective cohort study of vaccinated individuals in Israel (which approved booster doses of the Pfizer-BioNTech COVID-19 vaccine for individuals aged 60 years and older who had completed their primary vaccine series at least 5 months earlier), investigators analyzed the rates of COVID-19 among those who had and those who had not received a booster dose. Israel began administering booster doses on July 30, 2021, and the follow-up period of this study ended on August 30, 2021 (for severe COVID-19 the end date was August 26, 2021). The investigators limited the primary analysis of COVID-19 illnesses to those that occurred at least 12 days after the booster dose. Thus, the maximum possible follow-up period for any given individual was 20 days. Overall, the investigators found a lower rate of confirmed infection in the booster group (by a factor of 11.3, 95% CI, 10.4-12.3), as well as a lower rate of severe illness in the booster group (by a factor of 19.5, 95% CI, 12.9-29.5) (Bar-On, September 2021).

Limitations:
The durability of this improvement in vaccine effectiveness is unknown. Additionally, whether younger age groups experience a similar benefit from booster vaccination is unclear.

Q: What is waning immunity and how do we know if it is occurring?

Waning immunity refers to a phenomenon where an individual's initial immune response to a vaccine diminishes over time and thus makes them vulnerable to natural infection (despite vaccination), often referred to as "breakthrough infection." There is now extensive evidence that COVID-19 vaccine-induced antibodies decrease over time. However, this may have varying implications for clinical protection against symptomatic SARS-CoV-2 infection and severe COVID-19.

Evidence for whether waning immunity is leading to "waning protection" is almost always indirect because there are many factors that can influence vaccine effectiveness over time that are independent of waning immune responses. In fact, observations of waning protection, which may be suggested by lower population-level vaccine effectiveness estimates over time or rates of breakthrough infection out of proportion to what is expected, need not be attributable to waning immune responses.

Other factors that can contribute to time-dependent estimates of vaccine effectiveness include:

Changes in behavior, policy or local disease epidemiology that influence the "force of infection" (likelihood of being exposed/infected) over time. This means that the vaccine efficacy estimates determined in clinical trials are not fixed characteristics of the vaccines and cannot be extrapolated to all contexts.

Evolution of the pathogen that results in diminished protection conferred by vaccine-induced immune responses, such as novel variants. In other words, vaccine-induced immunity may be preserved, but may be less effective against a different version of the pathogen.

Differences in the comparison groups used to estimate vaccine effectiveness – for example, the unvaccinated population may experience fewer cases because it has a higher level of immunity (than what is assumed) because of natural infections that have accumulated over time; alternatively, individuals who were vaccinated earlier in the pandemic may differ from more recent vaccinees in their likelihood to have a poor initial response to the vaccine or to be exposed to SARS-CoV-2.

These issues are relevant because the relative contribution of these factors should inform the optimal use of vaccine "boosters" at a population level.

The key studies that contribute to our current understanding of waning protection, and their limitations, are summarized here:

Population-level evidence of decreasing vaccine effectiveness over calendar time

Several population-level observational studies have shown that COVID-19 vaccine effectiveness against infection has decreased over time (or that the incidence rate of SARS-CoV-2 infections in vaccinated individuals has increased over time) since the vaccines were first introduced (Rosenberg, September 2021; Scobie, September 2021; Fowlkes, August 2021; Nanduri, August 2021; Keehner, September 2021). Importantly, many of these same studies (and others) have shown that vaccine effectiveness against severe COVID-19 has remained stable (Bajema, September 2021; Tenforde, August 2021). Given that the follow-up period for these studies spanned the time period when the Delta variant emerged, several of these studies stratified

their analysis by time period, calculating vaccine effectiveness before and after Delta became predominant. In these analyses, vaccine effectiveness was essentially preserved (compared with vaccine efficacy estimates from clinical trials) before the emergence of Delta but decreased following the emergence of Delta.

Key limitations: None of these studies adjusted their VE estimates by time since vaccination, none computed SARS-CoV-2 variant-specific VE estimates, and the follow-up period for all these studies also coincided with a relaxation of control measures (e.g., masking, social distancing, etc.).

Individual-level evidence of decreasing vaccine effectiveness by time since vaccination

Some studies have specifically evaluated the potential role of waning immunity by stratifying VE calculations by time since vaccination. Studies from the U.S. (Self, September 2021; Fowlkes, August 2021; Tartof, October 2021), UK (Pouwels, October 2021; Public Health England report, September 2021) and Israel (Mizrahi, July 2021 – preprint, not peer-reviewed; Goldberg, August 2021 – preprint, not peer-reviewed) all suggest that a longer time period since the second dose of an mRNA COVID-19 vaccine is associated with decreased VE against symptomatic infection. Notably, VE against severe disease appears essentially preserved. In addition, in a 6-month follow-up study of participants in the multinational Phase 3 trial of the Pfizer-BioNTech COVID-19 vaccine, before the emergence of the Delta variant, VE against infection had decreased to 84% by 6 months, but VE against severe disease remained >90% (Thomas, September 2021).

Key limitations: Not all these studies computed SARS-CoV-2 variant-specific VE estimates, the follow-up period for most of these studies also coincided with a relaxation of control measures (e.g., masking, social distancing, etc.), and there may have been important differences between the groups who were vaccinated at different times that influenced their likelihood of infection.

Q: What is known about SARS-CoV-2 variants "Delta plus" (also known as Delta with K417N), Lambda and Mu?

Although the Delta variant (B.1.617.2) has become the dominant SARS-CoV-2 variant in many countries, while SARS-CoV-2 continues to circulate worldwide, new variants will continue to emerge.

The "Delta plus" variant is a sublineage of the Delta variant (Pango lineage B.1.617.2 AY1) that was first identified in June 2021 in India. The Delta plus variant has been identified in multiple countries, but its prevalence remains low compared with the parent lineage (B.1.617.2). This variant contains the same mutations as the Delta variant plus an additional mutation in the spike protein, K417N, which had previously been identified in the Beta (B.1.351) and Gamma (P.1.) lineages. Mutations at this site are predicted to result in decreased antibody binding to the spike protein, though not to the same degree as other mutations such as E484K, and have been associated with decreased neutralization by monoclonal antibodies from both convalescent and postvaccination sera (Harvey, June 2021; Wang, April 2021).

The Lambda variant (Pango lineage C.37) was first identified in November 2020 in Peru, where it is now the dominant variant. It has since been identified in multiple countries, but its prevalence outside of Peru remains low. This variant contains multiple unique mutations, including L452Q. Mutations at this position (including L452R in Delta) have been associated with decreased neutralization by monoclonal antibodies and convalescent sera (Liu, March 2021).

The Mu variant (Pango lineage B.1.621) was first identified in January 2021 in Colombia. It has since been identified in multiple countries, but its prevalence outside of Colombia remains low. This variant contains two key mutations, N501Y and E484K, that overlap with the Beta and Gamma variants of concern, which confer decreased susceptibility to neutralization by monoclonal antibodies, as well as convalescent and postvaccination sera (Harvey, June 2021; Wang, April 2021).

Notably, the Delta plus, Lambda, and Mu variants have not risen to the level of Variant of Concern designation by WHO or CDC. To date, there are no clinical data about the clinical effectiveness of monoclonal antibodies or currently authorized COVID-19 vaccines against these variants.

Q: What is known about "mixing and matching" vaccine doses of different types?
In the U. S., FDA has authorized the use of heterologous (or "mix and match") booster doses for currently available COVID-19 vaccines (i.e., FDA-authorized or approved).

To date, only one study has evaluated the immunogenicity of mixed schedules that include currently authorized mRNA vaccines (Pfizer-BioNTech or Moderna) and the Johnson & Johnson/Janssen COVID-19 vaccine. In this multicenter trial conducted at 10 sites in the U.S., participants who had previously been vaccinated with either two doses of an mRNA COVID-19 vaccine or one dose of the Johnson & Johnson/Janssen COVID-19 vaccine (at least 12 weeks earlier) received a booster dose of vaccine of either the same or a different product. A booster dose with any product augmented antibody concentrations, but heterologous boosts ("mixed" regimens) elicited a more robust response than homologous boosts ("matched" regimens) (Atmar, October 2021 – preprint, not peer-reviewed).

Several studies outside the U.S. have evaluated heterologous schedules containing mRNA vaccines and the Oxford-AstraZeneca COVID-19 vaccine, though the time between the first and second dose of vaccine in these studies has been variable. Most of these studies have concluded that a two-dose schedule that includes both vaccines, in either order, generates a robust antibody and cellular response, compared with a single dose of either vaccine. Furthermore, in the studies where a heterologous and homologous (i.e., containing two doses of the same vaccine product) were directly compared, the safety profile and immune responses with both schedules appeared to be similar (Borobia, June 2021; Shaw, May 2021; Liu, August 2021; Ostadgavahi, May 2021; Hillus, June 2021 - preprint, not peer-reviewed ; Schmidt, June 2021 –preprint, not peer reviewed; Tenbusch, July 2021; Dimeglio, August 2021). Similar to the study in the U.S., in one study, a heterologous schedule containing the Oxford-AstraZeneca and Pfizer-BioNTech COVID-19 vaccines elicited a more robust cellular response and higher neutralizing antibody titers against SARS-CoV-2 variants than a homologous schedule containing two doses of the Oxford-AstraZeneca vaccine (Barros-Martins, July 2021).

Mechanisms of COVID-19 Vaccines

Q: What are mRNA vaccines and how do they work?
A: mRNA vaccines contain messenger RNA, a single-stranded RNA molecule that encodes the vaccine antigen, or protein that elicits a protective immune response. Messenger RNA is normally created in the nucleus when DNA is transcribed by RNA polymerase to create pre-mRNA (Zipursky, 2000). Pre-mRNA is then spliced (segments are removed/rearranged) into mRNA, which is exported from the nucleus to the cytoplasm and "read" by ribosomes (the translation machinery of cells). Ribosomes then make proteins.

mRNA vaccines use lipid nanoparticles to deliver lab-created mRNA directly to the cytoplasm. Once the vaccine mRNA is in the cytoplasm, ribosomes can translate it, which results in the creation of a protein antigen that triggers an immune response (Schlake, November 2020). The vaccine mRNA does not enter the nucleus, and therefore cannot be incorporated into the genome. Its presence in the cell is transient, and it is quickly metabolized and eliminated via cellular processing mechanisms (Pardi, November 2015). Unlike conventional vaccines, which can take months to produce, mRNA vaccines can be created quickly and are more easily scaled because they use an organism's genetic code.

Two mRNA vaccines are available under emergency use authorization by FDA: the Pfizer-BioNTech COVID-19 vaccine and the Moderna COVID-19 vaccine, the latter of which was developed in partnership

with the National Institute of Allergy and Infectious Diseases. Both vaccines are lipid nanoparticle-formulated, nucleoside-modified mRNA vaccines encoding the prefusion spike glycoprotein of SARS-CoV-2, the virus that causes COVID-19. A third mRNA vaccine, CVnCoV, has been developed by CureVac and is currently being evaluated in a Phase 3 clinical trial.

Q: Can the vaccine mRNA alter cellular DNA or RNA?

A: No. For the vaccine mRNA to alter someone's DNA, several events would need to occur. First, the vaccine mRNA would need to enter the cell nucleus, where DNA resides. However, vaccine mRNA does not have the nuclear access signals that would allow it to enter the nucleus — it can't get in. Second, even if it made it into the nucleus, the mRNA would have to be converted to DNA. This would require an enzyme called reverse transcriptase, which the mRNA vaccines (and human cells) don't contain. Third, an enzyme (such as integrase) would be needed for DNA derived from the vaccine mRNA to insert itself into cellular DNA; the mRNA vaccines don't contain such an enzyme.

The vaccine mRNA also cannot alter cellular RNA. The vaccine mRNA is delivered to the cytoplasm, where it is translated by ribosomes, resulting in the creation of the SARS-CoV-2 spike protein. The vaccine does not contain any splicing enzymes and the mRNA does not encode any proteins that would allow for RNA modification. Furthermore, the vaccine mRNA is not self-amplifying and cannot be transferred from cell to cell. Following translation, it is rapidly degraded. The vaccine mRNA remains in the cell cytoplasm for just a few days before it is destroyed (Pardi, November 2015). Of note, there are more than 200,000 cellular mRNAs per cell, each making a host of proteins and enzymes. The mRNA vaccines introduce only a few copies of mRNA into cells.

In short, the mRNA vaccines lack all of the basic requirements necessary to alter DNA or RNA.

Q: What are viral vector vaccines and how do they work?

A: Viral vector vaccines utilize viruses to deliver genes that encode vaccine antigens into host cells (Vrba, November 2020). Genes of a pathogen — typically those that code for specific antigens that elicit a protective immune response — are first inserted into the genome of a viral vector. The vector is a virus different from the one the vaccine is targeting (for example, an adenovirus). The vaccine delivers the vector, which infects host cells; DNA virus vectors (like adenoviruses) then travel to the nucleus. In the nucleus, the genes of the pathogen are expressed, resulting in the creation of the antigen. The antigen is then expressed on the host cell surface, resulting in the induction of an immune response.

Viral vector vaccines can be replicating or nonreplicating:

- Replicating viral vector vaccines infect cells, resulting in the production of the vaccine antigen. The viral vector is also produced and is then able to infect new cells, which then create more viral antigen. The only currently licensed replication-competent vaccines are the recombinant vesicular stomatitis virus (rVSV)-Zaire Ebola virus vaccine and the live attenuated tetravalent dengue vaccine.
- Nonreplicating viral vector vaccines infect cells, resulting in the production of the vaccine antigen, but the viral vector cannot be reproduced (van Riel, July 2020). Several COVID-19 vaccines are based on this technology, including the Johnson & Johnson/Janssen, Oxford-AstraZeneca and Gam-COVID-Vac (Sputnik V) vaccines.

The Johnson & Johnson/Janssen COVID-19 is the only viral vector vaccine currently available in the U.S. under emergency use authorization by FDA. This vaccine uses a human adenovirus, Ad26, as the viral vector, and encodes for a stabilized variant of the SARS-CoV-2 spike protein.

The Oxford-AstraZeneca COVID-19 vaccine is another viral vector vaccine that has been authorized for use in many countries. This vaccine uses a chimpanzee adenovirus (ChAdOx1, which is based on ChAdY25) as the viral vector. It encodes for the spike protein of SARS-CoV-2. Finally, the Gam-COVID-Vac vaccine (Sputnik V), developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia, is another viral vector vaccine that uses two human adenovirus vectors, (Ad26 and Ad5), both of which encode for the SARS-CoV-2 spike protein.

Q: Can the viral vector alter cellular DNA?

A: No. The viral vectors used in COVID-19 vaccines do not integrate into the genome or contain the enzymes needed to insert vector DNA into cellular DNA. Once the viral vector DNA has been transcribed, the vector genome is degraded. The viral vectors enter the nucleus where the genome of the vector, including the gene encoding the vaccine antigen(s), are transcribed by host RNA polymerase into mRNA. The mRNA are exported to the nucleus, where they are transcribed into vaccine antigens. The viral vectors used in COVID-19 vaccines are non-replicating — this means they do not possess the machinery to generate more copies of themselves in vivo and they are degraded by the host cell once their genome has been transcribed.

Q: Can the viral vector COVID-19 vaccines be transmitted in vivo?

A: No. The viral vector used in the Oxford-AstraZeneca and Johnson & Johnson/Janssen COVID-19 vaccines are replication incompetent (sometimes called replication deficient). This means they do not replicate within the human body, and there is no possibility for transmission of the viral vector to other individuals.

Q: What happens to the spike protein generated by the COVID-19 vaccines after it is produced by ribosomes?

A: The spike protein may exist in three different forms after translation within the cell. First, the protein can be presented on the cell surface in its native form. Second, the protein can also be processed within the cell into different peptides, which can be presented by major histocompatibility complex class I and MHC class II molecules. MHC proteins play a key role in the adaptive branch of the immune system, presenting peptides on the cell surface for recognition by T cells. Finally, the protein may also be secreted into the extracellular space, where it may be recognized by B cells (which make antibodies) or taken up by antigen presenting cells and re-processed. The protein may be found on the surface of the cell in either its peptide form or its native form, likely until the cell dies or interacts with other immune cells.The protein lasts the same amount of time as other proteins made by the body. The exact time is not known, but it is estimated to be a few weeks.

Efficacy of COVID-19 Vaccines

Q: What does "vaccine efficacy" mean, and how was efficacy measured in the Pfizer-BioNTech, Moderna, Johnson & Johnson/Janssen and Oxford-AstraZeneca COVID-19 vaccine trials?

A: Vaccine efficacy refers to the percent reduction in cases of a disease among individuals who receive a vaccine compared with those who are unvaccinated. The primary efficacy endpoint in all the trials was clinical disease, meaning symptomatic COVID-19; reduction in infection, which would include both symptomatic COVID-19 as well as any positive test for SARS-CoV-2 in the absence of symptoms, was not assessed as a primary endpoint, although additional data utilizing serologic endpoints are being

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collected in all the trials. When the term "vaccine efficacy" is discussed in relation to these vaccines, it generally refers to efficacy at preventing clinical disease unless otherwise specified.

The primary endpoints for the Phase 3 trials of these vaccines were as follows:

- Pfizer-BioNTech: Efficacy against PCR-confirmed symptomatic COVID-19 with onset at least 7 days after the second dose of vaccine among participants without serologic or virologic evidence of prior SARS-CoV-2 infection at baseline.
- Moderna: Efficacy against PCR-confirmed symptomatic COVID-19 with onset at least 14 days after the second dose of vaccine among participants without evidence of prior SARS-CoV-2 infection at baseline.
- Johnson & Johnson/Janssen: Efficacy against PCR-confirmed moderate to severe/critical COVID-19 in the periods starting 14 days after vaccination and 28 days after vaccination among participants without evidence of prior SARS-CoV-2 infection at baseline.
- Oxford-AstraZeneca: Efficacy against PCR-confirmed symptomatic COVID-19 starting 14 days after dose 2 of the vaccine.

Q: How effective are current COVID-19 vaccines against emerging SARS-CoV-2 variants of concern?

A: The Phase 3 trials of most currently available COVID-19 vaccines began prior to the emergence of most SARS-CoV-2 variants of concern; therefore, their efficacy against these variants can only be extrapolated from post-authorization observational studies conducted in countries where these vaccines are in use and where variants are highly prevalent.

Of note, vaccine effectiveness can be measured using a variety of different outcomes, including prevention of transmission (which would encompass reduction in asymptomatic and symptomatic infections), reduction in symptomatic illness, and reduction in severe disease, hospitalization, or death due to COVID-19. Although all these outcomes may be relevant from a public health perspective, prevention of severe disease, hospitalization and death are most relevant to the individual vaccine recipient.

The Real-Time Learning Network has assembled a summary table of available data about vaccine and monoclonal antibody effectiveness against SARS-CoV-2 variants of concern, focusing on two outcomes – symptomatic infection and severe disease. Most of the available vaccine effectiveness data pertain to mRNA COVID-19 vaccines (largely Pfizer-BioNTech) or the Oxford-AstraZeneca COVID-19 vaccine. Finally, comparative vaccine effectiveness data depend on which variants were co-circulating at the time the analysis was done, thus estimates of vaccine effectiveness against Alpha were compared with ancestral strains (e.g., D614G), whereas estimates of vaccine effectiveness against Delta are compared with Alpha.

Delta variant

There are emerging data about vaccine effectiveness against the Delta variant. In a press release (not published, not peer-reviewed), public health authorities in Israel reported substantially decreased effectiveness of the Pfizer-BioNTech COVID-19 vaccine against symptomatic infection during the time period that Delta became the dominant circulating variant in that country. However, they also reported that vaccine effectiveness against severe illness and hospitalization was still >90%. Of note, these data are preliminary and have not been published.

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Investigators from Public Health England conducted a test-negative case-control study to evaluate the effectiveness of both the Pfizer-BioNTech and Oxford-AstraZeneca COVID-19 vaccines against the Delta variant over the time period when this variant emerged in the UK. In this analysis, a single dose of either vaccine had significantly lower effectiveness against SARS-CoV-2 infection due to Delta compared with Alpha (30.7% vs. 48.7%). However, after two doses, vaccine effectiveness was only slightly lower (88.0% vs. 93.7% for Pfizer-BioNTech and 67.0% vs. 74.5% for Oxford-AstraZeneca) (Bernal, July 2021). In a parallel analysis, vaccine effectiveness of two doses of both vaccines was >90% against hospitalization due to the Delta variant (Stowe, May 2021 -preprint not peer-reviewed). A cohort analysis of SARS-CoV-2 infections in Scotland similarly found decreased effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca COVID-19 vaccines against S gene target positive cases (a laboratory surrogate for Delta variant during the time period of the study) compared with S gene target negative cases (a laboratory surrogate for Alpha variant), but no difference in effectiveness against hospitalization due to the two variants (Sheikh, June 2021). Finally, a test-negative case-control study in Canada found that single doses of the Pfizer-BioNTech and Moderna COVID-19 vaccines were less protective against symptomatic infection due to the Delta variant compared with Alpha, but that two doses restored their protective effect comparable to that against Alpha – two doses of either the Pfizer-BioNTech, Moderna, or Oxford-AstraZeneca vaccines were >90% effective against hospitalization or death due to the Delta variant (Nasreen, July -preprint not peer-reviewed).

Other variants
mRNA COVID-19 vaccines
Alpha: In an analysis of a mass vaccination campaign among U.K. health care workers with the Pfizer-BioNTech COVID-19 vaccine, the investigators measured the incidence of new SARS-CoV-2 infections from Dec. 8, 2020 to Feb. 5, 2021, when the B.1.1.7 variant accounted for >50% of circulating SARS-CoV-2 strains (Hall, April 2021). In this study, vaccine effectiveness was 70% (95% CI, 55-85) against SARS-CoV-2 infection (asymptomatic and symptomatic cases) starting 21 days after the first dose, and increased to 85% (95% CI, 74-96) starting 7 days after the second dose.

In a separate study of nationwide SARS-CoV-2 surveillance data from Israel following a mass vaccination campaign with the Pfizer-BioNTech COVID-19 vaccine, vaccine effectiveness was 90.5% against symptomatic SARS-CoV-2 infection starting 7 days after dose 2. The prevalence of the B.1.1.7 variant was estimated to be 95%, based on the rate of spike gene target failure at one of the testing sites from which surveillance data were reported (Haas, May 2021).

In another analysis of the impact of a mass vaccination campaign with the Pfizer-BioNTech COVID-19 vaccine in Qatar, the investigators estimated the prevalence of the B.1.1.7 variant to be 44.5%. In this study, vaccine effectiveness was 89.5% against any documented infection with the B.1.1.7 variant. Vaccine effectiveness against severe, critical or fatal SARS-CoV-2 infection due to any variant was 97.4% (Abu-Raddad, May 2021).

Finally, in a test-negative design study of SARS-CoV-2 infections in Canada, the investigators found the vaccine effectiveness of the Pfizer-BioNTech vaccine to be 89% against Alpha (Nasreen, July -preprint not peer-reviewed).

Beta: In an analysis of the impact of a mass vaccination campaign with the Pfizer-BioNTech COVID-19 vaccine in Qatar, the investigators estimated the prevalence of the B.1.351 variant to be 50% respectively. In this study, vaccine effectiveness was 75% against any documented infection with the B.1.351 variant. Vaccine effectiveness against severe, critical or fatal SARS-CoV-2 infection due to any variant was 97.4% ([Abu-Raddad, May 2021](#)). In a separate test-negative design study of SARS-CoV-2 infections in Canada, the investigators found the vaccine effectiveness of the Pfizer-BioNTech vaccine to be 84% against Beta/Gamma ([Nasreen, July -preprint not peer-reviewed](#)).

Gamma: There are limited data specifically focused on mRNA COVID-19 vaccine effectiveness against the Gamma variant. Given the overlap in mutations present in this variant and the Beta variant, it is assumed that vaccine performance against this variant would be similar to that observed against Beta.

Viral vector COVID-19 vaccines
Alpha: In a post-hoc analysis of the Phase 2/3 clinical trial of ChAdOx1 conducted in the U.K., where the B.1.1.7 variant emerged in late 2020, vaccine efficacy was 70.4% against symptomatic COVID-19 due to the B.1.1.7 variant, and 81.5% against symptomatic COVID-19 due to non-B.1.1.7 variants, but this difference was not statistically significant ([Emary, April 2021](#)).

Beta: The Phase 3 trial of Ad26.COV2.S was conducted in multiple countries, where new SARS-CoV-2 variants did emerge, and strain sequencing analyses of COVID-19 cases in the study are being performed. As of Feb. 12, 2021, 71.7% of cases reported in the trial had been sequenced. In subgroup analyses of vaccine efficacy against moderate to severe/critical COVID-19 by country of participation, vaccine efficacy was lower in South Africa (vaccine efficacy of 52.0%; 95% CI, 30.3-67.4) compared to the United States (vaccine efficacy of 74.4%; 95% CI, 65.0-81.6). In the United States, 96.4% of strain sequences were identified as SARS-CoV-2 Wuhan-H1 variant D614G, whereas in South Africa, 94.5% of strain sequences were identified as 20H/501Y.V2 variant (B.1.351) ([Sadoff, April 2021](#)).

One of the Phase 3 trials of ChAdOx1 was conducted in South Africa. During that study, 41 (97.6%) of the 42 SARS-CoV-2 viruses involved in primary endpoint analyses were sequenced, of which 39 (95.1%) were the B.1.351 variant. There were 19 COVID-19 cases among ChAdOx1 recipients (15 mild, 4 moderate, 0 severe) and 23 among placebo recipients (17 mild, 6 moderate, 0 severe), giving an overall vaccine efficacy of 21.9% (95% CI, -49.9-59.8), suggesting that ChAdOx1 is not protective against the B.1.351 variant. As further evidence of this difference in efficacy, the investigators in this study conducted a post-hoc analysis of vaccine efficacy limited to cases occurring before Oct. 31, 2020 (i.e., before the B.1.351 variant emerged in South Africa). In this analysis, vaccine efficacy was determined to be 75.4% (95% CI, 8.7-95.5), similar to the reported vaccine efficacy in Phase 3 trials ([Madhi, February 2021](#)).

Gamma: There are limited data specifically focused on mRNA COVID-19 vaccine effectiveness against the Gamma variant. Given the overlap in mutations present in this variant and the Beta variant, it is assumed that vaccine performance against this variant would be similar to that observed against Beta.

Q: Are the mRNA vaccines more efficacious than the viral vector vaccines?

A: None of the COVID-19 vaccines have been directly compared head-to-head in the same population, and so the point estimates of vaccine efficacy for the mRNA vaccines (Moderna and Pfizer-BioNTech) and viral vector vaccines (Johnson & Johnson/Janssen and Oxford-AstraZeneca) cannot be directly compared with each other. The clinical trials for these vaccines were conducted at different times in different populations. Furthermore, the outcomes used to calculate the efficacy estimates differed between the studies (see previous question). The Pfizer-BioNTech, Moderna and Johnson & Johnson/Janssen vaccines have all been evaluated for emergency use authorization and met the efficacy criteria pre-specified by the FDA. They all have high efficacy, especially against severe COVID-19.

Q: When does immunity to symptomatic SARS-CoV-2 infection develop after completion of a COVID-19 vaccine series?

A: Our current knowledge regarding when vaccinated persons can expect to achieve a high level of protection from developing symptomatic COVID-19 is derived from the published clinical trial data. The Moderna COVID-19 vaccine demonstrated 95% efficacy for prevention of symptomatic COVID-19 starting 14 days after receiving the second dose; the Pfizer-BioNTech COVID-19 vaccine demonstrated 95% efficacy for prevention of symptomatic COVID-19 starting 7 days after receiving the second dose; the Johnson & Johnson/Janssen COVID-19 vaccine demonstrated 67% efficacy for prevention of moderate-severe/critical COVID-19 starting 14 days after vaccination; finally, the Oxford-AstraZeneca COVID-19 vaccine demonstrated 67% efficacy for prevention of symptomatic COVID-19 starting 14 days after receiving the second dose.

Q: What do we know about breakthrough SARS-CoV-2 infections in vaccinated individuals?

A: Our knowledge of SARS-CoV-2 breakthrough infections after vaccination is still evolving. Importantly, breakthrough infections occur at a much lower incidence compared with infections in unvaccinated individuals, therefore the occurrence of breakthrough infections does not diminish the critical importance of vaccination against COVID-19.

To date, the data suggest that most breakthrough infections are associated with mild illness or are asymptomatic. There are insufficient published data on the virologic and immunologic aspects of breakthrough infections to be able to draw definitive conclusions regarding risk assessment (for breakthrough infection) after vaccination, transmissibility of breakthrough infection (symptomatic or asymptomatic), or appropriate management. Below are critical summaries of selected reports of breakthrough SARS-CoV-2 infections in the published literature:

In an analysis of breakthrough SARS-CoV-2 infections reported to CDC through April 30, 2021, investigators described 10,262 cases, of which 27% (n=2,725) were asymptomatic, 10% (n=995) were hospitalized at the time of their infection and 2% (n=160) died. Notably, 29% of hospitalized patients with a reported breakthrough infection were asymptomatic or hospitalized for another reason and 18% of the deaths were asymptomatic at the time their breakthrough infection was identified or died from another cause. Only 5% (n=555) of the breakthrough infections had sequencing data available, and nearly two-thirds (64%, n=356) were identified as variants of concern (CDC, May 2021).

In one of the largest case series of breakthrough infections reported to date, CDC investigators described a cluster of SARS-CoV-2 infections associated with large public gatherings in Barnstable County, Massachusetts (CDC, August 2021). This investigation described 469 COVID-19 cases, of which 346 (74%) occurred in fully vaccinated individuals. Notably, of the 133 infections for which genome sequencing data were available, 119 (89%) were due to the Delta variant. Of the 346 breakthrough cases, 274 (79%) reported symptoms, 4 (1.2%) were hospitalized, and none died. In this study the investigators reported cycle threshold (Ct) values as a surrogate for viral load and noted that the median Ct values in vaccinated individuals were similar to those who were unvaccinated, partially vaccinated, or with unknown vaccination status.

Key limitations of this report include: incomplete data on the exposed population (which limits our ability to assess the relative incidence of infection in vaccinated and unvaccinated individuals); use of a surrogate measure of viral load (that does not distinguish between culturable virus, total RNA, or subgenomic RNA); and no description of the approach to viral detection (specimen type, timing of specimen in course of illness, etc.).

In a separate study, investigators in Israel analyzed a cohort of 39 breakthrough cases (<1% of the 1497 fully vaccinated healthcare workers that underwent PCR testing) and found that the majority (N=26, or 67%) were mild (and none required hospitalization) and the remainder were asymptomatic. Although 29 (74%) of the case patients had a cycle threshold (Ct) value of <30 at some point during their infection, no secondary infections were documented. Of note, the time point of this low Ct value was not reported or compared with an unvaccinated cohort (Bergwerk, July 2021).

In an analysis of SARS-CoV-2 infections identified through the HEROES-RECOVER network, an ongoing prospective cohort study of healthcare personnel, first responders, and other essential and frontline workers – investigators described 204 cases, of which 5 (2.5%) were fully vaccinated and 11 (5.4%) were partially vaccinated (the remaining >92% of cases were unvaccinated). Vaccinated or partially vaccinated individuals had fewer febrile symptoms and had fewer days of symptoms compared with unvaccinated individuals. In this study the investigators used quantitative RT-PCR to measure SARS-CoV-2 viral load in mid-turbinate nasal swabs and found that vaccinated individuals and lower viral loads and a shorter duration of RNA detection compared with unvaccinated individuals (Thompson, July 2021).

Q: What do we know about the ability of the COVID-19 vaccines to prevent asymptomatic infection?
A: The primary efficacy endpoints of all the COVID-19 vaccine trials were clinical disease; however, all of the studies collected data that provide some insight on the ability of these vaccines to prevent asymptomatic infection, including surveillance nasopharyngeal swabs for SARS-CoV-2 viral testing and/or serologies. Since baseline serostatus was known in all these studies, if a subject converted from negative to positive serology during the trial in the absence of a COVID-19 illness, it would imply asymptomatic infection. Some of the vaccines have additionally been evaluated in post-authorization studies in various settings where they have been deployed. Below is a summary of what is known about the impact of each vaccine on asymptomatic infection – note that these studies were conducted prior to the emergence of novel variants of concern, including Delta, and these findings may not be

generalizable to all variants whose viral kinetics may be substantially different from ancestral strains of SARS-CoV-2:

Moderna
As part of the Phase 3 trial of mRNA-1273, investigators collected pre-dose 1 and pre-dose 2 nasopharyngeal swabs for SARS-CoV-2 viral testing and performed a descriptive study comparing the number of positive swabs at the pre-dose 2 time point in baseline seronegative participants. Amongst baseline negative participants, 15 participants in the vaccine group and 39 participants in the placebo group had evidence of SARS-CoV-2 infection at the second dose without evidence of COVID-19 symptoms. There were approximately two-thirds fewer swabs that were positive in the vaccine group as compared to the placebo group at the pre-dose 2 time point, suggesting that some asymptomatic infections start to be prevented after the first dose (Baden, February 2021).

Pfizer-BioNTech
Multiple post-authorization observational studies of BNT162b2 in diverse settings suggest that this vaccine is effective against asymptomatic infection.

Israel: In an observational study that used data from the largest of four integrated health services in Israel, vaccine effectiveness was 46% against SARS-CoV-2 infection (positive PCR, with or without symptoms) from 14-20 days after dose 1 and 92% against infection from 7 days after dose 2. In an exploratory analysis, vaccine effectiveness was 90% against asymptomatic infection based on a proxy measure of SARS-CoV-2 test positivity without documented symptoms (Dagan, February 2021). In a separate analysis of nationwide surveillance data, vaccine effectiveness was 91.5% against asymptomatic SARS-CoV-2 infection starting 7 days after dose 2 (Haas, May 2021).

United States: In an analysis of the incidence of new (asymptomatic) SARS-CoV-2 infections detected by weekly surveillance PCRs among health care workers at the University of California, San Diego and the University of California, Los Angeles health systems, there were only 7 new infections identified among those who had received their second dose of BNT162b2 15 or more days earlier, compared with 145 who had just received their first dose of vaccine in the preceding 7 days (and so would not be expected to be protected) (Keehner, March 2021). In another analysis of pre-procedural asymptomatic SARS-CoV-2 test positivity within the Mayo Clinic health system, investigators determined a 72% reduction in the risk of having a positive SARS-CoV-2 test among individuals who had received at least 1 dose of an mRNA vaccine (94% of subjects in the study had received BNT162b2) at least 10 days earlier (Tande, March 2021).

United Kingdom: An analysis of new SARS-CoV-2 infections among U.K. health care workers following a mass vaccination campaign with BNT162b2 identified 51 asymptomatic cases (no symptoms within 14 days before and after the date of a positive test) among unvaccinated individuals compared with only 10 in the vaccinated cohort (Hall, April 2021).

Johnson & Johnson/Janssen
As part of the Phase 3 trial of Ad26.COV2.S, investigators collected serology against SARS-CoV-2 N protein from study subjects at day 71 — since N protein is not contained in the vaccine, a conversion from negative to positive would imply natural SARS-CoV-2 infection. Of the 2,650 individuals who had an anti-N serology result at day 71, there were 18 asymptomatic infections in the vaccine group and 50 in the placebo group, for an estimated vaccine efficacy of 65.5% (Sadoff, April 2021).

Oxford-AstraZeneca
As part of the Phase 3 trial of ChAdOx1 conducted in the U.K. (COV002), study subjects submitted self-collected nose and throat swabs on a weekly basis for SARS-CoV-2 PCR testing. In a preliminary analysis of these data, the vaccine effectiveness against SARS-CoV-2 infection without symptoms (or where symptoms were unknown) was 47.2% if the interval between dose 1 and 2 of the vaccine was 12 weeks or greater (Voysey, February 2021). In a vaccine effectiveness analysis stratified by SARS-CoV-2 variant status, ChAdOx1 was 69.7% effective against asymptomatic infection due to non-B.1.1.7 variants, but demonstrated no protection against asymptomatic infection due to the SARS-CoV-2 B.1.1.7 variant (Emary, April 2021).

In summary, vaccinated individuals can develop asymptomatic infection, though at significantly lower rates than unvaccinated individuals.

Q: What is known about the impact of COVID-19 vaccination on SARS-CoV-2 transmission?
A: There are limited data about the transmissibility of SARS-CoV-2 breakthrough infections, and apart from isolated case reports (Kernéis, August 2021), most of what is known is based on indirect evidence. Transmissibility depends on a variety of factors, including (but not limited to) the magnitude and duration of viral shedding. Prior to the emergence of the Delta variant, there was some evidence that COVID-19 vaccination may be associated with lower peak viral loads (Levine-Tiefenbrun, March 2021). Importantly, the increased transmissibility of the Delta variant has been attributed to higher viral loads and earlier viral shedding compared with ancestral strains of SARS-CoV-2 (Li, July 2021 -pre-print not peer-reviewed), which may have implications for the effect of COVID-19 vaccines on transmission of Delta. In a still unpublished study of Delta infections in Singapore, the investigators evaluated viral and serologic kinetics of infection in vaccinated and unvaccinated individuals – they found that although both vaccinated and unvaccinated individuals had similar initial cycle threshold (Ct) values, Ct values increased much faster (e.g., viral loads decreased much faster) in vaccinated individuals compared with unvaccinated individuals (Chia, July 2021 -pre-print not peer-reviewed).

Prior to the emergence of Delta, in two large studies of household contacts of vaccinated and unvaccinated individuals with SARS-CoV-2 infection in the UK (Shah, March 2021 -preprint not peer-reviewed) and Netherlands (de Gier, August 2021), the risk of secondary infection was lower in contacts of vaccinated individuals compared with unvaccinated individuals. These findings are suggestive that COVID-19 vaccination may be associated with less transmission to close contacts – if these conclusions can be generalized to Delta remains to be seen.

Q: What is the efficacy of a single dose of the two-dose vaccines against symptomatic COVID-19, i.e., the Moderna, Pfizer-BioNTech, and Oxford-AstraZeneca COVID-19 vaccines?

A: Single doses of the Pfizer-BioNTech, Moderna and Oxford-AstraZeneca COVID-19 vaccines have not been formally evaluated in clinical trials. Furthermore, the durability of protection after a single dose of any of the two-dose vaccines is unknown; therefore, it is still recommended that individuals complete the two-dose series of all the two-dose COVID-19 vaccines.

In a secondary analysis of data presented to FDA as part of the Moderna EUA application, the Moderna COVID-19 vaccine demonstrated 92% efficacy against symptomatic COVID-19 starting 14 days after the first dose of vaccine just through 28 days after the second dose (when participants received the second dose of the vaccine). Similarly, in a secondary analysis of the data that had been presented to FDA as part of the Pfizer-BioNTech EUA application, the Pfizer-BioNTech COVID-19 vaccine demonstrated 93% efficacy against symptomatic COVID-19 starting 14 days after the first dose of vaccine just through 21 days after the first dose (which is when participants received the second dose of the vaccine) (Skowronski, February 2021).

The efficacy of a single dose of the Oxford-AstraZeneca vaccine was evaluated in an exploratory analysis as part of a Phase 3 trial in which the timing of the second dose of vaccine was variable among study participants (Voysey, February 2021). In that analysis, a single dose of the vaccine was 76% effective against symptomatic COVID-19 starting 21 days after the first dose through 90 days.

Of note, in post-authorization studies of both mRNA COVID-19 vaccines and the Oxford-AstraZeneca COVID-19 vaccine, a single dose of any of these vaccines conferred significantly less protection against the Delta variant compared with their efficacy against the Alpha variant (see FAQ about vaccine efficacy against variants).

COVID-19 Vaccines & Immunity

Q: What is the evidence for administering additional COVID-19 vaccine doses beyond the number originally authorized by FDA EUAs (two for mRNA vaccines or one for J&J)?

A: Multiple small studies suggest that additional doses of mRNA COVID-19 vaccines can increase antibody concentrations in certain previously vaccinated individuals, and in short-term follow-up, these additional doses appear to be safe. Most of these data are from individuals with comorbidities associated with a weakened response to vaccination (e.g., solid organ transplantation (SOT), hematologic malignancy, or chronic kidney disease). Notably, because there is no immunologic correlate of protection against SARS-CoV-2 infection (i.e., immunity cannot be inferred from the results of current available antibody tests), how these findings translate into vaccine effectiveness remains unknown. In addition, the relevance of these findings to the general (non-immunocompromised) population is not clear.

In a randomized control trial (RCT) of 120 solid organ transplant recipients, subjects who had previously completed a two-dose series of the Moderna COVID-19 vaccine were randomized 1:1 to receive a third

dose of vaccine or saline placebo 2 months after the second dose of the primary vaccine series. Immunogenicity data were available from 117 subjects – prior to the study intervention, only 11.7 and 8.8% of the treatment and placebo groups respectively had an anti-receptor binding domain (RBD) antibody concentration above a pre-specified threshold of 100 U/mL. At 1 month after the study intervention, 55% (33 of 60) recipients of a third dose of Moderna COVID-19 vaccine achieved that concentration compared with only 18% (10 of 57) in the placebo group. Additionally, after the study intervention the median percent virus neutralization was 71% in the vaccine group compared with only 13% in the placebo group (Hall, August 2021).

In addition to this RCT, many similarly sized observational studies have also shown that additional doses of mRNA COVID-19 vaccines can increase antibody concentrations in certain previously vaccinated individuals (Longlune, May 2021; Werbel, June 2021; Kamar, June 2021; Ducloux, June 2021; Espi, July 2021 – preprint, not peer-reviewed; Re, July 2021 - preprint, not peer-reviewed; Del Bello, July 2021, Benotmane, July 2021; Karaba, August 2021 – pre-print, not peer-reviewed). Importantly, these studies used different schedules for the third dose, and they used a wide variety of antibody assays, thus their results cannot be easily pooled or compared with each other.

There are fewer data on the impact of additional doses of adenovirus vector vaccines – this includes an observational study in which 15 SOT recipients who had previously completed a two-dose series of an mRNA vaccine received an additional dose of the Johnson & Johnson/Janssen COVID-19 vaccine (Werbel, June 2021), a longitudinal immunogenicity study of the Johnson & Johnson/Janssen COVID-19 vaccine in which 10 healthy individuals received a second dose of the vaccine 2 months after the first dose (Barouch, July 2021 – preprint, not peer-reviewed), and 75 healthy subjects who received a third dose of the Oxford-AstraZeneca COVID-19 vaccines 8-16 weeks after the first two doses (Flaxman, SSRN pre-print June 2021). These studies showed mixed results with regard to the benefit of additional doses of adenovirus vector vaccines on antibody responses.

Q: What is the utility of laboratory testing to determine if an individual has mounted an adequate immune response following COVID-19 vaccination?
A: There is no established immunologic correlate of protection against SARS-CoV-2, and none of the commercially available immune assays (antibody or T cell) are FDA-approved to assess protective immunity against SARS-CoV-2 infection. This means it is not possible to reliably infer immunity from the results of such tests. As such, there is no current recommendation from the CDC or FDA to use currently available immune assays (antibody or T cell) against SARS-CoV-2 to assess for a protective immune response after vaccination. Furthermore, CDC does not recommend additional doses of COVID-19 vaccines based on the results of these tests.

Q: How does natural immunity compare with vaccine-induced immunity to COVID-19?
A: There are limited data comparing natural and vaccine-induced immunity to COVID-19. Observational studies of rates of reinfection among seropositive individuals cannot be directly compared with data from vaccine clinical trials or post-authorization studies of vaccine recipients. These studies were conducted in different populations, during different phases of the pandemic (when different control measures were in place and different variants were circulating) and using different methods of case ascertainment. Furthermore, in ecological studies that have examined rates of reinfection among

previously infected individuals, the period of observation for reinfections was less than one year (and in some cases, just a few months) after initial infection, which limits any conclusions about the long-term durability of protection after natural infection.

A few studies have compared the incidence of SARS-CoV-2 infection between individuals with evidence of either prior infection or vaccination in the same population over the same time period. These have found that the risk of infection was similarly low in those who had been previously infected or vaccinated (Bertollini, June 2021; Lumley, July 2021; Shrestha, June 2021 -preprint, not peer-reviewed).

Notably, these studies have several key limitations that constrain what can be concluded about the need for vaccination of previously infected individuals. First, other than age and sex, none of these studies reported baseline characteristics of previously infected individuals, such as comorbidities, immune status or severity of initial COVID-19 illness – factors that have been shown to influence the magnitude and durability of the immune response generated by natural infection, which likely also influences its protective effect. Thus, it remains unclear if the findings from these studies can be extrapolated to all individuals with laboratory evidence of prior infection. Second, the duration of follow-up in all these studies is at most a few months; therefore, the durability of protection from natural infection versus vaccination cannot be determined.

Finally, there are emerging data that *in vitro* immune responses following natural infection — especially mild infections — may not be as robust as compared with vaccine-induced responses, including against novel SARS-CoV-2 variants of concern (Marot, May 2021; Greaney, June 2021; Caniels, June 2021 - preprint, not peer-reviewed; Herzberg, June 2021 -preprint, not peer-reviewed; Psichogiou, June 2021 – preprint, not peer-reviewed).

Q: What is the evidence regarding waning immunity after COVID-19 vaccination (or natural infection)?

A: There are limited clinical data on waning immunity after COVID-19 vaccination. Since COVID-19 vaccines only began to be used in the general population in late 2020, studies are naturally limited in their ability to determine the effect of time on vaccine effectiveness. In addition, it is possible that in the future emerging variants of concern could evade vaccine-induced immunity enough to result in high rates of severe disease, which would make it difficult to discern whether vaccine effectiveness was decreasing due to waning immunity or vaccine escape.

Notably, population-based studies whose primary objective was to compare the effectiveness of COVID-19 vaccines against emerging variants (for example, Alpha vs. Delta) found that the Pfizer-BioNTech, Moderna, and Oxford-AstraZeneca vaccines were as effective against the Alpha variant as they were in earlier phases of vaccine roll-out (Bernal, July 2021; Nasreen, July -preprint not peer-reviewed).

As detailed in another FAQ, observational studies of previously infected individuals have demonstrated a protective effect of natural infection against re-infection; however, the duration of follow-up in all these studies is at most a few months; therefore, the durability of protection from natural infection cannot be determined.

Q: What is known about natural immunity following SARS-CoV-2 infection?

A: Multiple studies have demonstrated durable humoral (**Rodda, January 2021**; **Dan, February 2021**; **Sokal, March 2021**; **Turner, May 2021**; **Anand, June 2021**; **Cohen, June 2021** *-preprint, not peer-*

reviewed) and cell-mediated (**Rodda, January 2021**; **Dan, February 2021**; **Kang, March 2021**; **Breton, April 2021**; **Cohen, June 2021 *-preprint, not peer-reviewed***) immune responses to SARS-CoV-2 in individuals several months after recovery from SARS-CoV-2 infection. Some studies have also shown that these immune responses vary based on the severity of initial infection, with severe COVID-19 (i.e., requiring hospitalization, intensive care unit admission or mechanical ventilation) being associated with more robust antibody and T cell responses (**Lynch, January 2021**; **Kang, March 2021**; **Betton, April 2021**). Our understanding of the longevity of these responses is still evolving and naturally limited by the timeframe since the pandemic began.

In addition to *in vitro* studies, there is also compelling evidence that natural SARS-CoV-2 infection can decrease the risk of reinfection with SARS-CoV-2. For example, in large observational cohort studies in the U.S. (**Sheehan, March 2021**; **Letizia, April 2021**; **Harvey, May 2021**; **Rennert, May 2021**; **Shrestha, June 2021 *-preprint, not peer-reviewed***), U.K. (**Lumley, February 2021**; **Hall, May 2021**; **Lumley, July 2021**), Denmark (**Hansen, March 2021**), Italy (**Vitale, May 2021**; **Manica, July 2021**), France (**Dimeglio, January 2021**), Switzerland (**Leidi, July 2021**) and Qatar (**Abu-Raddad, December 2020**; **Bertollini, June 2021**), prior documented infection with SARS-CoV-2 (based on a PCR or antibody result) was associated with a decreased rate of subsequent infection in the ensuing months, including up to 12 months after the initial infection.

Despite these observations from laboratory and ecological studies, it is also clear that SARS-CoV-2 reinfections do occur. Although reinfections tend to be milder (**Qureshi, April 2021**; **Abu Raddad, May 2021**), severe (and even fatal) cases have been reported (**Tillet, January 2021**; **Cavanaugh, February 2021**; **Qureshi, April 2021**).

Importantly, how the magnitude and durability of the protective effect of natural infection varies by baseline factors such as age, comorbidities or immune status, or the severity of the initial SARS-CoV-2 infection, remains unclear. For example, in one study, the protective effect of prior infection observed among individuals aged greater than 65 years was significantly lower than that observed for the entire cohort (**Hansen, March 2021**). Furthermore, the follow-up period of most of the published observational studies of natural immunity occurred prior to the spread of SARS-CoV-2 variants against which immune responses may be less robust. In one analysis of U.K. health care workers, the degree of protection conferred by seropositivity did not vary based on whether the infecting strains were Alpha/B.1.1.7 (inferred based on S-gene target failure, or SGTF) or not (**Lumley, July 2021**). The protective effect of prior infection with historical SARS-CoV-2 variants against reinfections due to other novel variants of concern remains poorly characterized.

Q: What tests can be used to document prior SARS-CoV-2 infection, and how does one interpret the results?
A: Measures of the immune response to SARS-CoV-2 antigens (either antibody or T cell responses) can identify individuals previously infected with SARS-CoV-2. Currently, only antibody assays are commercially available. For vaccinated individuals, to differentiate between the immune response to past infection versus the COVID-19 vaccine itself — which all use the spike protein as the vaccine antigen — immune responses to non-spike SARS-CoV-2 antigens (i.e., nucleocapsid) should be measured.

The performance characteristics of commercial antibody assays are variable. In general, a positive antibody test result in an unvaccinated individual (or a positive anti-nucleocapsid antibody response in a vaccinated individual) is strong evidence for prior SARS-CoV-2 infection. However, a negative result does not exclude prior infection, because antibodies may wane to undetectable levels within a few months of infection. For more details, please refer to the **Overview of Testing for SARS-CoV-2 (COVID-19)** and **Interim Guidelines for COVID-19 Antibody Testing** pages maintained by CDC.

Importantly, **none** of the commercially available antibody assays are FDA-approved to assess protective immunity against SARS-CoV-2. Baseline serologic testing to assess for prior infection solely for the purpose of vaccine decision-making is not recommended, and CDC does not recommend "exempting" previously infected individuals from vaccination. Indeed, in one study of five FDA-approved antibody assays, neutralizing antibody concentrations in two seropositive individuals that were protected against reinfection during a wildtype SARS-CoV-2 outbreak on a fishing vessel were similar to those in five fully vaccinated individuals that experienced breakthrough infections with SARS-CoV-2 variants of concern (**Bradley, June 2021**). This underscores the point that serostatus may not be entirely predictive of general protection from or vulnerability to the virus, particularly variants of concern.

Safety of COVID-19 Vaccines

Q: Is there any association between the mRNA COVID-19 vaccines and neurologic adverse events, including Bell's palsy, transverse myelitis or Guillain-Barré syndrome?

A: There was a numerical imbalance in the number of cases of Bell's palsy identified among recipients of the Pfizer-BioNTech and Moderna COVID-19 vaccines in Phase 3 clinical trials. Four participants who received the Pfizer-BioNTech vaccine later developed Bell's palsy (compared to zero in the placebo group of that study) and three participants who received the Moderna vaccine later developed Bell's palsy (compared to one in the placebo group of that study). Overall, this was too few cases of Bell's palsy to establish a statistically significant association with vaccination (Ozonoff, April 2021), but surveillance is ongoing.

There have been no cases of transverse myelitis or Guillain-Barré syndrome reported following vaccination among participants in either of the mRNA COVID-19 vaccine clinical trials.

A history of any of these conditions is not a contraindication or precaution to vaccination with either mRNA COVID-19 vaccine. Any occurrence of these conditions following mRNA COVID-19 vaccination should be reported to VAERS.

Q: What is the association between mRNA COVID-19 vaccines and myocarditis/pericarditis?

A: Since April 2021, both CDC and the European Medicines Agency have been assessing cases of myocarditis and pericarditis temporally associated with mRNA COVID-19 vaccination. Based on data reported to the Vaccine Adverse Event Reporting System in the United States, such cases of myopericarditis occurred mostly in adolescent males and young adults aged 16 years or older and typically occurred within a few days of the second dose of an mRNA COVID-19 vaccine.

Several small case series of myocarditis following COVID-19 vaccination have since been published (Marshall, June 2021; Rosner, June 2021; Abu Mouch, June 2021). These reports describe a total of 20 individuals — all male, 85% (17 out of 20) under the age of 30 and 95% (19 out of 20) having received an

mRNA COVID-19 vaccine (18 Pfizer-BioNTech and 1 Moderna). Symptomatic myocarditis occurred within 4 days of receipt of the second dose of mRNA COVID-19 vaccine in 85% (17 out of 20) of these individuals. All of these patients had brief hospitalizations and made a full recovery.

In a presentation of VAERS safety data to the FDA Vaccines and Related Biological Products Advisory Committee, a total of 789 cases of myocarditis/pericarditis following mRNA COVID-19 vaccines were identified (216 after the first dose, 573 after the second dose). The observed rate of myocarditis/pericarditis was higher than what would be expected based on population-level background incidence rates. The median age at time of onset was 30 years (range 12-94) for cases after dose #1 and 24 years (range 14-87) for cases after dose #2. The majority of cases (75%) occurred in males.

The mechanism of myocarditis/pericarditis following mRNA COVID-19 vaccination remains unclear. Monitoring and follow-up of cases of myocarditis/pericarditis following COVID-19 vaccination is ongoing.

Q: What are the frequency and characteristics of anaphylaxis or serious allergic reactions after mRNA COVID-19 vaccines? What are the risk factors for developing an allergic reaction?

A: Anaphylaxis and serious allergic reactions were not observed in the clinical trials of mRNA COVID-19 vaccines, but were recognized shortly after they were authorized for use and deployed in mass vaccination campaigns.

In two separate analyses of data submitted to the Vaccine Adverse Events Reporting System, which comprised reports from 1,893,360 first doses of the Pfizer-BioNTech COVID-19 vaccine and 4,041,396 first doses of the Moderna COVID-19 vaccine in the U.S., there were just 175 cases of possible allergic reactions after the Pfizer-BioNTech vaccine and just 108 cases of possible allergic reactions after the Moderna vaccine.

- Of the 175 reactions reported after the Pfizer-BioNTech vaccine, only 21 (12%) met the Brighton Collaboration case definition criteria for anaphylaxis. Most of these were in women (n=19, 90%) and median time to onset of symptoms was 15 minutes. Four of the cases required hospitalization, while 17 were managed in the emergency department. Most of the cases of anaphylaxis had a documented history of allergies to drugs, foods or insect stings (n=17, 81%), and 7 (33%) had previously experienced anaphylaxis. The 83 non-anaphylaxis reactions were also predominantly in women (90%), with a 12-minute median interval to symptom onset. These reactions included pruritus, rash, itchy and scratchy sensations in the throat and mild respiratory symptoms (CDC COVID-19 Response Team, January 2021).
- Of the 108 reactions reported after the Moderna vaccine, only 10 (9%) met the Brighton Collaboration case definition criteria for anaphylaxis. All of these were in women and median time to onset of symptoms was 7.5 minutes. Six of the cases required hospitalization (5 in the ICU, 4 of whom required intubation) and 4 were managed in the emergency department. Most (n=9, 90%) of the cases of anaphylaxis had a documented history of allergies to drugs or foods, and 5 (50%) had previously experienced anaphylaxis. There were 43 non-anaphylaxis reactions that were also predominantly in women (91%) with the median interval to symptom onset being 14 minutes. These reactions included pruritus, rash, itchy sensations in the mouth or throat, sensation of throat closure and respiratory symptoms (CDC COVID-19 Response Team, January 2021).

Finally, in a prospective study of 64,900 Mass General Brigham employees who received a first dose of a mRNA COVID-19 vaccine between Dec. 16, 2020 and Feb. 12, 2021, 1,365 (2.1%) of employees reported any allergic symptoms, and there were 16 (0.025%) employees that experienced of anaphylaxis. Rates of

allergic reactions were slightly higher with the Moderna COVID-19 vaccine (2.20 vs. 1.95%, p=0.03). Nearly all (n=15, 94%) of the cases of anaphylaxis were among women, and nearly a third (n=5, 31%) had a history of anaphylaxis. One of the cases of anaphylaxis required ICU admission, 9 received IM epinephrine and all recovered without sequelae (Blumenthal, March 2021).

CDC has developed recommendations for management of individuals with a history of anaphylaxis or other allergic reactions to the specific ingredients contained within the COVID-19 vaccines or to other substances.

Q: In comparing the mRNA COVID-19 vaccines and the Ad26.COV2.S vaccine, which is safer and will have fewer side effects for people?
A: In the Phase 3 trial data submitted to FDA, the most common solicited adverse reactions among Ad26.COV2.S vaccinated individuals were injection site pain (48.6%), headache (38.9%), fatigue (38.2%), muscle pain (33.2%), nausea (14.2%) and fever (9.0%). These were more common in patients younger than 60 years of age. Overall, these rates were lower than those reported for both mRNA vaccines; however, all the currently authorized COVID-19 vaccines are safe.

Q: What are the hematologic/thrombotic adverse events that have been linked to the Johnson & Johnson/Janssen and Oxford-AstraZeneca COVID-19 vaccines?
A: In post-authorization surveillance of the Johnson & Johnson/Janssen COVID-19 vaccine, a small number (n=6) of rare thrombotic events — cerebral venous sinus thrombosis — associated with thrombocytopenia were identified among vaccine recipients based on data reported to VAERS. This led to a brief pause in the use of this vaccine on April 13, 2021 and a review of safety data by CDC's Advisory Committee on Immunization Practices on April 23, 2021. In this review, 15 total cases of thrombosis with thrombocytopenia syndrome were identified, including 12 cases of CVST. All the TTS cases occurred among women, and 13 of 15 were in women aged 18-49 years old. The median age of the case patients was 37 years, and the median interval from vaccination to symptom onset was 8 days (range, 6–15 days) (MacNeil, April 2021). There was one case of CVST with thrombocytopenia in a male during the Phase 3 trial of Ad26.COV2.S (Sadoff, April 2021).

The Oxford-AstraZeneca COVID-19 vaccine has been associated with both arterial and venous thrombotic events. In an analysis of data reported to EudraVigilance (a drug safety reporting system for the European Union), the European Medicines Agency identified 169 cases of CSVT and 53 cases of splanchnic vein thrombosis following receipt of the Oxford-AstraZeneca COVID-19 vaccine (out of more than 34 million doses administered). These thrombotic events occurred concurrently with thrombocytopenia, usually within 2 weeks of receipt of the vaccine, and mostly among women under age 60. Subsequently, three independent case series from Norway (Schultz, April 2021), Germany/Austria (Greinacher, April 2021) and the United Kingdom (Scully, April 2021) described a total of 39 patients (27 women, 12 men) with venous thromboses associated with thrombocytopenia that occurred within 4 weeks (range 5-24 days) after vaccination with the Oxford-AstraZeneca COVID-19 vaccine. Given the resemblance of this syndrome to heparin-induced thrombocytopenia, in two of these studies the investigators tested case patients for anti-platelet factor 4 antibodies and found elevated titers in the majority of patients, leading them to propose a new syndrome called vaccine-induced thrombotic thrombocytopenia.

Q: What is vaccine-induced thrombotic thrombocytopenia, and what is the hypothesized mechanism?
A: Vaccine-induced thrombotic thrombocytopenia is a syndrome characterized by venous or arterial thrombosis associated with thrombocytopenia and detectable anti-platelet factor 4 antibodies that

occurs within 3 weeks after receipt of either the Oxford-AstraZeneca or Johnson & Johnson/Janssen COVID-19 vaccine. The American Society of Hematology has developed a case definition with recommendations for diagnostic evaluation and management of patients with suspected VITT.

Q: What are the long-term safety implications of the vaccines?
A: In all the COVID-19 vaccine trials, the rate of serious adverse events was low. Additional data on long-term safety will be available with more time and as more individuals get vaccinated. Adverse events that occur in an individual following COVID-19 vaccination will be reported to VAERS. Furthermore, CDC has developed a voluntary smartphone-based tool, called v-safe, which uses text messaging and web surveys to provide near real-time health check-ins after patients receive COVID-19 vaccination.

COVID-19 Vaccination by Patient Population

Q: What is the current recommendation regarding additional vaccine doses in immunocompromised patients?
A: In August 2021 FDA amended the emergency use authorizations (EUAs) for both the Pfizer-BioNTech and Moderna COVID-19 vaccines to allow for the use of a third dose of both products in certain immunocompromised patients. CDC's Advisory Committee on Immunization Practices (ACIP) subsequently recommended consideration of a third dose of mRNA vaccine for the following patient populations:

Active treatment for solid tumor and hematologic malignancies
Receipt of solid-organ transplant and taking immunosuppressive therapy
Receipt of CAR-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
Advanced or untreated HIV infection
Active treatment with high-dose corticosteroids (i.e., ≥20mg prednisone or equivalent per day), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory.

The third vaccine dose should ideally be the same product as the initial two-dose mRNA COVID-19 vaccine series that the patient received (Pfizer-BioNTech or Moderna) – however, if that product is not available, the other mRNA COVID-19 vaccine can be used. The third dose should be administered at least 28 days after completion of the initial two-dose mRNA COVID-19 vaccine series.

There are no current recommendations to administer additional mRNA COVID-19 vaccine doses to prior recipients of the Johnson & Johnson/Janssen COVID-19 vaccine, or to administer additional doses of the Johnson & Johnson/Janssen COVID-19 vaccine.

Given the potential for a less robust immune response to COVID-19 vaccines among immunocompromised individuals, CDC continues to recommend that these individuals continue appropriate precautions (masking, social distancing, etc.) even after vaccination.

Q: What is the benefit of vaccinating individuals who have had COVID-19?

A: Multiple studies have shown that previously infected individuals mount a robust immune response following receipt of COVID-19 vaccines, even after just a single dose. Furthermore, there are accumulating data that vaccination after prior infection can boost immune responses against SARS-CoV-2 variants of concern – in fact, the vaccine response in previously infected individuals may be superior to that in individuals without prior infection (Wang, June 2021; Stamatatos, June 2021; Reynolds, June 2021; Lyski, June 2021 -preprint, not peer-reviewed; Leier, June 2021 -preprint, not peer-reviewed; Urbanowicz, August 2021).

Although the clinical trials of COVID-19 vaccines excluded seropositive individuals from their efficacy calculations, there are emerging data that vaccination can also confer protection against reinfection. In a case-control study of SARS-CoV-2 reinfections in Kentucky, investigators found that individuals who had had natural infection in 2020 and who did not receive a vaccine had 2.34 times the odds of reinfection compared with individuals who had natural infection and then subsequently received a COVID-19 vaccine (Cavanaugh, August 2021).

Q: What is known about vaccine immune responses among solid organ transplant (SOT) recipients?

A: There are accumulating data that SOT recipients may have a less robust antibody response to COVID-19 vaccines than healthy individuals (summary of data presented to the CDC Advisory Committee on Immunization Practices (ACIP) on July 22, 2021). Most of the available data are on anti-SARS-CoV-2 spike antibody responses using commercially available assays, which are not approved by the FDA for use as indicators of protective immunity. Substantially fewer data exist about neutralizing activity or cellular responses following vaccination in this patient population.

For more information, please see our Vaccines in Special Populations page as well as the Joint AST/ASTS/ISHLT Statement about Vaccine Efficacy in Organ Transplant Recipients.

Q: For racial/ethnic populations who were less well represented in the COVID-19 vaccine studies, how do we know if the vaccines are equally safe and efficacious?

A: All the COVID-19 vaccine Phase 3 trials included individuals from diverse racial/ethnic groups. There were no specific safety signals related to any of the vaccines by racial/ethnic group. There were too few cases in the subgroup of each of these populations to determine a robust point estimate for efficacy stratified by racial/ethnic group. Overall, there were no significant differences in efficacy for each of the vaccines between these groups.

More information on the patient populations included in the clinical trials of these vaccines is available on our vaccine-platform-specific pages.

Q: What is the efficacy of the vaccines in those with comorbidities, such as obesity, hypertension, chronic kidney disease, diabetes or chronic heart and lung disease?

A: All the COVID-19 vaccine Phase 3 trials included individuals with co-morbidities associated with an increased risk for severe COVID-19. In the analyses of the Pfizer-BioNTech, Moderna and Johnson & Johnson/Janssen COVID-19 vaccine trials, these individuals were pooled together for vaccine efficacy

calculations because there were too few cases in the subgroup of patients with each comorbidity to determine a robust point estimate stratified by individual condition. Overall, there were no significant differences in efficacy for each of the vaccines between individuals with "any comorbidity" and those with no comorbidities.

Q: What is known about the safety of the COVID-19 vaccines in pregnant or lactating individuals?

A: Pregnant people were excluded from the pre-authorization studies of all the COVID-19 vaccines. A small number of pregnancies did occur during the Phase 3 trials (23 in the Pfizer-BioNTech trial, 13 in the Moderna trial and 8 in the Johnson & Johnson/Janssen trial), but too few to draw any meaningful conclusions about safety. Thus, our knowledge of the safety of COVID-19 vaccines in pregnancy comes from post-authorization studies.

In an analysis of safety data collected through v-safe and VAERS (Shimabukuro, April 2021), investigators found 35,691 individuals who were identified as pregnant (30,887 or 86.5% were pregnant at the time of vaccination) and who had received a COVID-19 vaccine between Dec. 14, 2020 and Feb. 28, 2021. During this time, only the Pfizer-BioNTech and Moderna COVID-19 vaccines were authorized for emergency use in the U.S. Overall, local and systemic reactogenicity events occurred at a similar rate between pregnant and non-pregnant women.

The authors also analyzed the v-safe pregnancy registry, which included data from 3,958 pregnant people who had received a COVID-19 vaccine. Of these, nearly all (>98%) were between age 25-44 years, 2,136 (54%) had received the Pfizer-BioNTech COVID-19 vaccine and 1,822 (46%) had received the Moderna COVID-19 vaccine; additionally, 1,132 (28.6%) received their first dose of vaccine in the first trimester, 1,714 (43.3%) received it in the second trimester, and 1,019 (25.7%) received it in the third trimester. There were 827 individuals who completed their pregnancy during this time period, of whom 712 individuals delivered 724 live-born infants; of these 9.4% were born preterm, 3.2% were small for gestational age, and 2.2% had major congenital anomalies. These rates were similar to those reported for pregnancies prior to the pandemic; thus, no safety signal was identified for the mRNA COVID-19 vaccines in pregnancy.

No clinical safety data specific to the Johnson & Johnson/Janssen COVID-19 vaccine have been published, and the Phase 3 trial of Ad26.COV2.S excluded individuals who were pregnant at the time of screening or planned to become pregnant within 3 months of vaccination. Only 8 pregnancies occurred during the conduct of that study through Jan. 22, 2021 (4 in the vaccine group, 4 in the placebo group), thus no conclusions about safety can be drawn.

The Pfizer-BioNTech, Moderna and Johnson & Johnson/Janssen COVID-19 vaccine EUAs/approvals do not exclude pregnant or lactating individuals. Per CDC ACIP recommendations, people who are pregnant or breastfeeding may choose to be vaccinated with any of these vaccines. There is no recommendation for routine pregnancy testing before receipt of a COVID-19 vaccine. Those who are trying to become pregnant do not need to avoid pregnancy after COVID-19 vaccination. The EUA for the Johnson & Johnson/Janssen vaccine has been updated to include information about the risk of thrombosis with thrombocytopenia syndrome in women under age 50 (who are of childbearing age).

The American College of Obstetricians and Gynecologists maintains updated recommendations regarding COVID-19 vaccination in pregnant and lactating individuals.

Q: Can the COVID-19 vaccines make people of child-bearing age infertile?

A: No. There is no evidence linking any of the COVID-19 vaccines to infertility. This myth arose as a result of misinformation circulated on the internet regarding the antigen created by these vaccines (the SARS-CoV-2 spike protein) and its supposed similarity to a protein important for placental attachment (syncytin-1). None of the COVID-19 vaccines contain syncytin-1, nor does the genetic material used in the vaccines encode for syncytin-1. Furthermore, the SARS-CoV-2 spike protein that is generated as a result of vaccination with the currently available COVID-19 vaccines has no structural similarity to syncytin-1, and no data indicate that the antibodies formed as a result of COVID-19 vaccination target syncytin-1.

Q: What is known about the safety of COVID-19 vaccines in immunocompromised hosts, e.g., people with HIV, people who have received organ or stem cell transplants, people receiving chemotherapy for cancers or people receiving chronic immunosuppressive therapy for autoimmune and other disorders?

A: The theoretical risks of vaccination (of any kind, not just COVID-19 vaccines) in immunocompromised individuals fall into two main categories: 1) the risk associated with live virus vaccines, or 2) the risk of exacerbating an immunologically-driven process (e.g., an autoimmune disease or organ rejection) as a result of the immune activation generated by the vaccine.

Immunocompromised individuals were mostly excluded from the pre-authorization studies of the currently available COVID-19 vaccines; therefore, there are only limited safety data about these vaccines in these patient populations. However, none of the currently available COVID-19 vaccines are live virus vaccines; the viral vector vaccines are replication-deficient (or replication incompetent), meaning the viral vector used to deliver the SARS-CoV-2 genetic material does not have the capability for self-replication and transmission to other cells or other individuals. Thus, in terms of the theoretical risks associated with live virus vaccines, there is no risk to immunocompromised individuals associated with the currently authorized COVID-19 vaccines. Additionally, to date, there have been no data — either from clinical trials or from post-authorization observational studies — to suggest an elevated risk of autoimmune or inflammatory conditions among COVID-19 vaccine recipients.

Q: Is the vaccine safe for transplant patients?

A: Immunocompromised people may be at risk for severe COVID-19; therefore, CDC states these groups may receive the vaccine if there are no contraindications. Transplant recipients should be counseled that the effectiveness and safety profile of these vaccines for them are not currently known. However, as these are not live virus vaccines, it is unlikely that these vaccines would pose a safety risk. It is important for there to be intact host immunity in individuals receiving the vaccine for there to be optimal protective immunity post-vaccination, especially with respect to antigen presentation, B and T cell activation and plasma B cell antibody generation. Therefore, individuals lacking functional adaptive immune cells may be unable to generate a fully protective immune response to the SARS-CoV-2 vaccine. Therefore, transplant recipients should be advised regarding the importance of maintaining all current guidance to protect themselves even after vaccination. Additionally, caregivers and household contacts should be strongly encouraged to get vaccinated when vaccine is available in an effort to protect the patient.

Q: Are there any considerations regarding COVID vaccination in oncology patients, many of whom are immunocompromised either by virtue of their disease of cancer or their treatment, e.g., chemotherapy, radiation, stem cell transplant? Do we think it will be safe and efficacious in this group?

A: Persons with HIV infection or other immunocompromising conditions, or who take immunosuppressive medications or therapies, might be at increased risk for severe COVID-19. Data are not currently available to establish vaccine safety and efficacy in these groups. Persons with stable HIV infection were included in mRNA COVID-19 vaccine clinical trials, though data remain limited. Immunocompromised individuals may receive COVID-19 vaccination if they have no contraindications to vaccination. However, they should be counseled about the unknown vaccine safety profile and effectiveness in immunocompromised populations, as well as the potential for reduced immune responses and the need to continue to follow all current guidance to protect themselves against COVID-19.

Oncology patients should be counseled that the effectiveness and safety profile of these vaccines for them are limited. As these are not live virus vaccines, it is unlikely that these vaccines would pose a safety risk. It is important for there to be intact host immunity in individuals receiving the vaccine for there to be optimal protective immunity post-vaccination, especially with respect to antigen presentation, B and T cell activation and plasma B cell antibody generation. Therefore, individuals lacking functional adaptive immune cells may be unable to generate a fully protective immune response to the SARS-CoV-2 vaccine. Therefore, patients with cancer should be advised regarding the importance of maintaining all current guidance to protect themselves even after vaccination. Additionally, caregivers and household contacts should be strongly encouraged to get vaccinated when vaccine is available in an effort to protect the patient.

Q: Can patients with autoimmune diseases receive the vaccines? Is there concern for triggering autoimmune diseases/responses in susceptible individuals?

A: Autoimmune disease is not a contraindication for the mRNA vaccines. The study populations for both mRNA vaccine trials included participants with autoimmune disease. No imbalances were observed in the occurrence of symptoms consistent with autoimmune conditions or inflammatory disorders in clinical trial participants who received an mRNA COVID-19 vaccine compared to placebo.

Q: In patients with HIV, are there any recommendations for getting the vaccine in patients based on CD4 count and viral suppression?

A: Individuals with well-controlled HIV were included in the mRNA vaccine trials; however, the number was small. Therefore, there are insufficient data to establish efficacy and safety in this group. Because people with HIV may be at risk for severe COVID-19, CDC recommends this group may still receive the vaccine if there are no contraindications. People with HIV, particularly those with low CD4 counts or who are not on HAART, should be counseled that they may have a weakened immune response when compared to the general population, and thus should be advised regarding the importance of maintaining all current guidance to protect themselves even after vaccination. Additionally, caregivers and household contacts should be strongly encouraged to get vaccinated when the vaccine is available in an effort to protect the patient.

Q: In the Johnson & Johnson/Janssen COVID-19 vaccine trial, what was the vaccine efficacy in HIV patients? What are the implications?

A: The Phase 3 trial of Ad26.COV2.S included 1,218 individuals with HIV, which constituted 2.8% of the total study population. There were too few outcomes among this subgroup to draw any meaningful

conclusions about vaccine efficacy. Specifically, there were 5 cases of moderate to severe/critical COVID-19 in both the vaccine and placebo group starting at least 14 days after vaccination, and 2 cases in the vaccine group and 4 in the placebo group starting at least 28 days after vaccination. Safety and immunogenicity studies in immunocompromised individuals are planned, but details of these studies are not yet available.

Q: What concomitant medications or diseases may inhibit or prevent the vaccine from inducing immune response?

A: According to the American Society of Hematology and the American Society for Transplantation and Cellular Therapy, the following immunocompromised patient populations could have attenuated or absent response to SARS-CoV-2 vaccines (this list is not comprehensive):

- "Primary and secondary immunodeficiencies involving adaptive immunity;
- Splenectomy or functional asplenia (e.g., sickle cell disease);
- B cell directed therapies (e.g., blocking monoclonal antibodies against CD20 or CD22, bispecific agents like blinatumomab, CD19 or CD22-directed CAR-T cell therapies, BTK inhibitors);
- T cell directed therapies (e.g., calcineurin inhibitors, antithymocyte globulin, alemtuzumab);
- Many chemotherapy regimens;
- High-dose corticosteroids (20 mg per dose or >2 mg/kg/day daily prednisone or equivalent);
- Hematopoietic cell transplantation, especially within the first 3-6 months after autologous HCT and often longer after allogeneic HCT;
- Underlying aberrant immunity (e.g., graft-vs.-host disease, graft rejection, absent or incomplete immune reconstitution, neutropenia, lymphopenia)."

COVID-19 Vaccine Practical Considerations

Q: What is known about "mixing and matching" vaccine doses of different types?

A: In the United States, "mixed-product" vaccine schedules – using more than one vaccine type to complete a series – are not currently recommended, unless the product needed to complete a two-dose vaccine series is not available at the time of the second dose, or the individual experienced a severe adverse event related to the first dose (making the second dose contraindicated). However, given the availability of multiple vaccine formulations, and ongoing development of additional vaccine products (e.g., nanoparticle and subunit vaccines), there is considerable interest in understanding the safety and efficacy of a "mixed" or heterologous vaccine schedule.

To date, there are no published data about the immunogenicity or efficacy of a mixed schedule that includes currently authorized mRNA vaccines (Pfizer-BioNTech or Moderna) and the Johnson & Johnson/Janssen COVID-19 vaccine. Several studies outside the US have evaluated heterologous schedules containing mRNA vaccines and the Oxford-AstraZeneca COVID-19 vaccine, though the time between the first and second dose of vaccine in these studies has been variable. Most of these studies have concluded that a two-dose schedule that includes both vaccines, in either order, generates a robust antibody and cellular response, compared with a single dose of either vaccine. Furthermore, in the studies where a heterologous and homologous (i.e., containing two doses of the same vaccine product) were directly compared, the safety profile and immune responses with both schedules appeared to be similar (Borobia, June 2021; Shaw, May 2021; Liu, August 2021; Ostadgavahi, May 2021; Hillus, medRxiv pre-print June 2021; Schmidt, medRxiv pre-print June 2021; Tenbusch, July 2021;

Dimeglio, August 2021). In one study, a heterologous schedule containing the Oxford-AstraZeneca and Pfizer-BioNTech COVID-19 vaccines elicited a more robust cellular response and higher neutralizing antibody titers against SARS-CoV-2 variants than a homologous schedule containing two doses of the Oxford-AstraZeneca vaccine (Barros-Martins, July 2021).

Q: How should we counsel patients about taking acetaminophen or non-steroidal anti-inflammatory drugs to prevent or treat vaccine-associated local or systemic adverse effects?

A: Routine prophylactic administration of these medications for the purpose of preventing post-vaccination symptoms is not currently recommended, as information on the impact of this on both the immune response to the vaccine and on post-vaccine symptoms is not currently available. Per CDC, acetaminophen or NSAIDs may be taken for the treatment of post-vaccination local or systemic symptoms. In those that are pregnant, acetaminophen is preferred.

Q: What are the recommendations regarding co-administration of other non-COVID-19 vaccines at the same time as or closely spaced with COVID-19 vaccines?

A: Per CDC recommendations, COVID-19 vaccines can be administered with regard to timing of other vaccines. Of note, the effect of co-administration or closely spaced administration of COVID-19 and non-COVID-19 vaccines on reactogenicity has not yet been well characterized.

Q: How should early, late or missed doses of vaccine be managed? What if an individual experiences an adverse reaction to the first dose of a two-dose COVID-19 vaccine?

A: CDC maintains up-to-date recommendations about COVID-19 vaccine administration. The Pfizer-BioNTech and Moderna COVID-19 vaccines are two-dose vaccines, whereas the Johnson & Johnson/Janssen COVID-19 vaccine is a single dose. The recommended interval between the two doses of the mRNA COVID-19 vaccines are as follows:

- Pfizer-BioNTech COVID-19 vaccine – dose 2 should be given 21 days (3 weeks) after dose 1
- Moderna COVID-19 vaccine – dose 2 should be given 28 days (4 weeks) after dose 1

In general, if an individual receives two doses of an mRNA vaccine, there is no need to repeat the series and the individual should be considered fully vaccinated starting 14 days after the second dose. If the second dose is missed or delayed for any reason, it should be scheduled at the earliest opportunity.

In limited exceptional circumstances where an individual cannot be administered the same mRNA vaccine product for their second dose as they received for their first — either because it is not available or because the identity of the first dose is unknown — any available mRNA vaccine product can be administered at a minimum interval of 28 days after the individual's first dose. If this occurs, this is considered an administration error that should be reported to VAERS.

Finally, in limited situations where an individual develops an adverse reaction to the first dose of an mRNA vaccine that is considered a contraindication to the second dose (with the same or a different mRNA vaccine), the Johnson & Johnson/Janssen COVID-19 vaccine can be administered at a minimum interval of 28 days after the first dose of the mRNA vaccine. This individual should be considered fully vaccinated with the Johnson & Johnson/Janssen COVID-19 vaccine starting 14 days after the dose.

Q: Why is it necessary to vaccinate people who have had COVID-19?

A: Given that we do not know how long immunity after COVID-19 infection lasts (notably, reinfection cases have happened 3 months following COVID-19 infection), and given people have variable immune responses after having COVID-19 (some data suggest people with mild cases may have a less robust immune response than those with severe disease), CDC recommends offering vaccination to individuals regardless of history of prior symptomatic or asymptomatic SARS-CoV-2 infection. Viral testing to assess for acute SARS-CoV-2 infection or serologic testing to assess for prior infection solely for the purpose of vaccine decision-making is not recommended. Vaccination of individuals with known current SARS-CoV-2 infection should be deferred until they have recovered from the acute illness (if they had symptoms) and criteria have been met for them to discontinue isolation.

Q: If someone has a history of COVID-19, are they more likely to experience a side effect from a COVID-19 vaccine?

A: Large-scale data on side effects in this particular group are not yet available. All of the currently available COVID-19 vaccines have been demonstrated to be safe in patients with a prior history of documented SARS-CoV-2 infection (whether asymptomatic or symptomatic). In an immunogenicity study of 110 individuals with and without prior SARS-CoV-2 infection who received an mRNA COVID-19 vaccine, participants who were seropositive at baseline did experience more systemic adverse events associated with vaccination compared with those who were seronegative at baseline, but there were no serious adverse events reported in either group (Krammer, April 2021).

Q: Are there any data concerning vaccine administration during PCR- and/or symptom-diagnosed SARS-CoV-2 infection?

A: Vaccination of persons with known current SARS-CoV-2 infection should be deferred until they have recovered from the acute illness (if they had symptoms) and criteria have been met for them to discontinue isolation. This recommendation applies to persons who develop SARS-CoV-2 infection before receiving any vaccine doses as well as those who develop SARS-CoV-2 infection after the first dose but before receipt of the second dose.

Q: If a fully or partially vaccinated individual develops COVID-19, should their infection be managed differently than an unvaccinated individual?

A: There are limited data on breakthrough SARS-CoV-2 infections after vaccination. Based on current knowledge, prior receipt of a COVID-19 vaccine should not affect treatment decisions (including use of monoclonal antibodies, convalescent plasma, antiviral treatment or corticosteroid administration) or timing of such treatments.

Q: How does prior receipt of antivirals (such as remdesivir), convalescent plasma or monoclonal antibodies against SARS-CoV-2 impact the choice and timing of COVID-19 vaccination?

A: Prior receipt of antiviral therapy for SARS-CoV-2 infection should not impact vaccination decisions, including viral vector vaccines. There are no data on the safety and efficacy of COVID-19 vaccines in persons who received convalescent plasma or anti-SARS-CoV-2 monoclonal antibodies as part of COVID-19 treatment. Based on the estimated half-life of such therapies as well as evidence suggesting that reinfection is uncommon in the first 90 days after initial infection, vaccination should be deferred for at least 90 days after receipt of those products as a precautionary measure to avoid interference of the antibody treatment with vaccine-induced immune responses. This recommendation does not apply to

non-SARS-CoV-2-specific immunoglobulin therapies, such as intravenous or intramuscular immunoglobulin or RhoGAM, given for other indications.

Q: Do COVID-19 vaccines affect the performance of SARS-CoV-2 diagnostic tests?

A: Receipt of a COVID-19 vaccine will not affect the result of PCR or antigen-based tests for SARS-CoV-2 infection. Antibody-based tests may or may not be affected by prior COVID-19 vaccination depending on the type of assay being used. Assays that measure IgM or IgG antibodies against SARS-CoV-2 nucleocapsid protein will not be affected by currently authorized COVID-19 vaccines because the vaccine does not contain or encode the nucleocapsid protein. Assays that measure antibodies against SARS-CoV-2 spike protein may be variably affected by prior vaccination; however, none of the currently available anti-spike antibody assays is authorized for assessing post-vaccination immunity.

Q: Are there recommendations to test for antibodies to the vaccine after administration?

A: No. At this time antibody testing is not recommended to assess for immunity to COVID-19 following vaccination with any COVID-19 vaccine. A correlate of protection against SARS-CoV-2 infection has not been definitively established; therefore, the results of antibody testing following vaccination should not be used to make vaccination decisions.