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CDC Recommendation Updates

The CDC made updates to several key recommendations on mask use for **vaccinated** individuals and the mode of transmission of SARS-CoV-2.

> **The mask recommendations from the CDC have changed only for vaccinated individuals. As the rate of community transmission is still high throughout the United States, mask use continues to be a necessity for unvaccinated individuals.**

Mode of Transmission

Much of the information in the updated recommendations is not new but has been confirmed through additional studies, and the presentation of the information has been "reformatted to be more concise" (CDC Scientific Brief, 2021). In the scientific brief released by the CDC, they state that "The principal mode by which people are infected with SARS-CoV-2 … is through exposure to respiratory fluids carrying infectious virus."

> **People produce infectious respiratory droplets during exhalation, and infectious particles from SARS-CoV-2 can be released during quiet breathing, speaking, singing, and exercise, as well as symptomatic coughing and sneezing.**

This statement is a change that expands transmission of SARS-CoV-2 to include airborne transmission as well as droplet transmission. Large droplets will settle out of the air within minutes while very fine droplets, and aerosol particles formed when these fine droplets rapidly dry, are small enough that they can remain suspended in the air for minutes to hours.

There are multiple methods that individuals can be exposed to the respiratory droplets released by infectious individuals.

Exposure to infectious particles occurs in three principal ways:

1. Inhalation of very fine respiratory droplets and aerosol particles. Risk of transmission is greatest within three to six feet of an infectious source where the concentration of these very fine droplets and particles is largest.
2. Deposition of respiratory droplets and particles on exposed mucous membranes in the mouth, nose, or eye by direct splashes and sprays
3. Touching mucous membranes with hands that have been soiled either directly by virus-containing respiratory fluids or indirectly by touching surfaces with virus on them.

Researchers have also determined that the risk of infection varies based on the amount of virus an individual is exposed to. However, the amount required to transmit an infection to an uninfected person, or the infectious dose, has not yet been determined.

Because a certain level of virus is needed to cause an infection and levels produced by an infectious individual are largely increased within three to six feet, the CDC continues to suggest keeping at least six feet of distance between people to reduce the dose of virus that might be encountered.

As virus is released from an infected individual, it becomes diluted in the air surrounding the individual, and therefore, the risk for infection decreases with increasing distance from the source and time after exhalation occurred. A combination of mixing of fresh air with the exhaled breath of an infectious person as well as the eventual settling out of heavier droplets over time will dilute the infectious particles. Additionally, exposures to harsh environmental conditions, such as heat and humidity, can lead to a loss of viability of the virus over time. Likewise, when these conditions are not present, the virus will not be diluted, and can linger for longer time periods and spread further from an infectious individual.

Indoor, airborne transmission occurs when infectious individuals are in an enclosed space for an extended time, e.g. more than 15 minutes, allowing for levels of the virus in the air to build up to a concentration sufficient to transmit infections to people more than 6 feet away or to linger after the infectious individual left the area.

The environmental conditions associated with higher risk of airborne infection include

- Enclosed spaces with inadequate ventilation or air handling leading to a high concentration of exhaled respiratory fluids in the form of very fine droplets and aerosol particles.
- Increased exhalation of respiratory fluids when the infectious person is engaged in physical exertion or raises their voice (e.g., exercising, shouting, and singing).
- Prolonged exposure to these conditions, typically more than 15 minutes.

It has been mentioned in some past recommendations by researchers that airborne transmission may require increased spacing between individuals when indoors. However, the CDC has recommended increased ventilation and masking to prevent infection when the levels of virus are likely to increase due to indoor environmental conditions instead of increased spacing. The use of increased ventilation and masking have been shown to be effective at reducing the risks from indoor transmission.

While transmission of the virus is possible through contact with contaminated surfaces, current evidence strongly suggests this type of transmission does not contribute substantially to new infections.

The CDC researchers conclude that

> The available evidence continues to demonstrate that existing recommendations to prevent SARS-CoV-2 transmission remain effective. These include physical distancing, community use of well-fitting masks (e.g., barrier face coverings, procedure/surgical masks), adequate ventilation, and avoidance of crowded indoor spaces. These methods will reduce transmission both from inhalation of virus and deposition of virus on exposed mucous membranes. Transmission through soiled hands and surfaces can be prevented by practicing good hand hygiene and by environmental cleaning.

Updated Mask Recommendations

The CDC has removed the recommendation for fully vaccinated individuals to wear masks except for a few situations (CDC Interim, 2021).

Individuals are considered to be fully vaccinated two weeks after their second dose of a vaccine that requires two doses, such as the Pfizer-BioNTech or Moderna vaccines, or two weeks after a single-dose vaccine, such as the Johnson & Johnson vaccine.

Some people with compromised immune systems, or those who are taking immunosuppressing medications, may still be susceptible to infection with SARS-CoV-2 even after two weeks has elapsed after the final dose. Individuals fitting this description will need to continue to use precautions to minimize the risk of virus transmission as the community transmission rate is still high in the United States, and the possibility of encountering an infectious individual is therefore also still high.

Specifically, the CDC has stated that individuals who have been fully vaccinated

- Can resume activities they did prior to the pandemic without wearing a mask or staying 6 feet apart, except where required by federal, state, local, tribal, or territorial laws, rules, and regulations, including local business and workplace guidance.
- Can travel in the United States without getting tested before or after travel.
- No longer need to self-quarantine after domestic travel.
- No longer need to get tested before leaving the United States unless the destination requires it. A negative test result or documentation of recovery from COVID-19 is required before boarding an international flight to the United States.
- No longer need to get tested 3 to 5 days after international travel.
- No longer need to self-quarantine after arriving back in the United States.
- No longer need to quarantine or be tested for COVID-19 after exposure to someone with COVID-19 unless symptoms consistent with COVID-19 develop. Individuals who work or live in congregate living spaces should get tested regardless of symptoms due to the high risk of facility outbreaks.

It is still necessary to follow local guidance for wearing a mask, including at work or in businesses.

Additionally, it is still a requirement to wear a mask on planes, buses, trains, and other forms of public transportation traveling into, within, or out of the United States, and in United States transportation hubs such as airports and stations.

The change to the recommendations were announced by the Director of the CDC, Rochelle Walensky. The *Washington Post* reported that at the press briefing for the announcement Dr. Walensky described “a growing body of real-world evidence demonstrating the efficacy of the coronavirus vaccines and noted the shots offer protection even against more contagious variants circulating in the United States. She also noted the rarity of breakthrough infections in those who are fully vaccinated and the lesser severity of the relatively few infections that have occurred” (Abutaleb and McGinley, 2021).

Initially, vaccinated individuals were asked to continue using masks because it was not known how well the Pfizer-BioNTech and Moderna vaccines prevented asymptomatic infections. In other words, it was possible that vaccinated individuals may have been infected with COVID-19

and because of the protective effects of the vaccine, been more likely to be asymptomatic and unaware of their illness and spread the virus to a mostly unvaccinated public. In this case, the continuation of mask use was for the protection of others in the community rather than those who had already been vaccinated. Studies in both Israel and the United States of healthcare workers, who were both the first to be vaccinated and who participate in screening programs for COVID-19 regardless of symptoms, allowed for the determination of the effectiveness of the vaccines against asymptomatic infection (Haas et al., 2021 and Thompson et al., 2021).

In the studies in Israel, the vaccine effectiveness at 7 days or longer after the second dose was 91.5% against asymptomatic SARS-CoV-2 infection.

The high level of protection against both asymptomatic and symptomatic infections means that vaccinated individuals are unlikely to be infectious without their knowledge. Other studies have shown that vaccinated individuals with breakthrough cases of COVID-19 after vaccination appear to be less likely to transmit the virus to others even if they have symptoms. In a study in England, there was a 50% reduction in the risk of infection from a vaccinated family member compared to an unvaccinated family member (Harris et al., 2021).

Studies of how the vaccines have worked in real-world scenarios show that the risk of vaccinated individuals causing SARS-CoV-2 infections in unvaccinated people was low.

Another initial concern about the effectiveness of the vaccines against the variants that emerged at around the same time vaccination campaigns has also been allayed. B.1.1.7 was the first identified variant, and the extremely rapid spread in the United Kingdom even after lock-down precautions were put into place made researchers uncertain whether the vaccines would continue to be as effective. Laboratory experiments suggested that the Pfizer-BioNTech and Moderna vaccines were not largely affected by the mutations in B.1.1.7, but it was not possible to accurately predict what the effect on the immune system response and the resulting protection from the vaccine would be. Additionally, B.1.351 and P.1 were also becoming more widespread, and laboratory experiments suggested that there were mutations in these variants that could reduce the effectiveness of all of the vaccines available. The argument for the continuation of mask use for vaccinated individuals in regards to variant viruses was for the protection of those who were already vaccinated.

Since the CDC recommended that vaccinated individuals continue wearing masks, more information has become available about the variants. First, B.1.351 and P.1 have not been found to be present at high levels in the United States. The main variant currently circulating in the United States is B.1.1.7 at 66.2% of infections as measured from samples collected in the two weeks ending April 24, 2021. The next two most prevalent variants in the United States are B.1.526 at 6.9% and P.1 at 5.2%. B.1.351 is present at a rate of 0.8% (CDC-Variant Proportions, 2021). B.1.526 is a variant of interest that was first detected in November, 2020 in New York City and is currently being watched closely because it contains the E484K mutation similar to B.1.351 and P.1. However, as evidenced by the low proportion of cases in the United States, it has not become widespread.

At this time, the variant that is most prevalent in the United States, B.1.1.7, is one that the Pfizer-BioNTech and Moderna vaccines are 85% effective against in

studies in the United Kingdom where 80% of tested samples were B.1.1.7 (Hall et al., 2021)**.**

Therefore, the two main concerns, asymptomatic spread and emergence of variants with unknown properties, that led to public health officials to suggest that vaccinated individuals continue to wear masks have now been shown by scientific evidence to be of negligible concern.

However, there are scenarios when the level of risk may again increase to a point that use of masks is beneficial. The most obvious of these scenarios is if a different variant with more virulent characteristics becomes the most prevalent strain in the United States. It is not yet clear what the effectiveness of the Pfizer-BioNTech and Moderna vaccines are against the B.1.351 or P.1 variant because neither variant is widespread in an area where the two vaccines have been used in a large part of the population. Preliminary information has been reported from Qatar where the B.1.351 and B.1.1.7 are the most prevalent variants circulating and there is a high use of the Pfizer-BioNTech vaccine (Abu-Raddad et al., 2021). The details of the report are discussed in more detail below.

In this study, the effectiveness of the Pfizer-BioNTech vaccine against any documented SARS-CoV-2 infection with the B.1.351 variant was 75.0%.

This is a high level of effectiveness in the prevention of illness, and the protection against severe disease is higher, suggesting that the mRNA vaccines should continue to provide good protection. The response of vaccines to P.1 and B.1.617, the new variant detected in India, is not yet known, and new variants are likely to arise with the continued high transmission rates around the world.

Finally, it is important to understand that the overall process of infection from SARS-CoV-2 is the same for both vaccinated and unvaccinated individuals.

Brief description of the SARS-CoV-2 infection process

- An individual comes into contact with someone who is infectious, and the cells in the upper respiratory tract are exposed to virus particles.
- The virus particles interact with the ACE-2 receptor on cells lining the respiratory tract and infect the cells.
- If a large amount of virus was present, too many cells become quickly infected for the immune system to deal with, leading to an infection that continues to multiply.

This process is aided by the presence of neutralizing antibodies in vaccinated individuals. A neutralizing antibody interacts with the spike protein of the virus so that it can no longer attach to the ACE-2 receptor, preventing the infection. If there are mutations in the spike protein, neutralizing antibodies may not attach as tightly allowing for infections to occur. There may also be instances where the vaccine does not prevent infection against variants where it has had a

high reported effectiveness, which is called a breakthrough infection. A breakthrough infection occurs when a vaccinated person is exposed to enough infectious virus to overcome the protections of the immune system and the vaccine. In many cases, people who have breakthrough infections are those who had a lower than normal response to the vaccine and produced a smaller amount of neutralizing antibodies. There are some individuals where the reasons for a breakthrough infection are not obvious, and it is not feasible for everyone to determine the level of response to the vaccine. Researchers determine how many people have a high response by looking at the number of breakthrough infections that occur after vaccine campaigns begin.

Most of the tests commercially available for detection of antibodies from a previous SARS-CoV-2 infection measure antibodies from the N protein of the virus and not the spike protein that is used in the vaccine. Even in tests that do detect antibodies from the spike protein, tests designed to identify a previous infection are not able to quantify the amount of antibody present in the blood. Therefore, **they cannot determine the magnitude of the response to a vaccine**. There are tests that can specifically measure the antibody response to a vaccination, but these specialized tests must be ordered by a physician and are typically reserved for individuals who are immunocompromised or taking medications that suppress the immune system.

The CDC reported the overall number of breakthrough cases up to April 26, 2021 (CDC Previous, 2021). At that point, 95 million people had been fully vaccinated, and there were 9,245 breakthrough infections. This corresponds to approximately 97 breakthrough infections per million fully vaccinated people, or 0.0097% of those who were fully vaccinated getting COVID-19 after vaccination.

> **Breakthrough infections with the currently available COVID-19 vaccines have been incredibly rare suggesting that antibodies produced in response to the vaccines are effective in neutralizing the virus and most individuals produce sufficient amounts to protect from infection.**

Because breakthrough infections are possible, the CDC recommends that

> **Even if you are fully vaccinated, if you have symptoms of COVID-19 you should get tested and stay away from others.**

Breakthrough infections in vaccinated individuals would be expected to be more frequent in people who were exposed to more infectious individuals in the same manner that infection would be more likely in those who are unvaccinated. Currently, the level of community transmission in the United States is falling, but it is falling from a very high level. Therefore, the community transmission rate is still considered very high.

Continuing mask use and limiting interactions in the types of environments described above that promote concentration of airborne infectious particles (poor ventilation for long time periods) in groups where it is not possible to know the vaccination status of the members is not currently part of the CDC recommendations, but has been suggested by PCI Medical Directors as a way to continue to protect your health and the health of those around you as more information becomes available.

Some experts fear that individuals who have not been vaccinated yet, including those who are not yet eligible such as children under the age of 12, may see an increased risk of transmission because unvaccinated adults may stop using masks (Wen, 2021).

For those who are not yet fully vaccinated, it continues to be important to use high-quality, well-fitting masks when in indoor public places where the vaccination status of individuals are not known and/or mask use is not being observed.

Transmission outdoors where there is fresh air circulating has been found to be very rare (less than 1%), and have been observed only in a few cases (Leonhardt, 2021). Since the risk of transmission outside is very low even for those who are unvaccinated, use of masks is less important.

The highest danger is indoors for the unvaccinated due to a potential increase in transmission risk from the actions of other unvaccinated individuals.

Vaccine Updates

The CDC has also changed the recommendations for the timing of COVID-19 vaccines with other vaccines. Previously, it was suggested that the COVID-19 vaccine not be given within 14 days of other vaccines, but the good safety profile across multiple different groups suggests that side effects from the COVID-19 vaccines would not be increased due to interactions with other vaccines.

COVID-19 vaccines and other vaccines may now be administered on the same day or at any time that is consistent with the other vaccine's directions for use.

Vaccine Effectiveness and Breakthrough Infections

Additional information from the vaccination campaign in Israel with the Pfizer-BioNTech vaccine has been reported (Chodick et al., 2021). The data in this report includes about 1,178,597 individuals in the Maccabi Healthcare Services, which is a state-run healthcare fund that covers approximately 25% of the population of Israel. There were 4514 infections before the participants were considered fully vaccinated and 728 in the seven to 27 days after the second dose. Based on this data, the proportion of breakthrough infections for fully vaccinated individuals was 0.08%.

The vaccine effectiveness in prevention of infection with SARS-CoV-2 was 90% and 94% against symptomatic COVID-19.

Among immunosuppressed participants, vaccine effectiveness against infection was 71%. The reduction in risk for hospitalization for those who became ill after reaching full vaccination status was 82% for individuals 16 to 44, 45% for those 45 to 64, and 56% for individuals 75 and older. The authors report that these values are comparable to those observed in the clinical trials for the Pfizer-BioNTech vaccine.

Effects on the Number of Cases Based on Vaccine Characteristics and Coverage

Researchers modeled how changes in the efficacy, proportion of the population covered by the vaccine, and the speed at which that vaccine is deployed can affect the number of cases, hospitalizations, deaths, quality-adjusted life-years, medical costs, and productivity costs from SARS-CoV-2 infections in the United States between February, 2020 and December, 2022 (Bartsch et al., 2021).

In the first scenario, the researchers started with a population where 20% had previously been infected with COVID-19. Based on the number of confirmed cases on May 20, 2021, approximately 10% of the United States has had COVID-19 (JHU, 2021).

With 50% vaccine coverage in 180 days and using a vaccine that is 70% effective, vaccination would result in a decrease of 20.9 million cases, 775,980 hospitalizations, and 91,660 deaths with an increase of 977,730 life-years gained compared to a scenarios where a 40% vaccine coverage was achieved in the same time period.

The decreased number of illnesses would also lead to a savings of $9.6 billion in direct medical costs and $19.8 billion in productivity losses. In this range, for every 1% increase in vaccine coverage there is a resulting 2.1 million fewer COVID-19 cases, 77,590 fewer hospitalizations, 9,160 fewer deaths, and 97,770 life-years gained along with a savings of $960.7 million in direct medical costs saved and $1.9 billion in productivity losses.

Shortening the time it took to reach vaccination coverage levels from 360 to 270 or 180 days further reduced the number of cases, deaths, and costs.

For example, reaching a 50% vaccine coverage level by 270 days instead of 360 days using a 70% efficacious vaccine decreased the number of cases by 4.2 million and deaths by 18,500 and saved $4.5 billion in total costs. When the time frame was further shortened to 180 days from 270 the number of cases decreased by 2.6 million and the number of deaths decreased by an additional 11,300 with savings of $5.3 billion in total costs. This analysis highlights how a slow roll-out of a vaccine can reduce the value of a highly effective vaccine, and a 90-day delay in reaching 50% would result in 5.8 million additional cases, 24,370 more deaths, and cost $3.5 billion more in direct medical costs. This may be more important as well since the current timeline would put the 90-day delay from summer to fall when virus transmission would be

expected to increase due to the change in environmental conditions from hot and humid to cold and dry.

The authors state that the model shows that investment in vaccination of the population leads to a cost savings with increased vaccine coverage due to a reduction in medical costs and lost productivity, which could be important for giving decision-makers a sense of value in making vaccines more accessible.

Overall, the model also illustrates that vaccine coverage can overcome a less effective vaccine, which may become important if variants of SARS-CoV-2 become resistant to currently available vaccines. The authors give the example that increasing vaccination coverage from 50% to 70% using a vaccine with 70% vaccine efficacy will prevent 9.2 million cases while going from a 70% efficacious vaccine to 90% prevent 7.1 million cases with a constant 50% coverage.

Vaccines in Pregnant and Lactating Women

In a study of 103 women, researchers investigated the effect of vaccination on pregnant, lactating, and non-pregnant participants (Collier et al, 2021). There were 30 participants who were pregnant, and 16 who were lactating. After the second vaccine, 14% of pregnant participants, 44% of lactating participants, and 52% of non-pregnant participants reported a fever. The researchers also tested for the production of antibodies, the presence of neutralizing antibodies, antibodies that functioned by attaching in a way that was not neutralizing, and the response of T cells.

All of these immune responses were observed in all of the participants, and vaccine-elicited antibodies were transported to infant cord blood and breast milk, indicating a level of protection to infants born to vaccinated mothers.

The response of antibodies produced after vaccination to the SARS-CoV-2 variants B.1.1.7 and B.1.351 were reduced, as observed in other studies, but T-cell responses were preserved against viral variants.

Infections in Nursing Homes after Vaccination Campaigns

Researchers investigated the incidence of SARS-CoV-2 infection among vaccinated residents and unvaccinated residents of 280 nursing homes across 21 states after the completion of vaccination campaigns (White et al., 2021). Of the residents in the study, 18,242 received at least one dose of mRNA vaccine, 13,048 also received the second dose of vaccine, and 3990 residents received no doses and were unvaccinated.

The incidence of infection decreased over time among both vaccinated residents and unvaccinated residents. For example, after receipt of the first vaccine dose, there were 822 cases of COVID-19, corresponding to 4.5% of vaccinated residents, within zero to 14 days and 250 cases, corresponding to 1.4% of vaccinated residents, at 15 to 28 days. There were 130 COVID-19 incident cases, corresponding to 1.0% of vaccinated residents, within zero to 14 days after receipt of the second dose and 38 cases, or 0.3% of vaccinated residents, after 14 days.

Among unvaccinated residents, incident cases decreased from 173 cases, corresponding to 4.3% of unvaccinated residents, within zero to 14 days after the first vaccination clinic to 12 cases, or 0.3% of unvaccinated residents, at more than 42 days after the clinic.

There was not a consistent pattern with the incidence of infection among residents relative to rates of vaccination among staff members.

Vaccine Effectiveness in Individuals with Lower Immune Responses

Individuals who have received solid organ transplants who must take maintenance immunosuppression medications are known to have a lower response to vaccinations (Boyarsky et al., 2021). An earlier report from researchers measuring the response of these individuals after the first dose of mRNA COVID-19 vaccines indicated that only 17% had a positive antibody response. An expanded study was published of 658 individuals who received their second dose between December 16, 2020, and March 13, 2021 and were observed until April 13, 2021. There were 473 participants who were taking maintenance immunosuppression medications in this study and 185 who were not.

At a median of 21 days, with a range between 18 and 25 days, after the first dose, antibody was detectable in 15% of participants. When tested a median of 29 days, with a range between 28 and 31 days, after the second dose antibody was detectable in 54% of participants. As a group, 15% had measurable antibody response after dose 1 and dose 2, 46% had no antibody response after dose 1 or 2, and 39% had no antibody response after dose 1 but produced antibodies after dose 2. In the 473 individuals who were taking maintenance immunosuppression medications, 8% had an antibody response after dose one and dose two, 57% had no antibody response after dose one or dose two, and 35% had no antibody response after dose one but produced antibodies after dose two.

The authors conclude that there is an improvement in vaccine response after the second dose, but a substantial proportion of transplant recipients likely remain at risk for COVID-19 after 2 doses of mRNA vaccine.

In a group of individuals receiving hemodialysis, researchers also found a reduced response to COVID-19 vaccines (Goupil et al., 2021). The study included 154 participants of which 135 received hemodialysis and had not had COVID-19, 19 received hemodialysis and had a previous SARS-CoV-2 infection, and 40 healthcare workers who did not receive hemodialysis. All of the participants received one dose of the Pfizer-BioNTech vaccine, and response to vaccination was assessed by examination of blood samples every four weeks.

Four weeks after the first dose, 75 out of 131, or 57%, of participants receiving hemodialysis who had not previously had COVID-19 had undetectable levels of antibody to the vaccine.

Of the healthcare workers who had not had COVID-19 before vaccination, one participant out of 20, or 5%, had undetectable levels of antibody. By eight weeks after vaccination, none of the

participants with undetectable levels at four weeks had developed antibodies. During the study, four participants receiving hemodialysis were diagnosed with COVID-19, and three were admitted to the hospital due to hypoxia. As of the publication of the study, one had died, one remained in the intensive care unit, and one had been discharged.

A single dose of the Pfizer-BioNTech vaccine failed to elicit an antibody response in most individuals receiving hemodialysis who had not had COVID-19 previously.

In participants receiving hemodialysis who had previously had COVID-19, the level of antibodies to the spike protein four weeks after vaccination were lower than the levels measured in healthcare workers with a previous SARS-CoV-2 infection three weeks after being vaccinated, but they were similar by eight weeks. The levels measured in individuals receiving hemodialysis were not substantially different from those observed in convalescent plasma.

The response to a single dose of vaccine in individuals receiving hemodialysis who had previously had COVID-19 was slower than the response in healthy individuals, but the magnitude of the response was similar.

Delaying Second Dose

Due to initial vaccine shortages, public health officials in the United Kingdom opted to delay the second dose of vaccines to extend the number of people who could be treated (Parry et al., 2021). The production of the vaccines has now caught up to a certain extent, allowing for the second dose to be administered and researchers were able to evaluate the effect of the delay.

The study included 172 individuals over the age of 80 in Birmingham, United Kingdom who received the Pfizer-BioNTech vaccine. There were 99 participants of the group who received the vaccine with the typical 3-week dosing schedule, and 73 participants received the two vaccine doses 11 to 12 weeks apart on an extended schedule. Two blood samples were taken for the study to evaluate the response to the vaccine. In individuals with the standard interval between doses, the first sample was taken at two to three weeks after the second dose and the second sample was taken eight to nine weeks after the second vaccine dose. In participants with an extended interval between doses, blood samples were taken five to six weeks following the first dose vaccine and two to three weeks after the second dose. The participants were also screened for the presence of natural infection with SARS-CoV-2 at these time points and those who had been infected were excluded from further study because the researchers wanted to determine the difference in immune response from the change in the timing of the doses only.

In the group that had the standard interval between doses, vaccine elicited antibodies to the spike protein were observed in 100% of the participants at both the first and second time points. In the extended interval group, antibodies were detectable in 91% of the group five to six weeks after the first dose and in 100% of the group after the second dose.

When the researchers measured the magnitude of the antibody response, the peak antibody response of the extended interval group was 3.5-times higher than the standard interval group.

However, in the two to three week period where the extended interval group had only one dose the antibody levels were 67-times lower than those of the standard interval group.

The researchers also investigated the response of T cells to the two dosing strategies. Two weeks after the second dose, the 60% of the standard interval group had a T-cell response, but the proportion of responders declined to 15% eight to nine weeks after the second dose. Five to six weeks after the first dose, 8% of participants in the extended interval group had a T-cell response, which rose to 31% two weeks after the second dose. The magnitude of the response was higher in those receiving the standard interval vaccination. Overall, the T-cell response of both groups was lower than that seen in younger individuals, which may reflect the reduced immune capacity that occurs with age.

The relative contribution of antibodies compared to T-cells in the immune response to SARS-CoV-2 is not yet known. However, recent studies have shown that antibody levels remain robust for six months following standard-interval mRNA vaccination, but begin declining around 53 days after the second dose. The authors conclude that extending the period between the two doses may increase the level of antibodies thereby extending the time before additional boosters are needed. They add that the "potential disadvantage of this approach is that it extends the period of partial protection prior to the second dose" when antibody and T-cell levels are still low. Results from other studies indicate that single vaccination delivers protection against severe COVID-19 and hospitalization or death, however.

In a discussion of the results in the journal *Nature*, Stephen Griffin, a virologist at the University of Leeds, in the United Kingdom, stated that the importance of the United Kingdom being in lockdown while the extended interval doses were used also should be part of any overall analysis (Ledford, 2021). He also said, "People are theoretically vulnerable between their first and second jab. What's worked in the UK is maintaining restrictions at the same time as vaccinating."

The *New York Times* has also reported that the United Kingdom is changing its vaccination strategy to swiftly deliver the second dose to all individuals over the age of 50 due to indications that the new variant B.1.617 was spreading in Britain (New York Times, 2021). The variant is discussed in more detail below. The number of cases of the variant increased in Britain from 520 cases to 1,313 in one week.

Mixed Vaccine Results

All of the vaccines developed to date target the spike protein of SARS-CoV-2, and they all stimulate the immune system to produce antibodies that target the spike protein. Theoretically, therefore, it should be possible to get an initial dose of one and use a different company's vaccine as a booster because they both lead to the production or deliver the same viral protein. This would be useful with the current supply issues around the world and the logistical difficulties in making sure sufficient quantities are available at the same location in three weeks for follow-up doses.

Researchers in the United Kingdom investigated the safety of using the AstraZeneca-Oxford vaccine with the Pfizer-BioNTech vaccine in the four possible initial and boost scenarios (Shaw et al., 2021). There were 463 participants randomized to get the initial and booster shot 28 days apart and 367 participants randomized to the initial and booster shot 84 days apart.

They found that mixing the different types of vaccines led to a higher rate of side effects after the second dose. The most common was fever with 34% of those who received a first dose of AstraZeneca-Oxford followed by a dose of the Pfizer-BioNTech vaccine reporting a fever compared to 10% of those who got two doses of the AstraZeneca-Oxford vaccine. Overall, there were more reports of chills, fatigue, headache, joint pain, malaise, and muscle aches among participants who received two different vaccines.

The researchers are currently analyzing the immune reactions to the vaccinations, but stated that using vaccines from different manufacturers may have short-term disadvantages due to an increase in side effects.

In a commentary on the study, Daniel Altmann, an immunologist at Imperial College London, said that mixing of different vaccines makes sense because it should lead to a stronger immune response (Callaway, 2021). What is not certain is what occurs if additional boosters of COVID-19 vaccines are needed to provide continuing long-term protection. Previous studies have shown that adenovirus vaccines, like the AstraZeneca-Oxford vaccine, become less effective when given over time because the body begins to response more to the adenovirus than the inserted vaccine targets. mRNA vaccines in contrast may cause stronger side effects with added doses.

Vaccine Effectiveness with Variants

Real-world data from the vaccine campaign in Qatar allowed for an assessment of the effectiveness of the Pfizer-BioNTech vaccine against both B.1.1.7 and B.1.351 (Abu-Raddad et al., 2021). As of March 31, 2021, a total of 385,853 individuals in Qatar had received at least one vaccine dose, and 265,410 had completed the two doses. Cases of B.1.1.7 began circulating in mid-January of 2021, and B.1.351 was first identified in the country in mid-February of 2021 with rapid expansion observed by mid-March.

Viral genome sequencing conducted from February 23 through March 18 indicated that 50.0% of cases of Covid-19 in Qatar were caused by B.1.351 and 44.5% were caused by B.1.1.7.

Researchers found that the Pfizer-BioNTech vaccine effectiveness against B.1.1.7 was 89.5% at 14 or more days after the second dose, which is similar to the effectiveness reported previously in the United Kingdom.

The effectiveness against any documented infection with the B.1.351 variant was 75.0%.

Reassuringly, the vaccine effectiveness against severe, critical, or fatal disease due to infection with any SARS-CoV-2 infection, with the B.1.1.7 and B.1.351 variants being predominant within Qatar at the time, remained very high, at 97.4%.

The researchers also investigated the effectiveness in people who had been tested and had not had a previous infection with SARS-CoV-2. In this sub-group of individuals, the effectiveness of the vaccine remained similar, with a vaccine effectiveness of 87.0% against the B.1.1.7 variant and 72.1% against the B.1.351 variant.

The authors conclude that while there was a higher rate of breakthrough infection with B.1.351, the reduced protection against infection with the B.1.351 variant did not seem to translate into poor protection against the severe forms of infection, leading to hospitalization or death.

Researchers have also been able to test the effects of the Novavax vaccine in areas where the B.1.351 variant is prevalent (Shinde et al., 2021). The Phase 2 trial in South Africa included 4387 individuals who were HIV-negative (94%) or those who were HIV-positive and medically stable (6%). There were 30% of the participants who had antibodies for SARS-CoV-2 before the study, suggesting a prior infection. At the time of the study, 92.7% of the tested samples in the area were the B.1.351 variant.

Overall, the vaccine efficacy against all SARS-CoV-2 variants for the Novavax vaccine among HIV-negative participants was 60.1%.

When the specific efficacy for just B.1.351 was calculated, the vaccine efficacy in HIV-negative individuals was 51%.

Ongoing Vaccine Research

Researchers are continuing to work on additional vaccines to prevent sickness from variants and also potentially prevent sickness from all beta-coronaviruses.

Moderna announced it has initial data from a Phase 2 study of a booster vaccine specifically designed against the B.1.351 and P.1 variants that includes the mutation in the spike protein that allows for immune system avoidance (E484K) (Moderna, 2021). The new booster vaccine caused a higher level of neutralizing antibodies against B.1.351 compared to receiving a third shot of the currently approved Moderna vaccine.

Researchers have also tested a vaccine in macaques that is designed to prevent infection from all strains in the beta-coronavirus family, including SARS-CoV-2, SARS-CoV-1, and MERS-CoV (Saunders et al., 2021). The vaccine led to production of antibodies that were effective against coronaviruses from bats, SARS-CoV-1, SARS-CoV-2, and the SARS-CoV-2 variants B.1.1.7, P.1, and B.1.351. The authors conclude that current mRNA vaccines may provide protection from future coronavirus outbreaks, and the vaccine used in the study is a good basis to continue to create a vaccine that would be effective against all coronaviruses.

Update on SARS-CoV-2 Variants

Researchers have identified a new variant of concern that is circulating in India called B.1.617, which is thought to be a part of the recent massive surge in cases occurring there (Vaidyanathan et al., 2021 and Mallapaty, 2021). The variant has mutations that allow it to be both more transmissible and more likely to evade the immune response after a previous infection or vaccination. Initially, the surge in India had become dominant in the areas around Delhi and Punjab where B.1.1.7 was common. However, two new variants, B.1.618 and B.1.617 were identified in other parts of the country, and B.1.617 has since spread more widely throughout the country.

The variant has also been found in nearby Sri Lanka and Nepal with outbreaks in Bhutan and Laos. Overall the area has little genomic sequencing occurring so it is difficult to monitor the levels of specific strains occurring. It is also not possible to track how and where the spread originated from.

The *New York Times* reports that the new variant has been detected in 44 countries, but as ever, genomic sequencing is not at adequate levels to follow the transmission (NYT, 2021). As mentioned above, there has been widespread community transmission of the variant in Britain, with an increase from 520 cases to 1,313 in a single week. Prime Minister Boris Johnson stated that government officials believe that B.1.617 is more transmissible than previous variants, including B.1.1.7, leading public health officials to change the strategy to delay the second dose of the vaccine for those over the age of 50.

Preliminary studies indicate that B.1.617 has two key mutations in the spike protein that appear to reduce the interaction between the virus and antibodies generated in response to vaccines or previous infection, L452R and E484Q (Hoffman et al., 2021). It was also resistant to Bamlanivimab, the antibody used as a treatment for COVID-19.

COVID-19 and NSAID use

There was concern about the use of non-steroidal anti-inflammatory (NSAID) medication at the start of the pandemic because the use of NSAIDs has been shown to increase the amount of ACE-2 receptors on the surface of cells. The ACE-2 receptor is the protein that SARS-CoV-2 interacts with enter the cell, and there was a worry that use of NSAIDS would increase the risk of infection (Drake et al., 2021).

Researchers in the United Kingdom reported a study of 78,674 participants across 255 healthcare facilities who were admitted to the hospital for treatment for COVID-19 between January 17, 2020 and August 10, 2020. In the group, 5.8% were recorded as taking NSAIDs before admission to the hospital. There was no difference in the severity of disease at the time of admission between those who had and had not taken NSAIDs. Use of NSAID was not associated with worse in-hospital mortality, critical care admission, requirement for invasive ventilation, requirement for non-invasive ventilation, requirement for oxygen, or occurrence of acute kidney injury.

Long COVID

Early reports had suggested that COVID-19 may lead to heart damage after the infection (Mandrola et al., 2021).

However, a new study indicates that cardiovascular abnormalities are no more common in individuals 6 months after a mild case of COVID-19 than in a representative healthy, comparator group.

The study included 731 healthcare workers at three hospitals where 21.5% were found to have been infected with SARS-CoV-2 by either PCR-based testing or antibody testing (Joy, 2021). Six months after the infection, 74 of those with COVID-19 were tested for cardiovascular abnormalities using MRI scanning and blood tests, and their results were compared to similar individuals who had not had COVID-19. There were no differences in cardiac structure, function, tissue characterization, or biomarkers. Any abnormalities observed were distributed equally between both groups.

A Danish study investigated the differences in healthcare use between individuals who had had a diagnosis of COVID-19 and those who had not over the six months after diagnosis (Lund et al., 2021). Because of the national health service, it was possible to look at the anonymous health records of all of the individuals in the country who had tested positive for COVID-19 between February 27 and May 31, 2020. The healthcare usage of the 8983 people who were eligible for the study were compared to 80,894 individuals who had not been diagnosed with COVID-19.

Those who had had COVID-19 were not at an increased risk for starting a new prescription except for two types of bronchodilating agents, which make it easier to breath. There was an increased risk of receiving a hospital diagnosis of dyspnea, or difficulty breathing, but no increase in other diagnoses. There were increases in visits to general practitioners and outpatient hospital visits for those who had had COVID-19 compared to those who had not.

The multidisciplinary COVID-19 Activity Rehabilitation Program at the Mayo Clinic reported the clinical characteristics of the first 100 patients receiving evaluation and management between June 1, 2020 and December 31, 2020 (Vanichkachorn et al, 2021). The mean age of the individuals was 45, and 68% were women who were seen at the clinic a mean of 93 days after their infection with SARS-CoV-2. Out of the group, 75% had not been hospitalized for treatment of COVID-19.

Common symptoms reported included

- Fatigue (80%)
- Respiratory complaints (59%)
- Neurologic complaints (59%)
- Cognitive impairment
- Sleep disturbance
- Mental health symptoms
- Difficulties with performing basic activities of daily living (34%)

Only 33% had returned to unrestricted work duty at the time of the first appointment. For most of the individuals, laboratory and imaging studies were normal or non-diagnostic despite debilitating symptoms. It was determined that most patients required physical therapy, occupational therapy, or brain rehabilitation.

The authors conclude that

> "Many of the patients did not experience COVID-19-related symptoms that were severe enough to require hospitalization, were younger than 65 years of age, more likely to be female, and most had no pre-existing comorbidities prior to SARS-CoV-2 infection. Symptoms… resulted in severe negative impacts on the resumption of functional and occupational activities in patients experiencing prolonged effects"

References

Abu-Raddad LJ, Chemaitelly H, Butt AA; National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. *N Engl J Med.* 2021 May 5:NEJMc2104974. doi: 10.1056/NEJMc2104974. Epub ahead of print. PMID: 33951357; PMCID: PMC8117967.

Abutaleb Y, McGinley L. CDC says fully vaccinated Americans no longer need masks indoors or outdoors in many cases. *The Washington Post.* Published May 13, 2021. Accessed on May 14, 2021 at https://www.washingtonpost.com/health/2021/05/13/cdc-says-fully-vaccinated-americans-no-longer-need-masks-indoors-or-outdoors-most-cases/

Bartsch SM, Wedlock PT, O'Shea KJ, Cox SN, Strych U, Nuzzo JB, Ferguson MC, Bottazzi ME, Siegmund SS, Hotez PJ, Lee BY. Lives and Costs Saved by Expanding and Expediting COVID-19 Vaccination. *J Infect Dis*. 2021 May 6:jiab233. doi: 10.1093/infdis/jiab233. Epub ahead of print. PMID: 33954775; PMCID: PMC8136017.

Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, Garonzik-Wang JM. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant

Recipients. *JAMA.* 2021 May 5. doi: 10.1001/jama.2021.7489. Epub ahead of print. PMID: 33950155.

Callaway E. Mix-and-match COVID vaccines trigger potent immune response. *Nature*. Published May 19, 2021. Accessed May 20, 2021 at https://www.nature.com/articles/d41586-021-01359-3

CDC. Interim Public Health Recommendations for Fully Vaccinated People. Published May 13, 2021. Accessed May 19, 2021 at https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated-guidance.html

CDC. Previous COVID-19 Breakthrough Case Data. Updated April 26, 2021. Accessed May 22, 2021. https://www.cdc.gov/vaccines/covid-19/health-departments/past-breakthrough-data.html

CDC. Scientific Brief: SARS-CoV-2 Transmission. Updated May 7, 2021. Accessed on May 11, 2021 at https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html

CDC Variant Proportions. Published April 24, 2021. https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fvariant-surveillance%2Fgenomic-surveillance-dashboard.html#variant-proportions

Chodick G, Tene L, Rotem RS, Patalon T, Gazit S, Ben-Tov A, Weil C, Goldshtein I, Twig G, Cohen D, Muhsen K. The effectiveness of the TWO-DOSE BNT162b2 vaccine: analysis of real-world data. *Clin Infect Dis*. 2021 May 17:ciab438. doi: 10.1093/cid/ciab438. Epub ahead of print. PMID: 33999127.

Collier AY, McMahan K, Yu J, Tostanoski LH, Aguayo R, Ansel J, Chandrashekar A, Patel S, Apraku Bondzie E, Sellers D, Barrett J, Sanborn O, Wan H, Chang A, Anioke T, Nkolola J, Bradshaw C, Jacob-Dolan C, Feldman J, Gebre M, Borducchi EN, Liu J, Schmidt AG, Suscovich T, Linde C, Alter G, Hacker MR, Barouch DH. Immunogenicity of COVID-19 mRNA Vaccines in Pregnant and Lactating Women. *JAMA*. 2021 May 13. doi: 10.1001/jama.2021.7563. Epub ahead of print. PMID: 33983379.

Drake TM, Fairfield CJ, Pius R, Knight SR, Norman L, Girvan M, Hardwick HE, Docherty AB, Thwaites RS, Openshaw PJM, Baillie JK, Harrison EM, Semple MG; ISARIC4C Investigators. Non-steroidal anti-inflammatory drug use and outcomes of COVID-19 in the ISARIC Clinical Characterisation Protocol UK cohort: a matched, prospective cohort study. *Lancet Rheumatol.* 2021 May 7. doi: 10.1016/S2665-9913(21)00104-1. Epub ahead of print. PMID: 33997800; PMCID: PMC8104907.

Goupil R, Benlarbi M, Beaubien-Souligny W, Nadeau-Fredette AC, Chatterjee D, Goyette G, Gunaratnam L, Lamarche C, Tom A, Finzi A, Suri RS. Short-term antibody response afer 1 dose of BNT162b2 vaccine in patients receiving hemodialysis. *CMAJ*. 2021 May 12:cmaj.210673. doi: 10.1503/cmaj.210673. Epub ahead of print. PMID: 33980499.

Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, Brooks N, Smaja M, Mircus G, Pan K, Southern J, Swerdlow DL, Jodar L, Levy Y, Alroy-Preis S. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *Lancet*. 2021 May 15;397(10287):1819-1829. doi: 10.1016/S0140-6736(21)00947-8. Epub 2021 May 5. PMID: 33964222; PMCID: PMC8099315.

Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, Wellington E, Stowe J, Gillson N, Atti A, Islam J, Karagiannis I, Munro K, Khawam J, Chand MA, Brown CS, Ramsay M, Lopez-Bernal J, Hopkins S; SIREN Study Group. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. *Lancet*. 2021 May 8;397(10286):1725-1735. doi: 10.1016/S0140-6736(21)00790-X. Epub 2021 Apr 23. PMID: 33901423; PMCID: PMC8064668.

Harris RJ et al. Impact of vaccination on household transmission of SARS-COV-2 in England. *Public Health England*. Published April 28, 2021. Accessed May 3, 2021 at https://www.gov.uk/government/news/one-dose-of-covid-19-vaccine-can-cut-household-transmission-by-up-to-half

Hoffman M et al. SARS-CoV-2 variant B.1.617 is resistant to Bamlanivimab and evades antibodies induced by infection and vaccination. *bioRxiv*. Published May 5, 2021. Accessed May 22, 2021 at https://www.biorxiv.org/content/10.1101/2021.05.04.442663v1

JHU. COVID-19 Dashboard. https://coronavirus.jhu.edu/map.html Accessed May 20, 2021.

Joy G, Artico J, Kurdi H, Seraphim A, Lau C, Thornton GD, Oliveira MF, Adam RD, Aziminia N, Menacho K, Chacko L, Brown JT, Patel RK, Shiwani H, Bhuva A, Augusto JB, Andiapen M, McKnight A, Noursadeghi M, Pierce I, Evain T, Captur G, Davies RH, Greenwood JP, Fontana M, Kellman P, Schelbert EB, Treibel TA, Manisty C, Moon JC; COVIDsortium Investigators. Prospective Case-Control Study of Cardiovascular Abnormalities 6 Months Following Mild COVID-19 in Healthcare Workers. *JACC Cardiovasc Imaging*. 2021 May 5:S1936-878X(21)00356-9. doi: 10.1016/j.jcmg.2021.04.011. Epub ahead of print. PMID: 33975819; PMCID: PMC8105493.

Ledford H. Delaying a COVID vaccine's second dose boosts immune response. *Nature*. Published. May 13, 2021. Accessed Mau 14, 2021 at https://www.nature.com/articles/d41586-021-01299-y

Leonhardt D. A Misleading C.D.C. Number. *The New York Times*. Published May 11, 2021. Updated May 24, 2021. Accessed on May 24, 2021 at https://www.nytimes.com/2021/05/11/briefing/outdoor-covid-transmission-cdc-number.html

Lund LC, Hallas J, Nielsen H, Koch A, Mogensen SH, Brun NC, Christiansen CF, Thomsen RW, Pottegård A. Post-acute effects of SARS-CoV-2 infection in individuals not requiring hospital admission: a Danish population-based cohort study. *Lancet Infect Dis*. 2021 May 10:S1473-3099(21)00211-5. doi: 10.1016/S1473-3099(21)00211-5. Epub ahead of print. PMID: 33984263; PMCID: PMC8110209.

Mallapaty S. India's neighbours race to sequence genomes as COVID surges. *Nature*. Published May 14, 2021. Accessed May 14, 2021 at https://www.nature.com/articles/d41586-021-01287-2

Mandrola J, Foy A, Prasad V. Setting the record straight: There is no 'Covid heart'. *STAT News*. Published May 14, 2021. Accessed on May 14, 2021 at https://www.statnews.com/2021/05/14/setting-the-record-straight-there-is-no-covid-heart/

McLernon LM. Mixed reactions to CDC's revised COVID mask mandate. *CIDRAP News*. Published May 14, 2021. Accessed May 18, 2021 at https://www.cidrap.umn.edu/news-perspective/2021/05/mixed-reactions-cdcs-revised-covid-mask-mandate

Moderna. Moderna Announces Positive Initial Booster Data Against SARS-CoV-2 Variants of Concern. Published May 5, 2021. Accessed May 11, 2021 at https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-positive-initial-booster-data-against-sars-cov

New York Times. Britain Changing Protocols to Combat Virus Variant. *The New York Times.* Published May 14, 2021. Accessed May 19, 2021 at https://www.nytimes.com/live/2021/05/14/world/covid-vaccine-coronavirus-cases

Parry H et al. Extended interval BNT162b2 vaccination enhances peak antibody generation in older people. *medRxiv*. Published May 17, 2021. Accessed May 22, 2021 at https://www.medrxiv.org/content/10.1101/2021.05.15.21257017v1

Saunders KO, Lee E, Parks R, Martinez DR, Li D, Chen H, Edwards RJ, Gobeil S, Barr M, Mansouri K, Alam SM, Sutherland LL, Cai F, Sanzone AM, Berry M, Manne K, Bock KW, Minai M, Nagata BM, Kapingidza AB, Azoitei M, Tse LV, Scobey TD, Spreng RL, Rountree RW, DeMarco CT, Denny TN, Woods CW, Petzold EW, Tang J, Oguin TH 3rd, Sempowski GD, Gagne M, Douek DC, Tomai MA, Fox CB, Seder R, Wiehe K, Weissman D, Pardi N, Golding H, Khurana S, Acharya P, Andersen H, Lewis MG, Moore IN, Montefiori DC, Baric RS, Haynes BF. Neutralizing antibody vaccine for pandemic and pre-emergent coronaviruses. *Nature*. 2021 May 10. doi: 10.1038/s41586-021-03594-0. Epub ahead of print. PMID: 33971664.

Shaw RH, Stuart A, Greenland M, Liu X, Van-Tam JSN, Snape MD; Com-COV Study Group. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. *Lancet*. 2021 May 12:S0140-6736(21)01115-6. doi: 10.1016/S0140-6736(21)01115-6. Epub ahead of print. Erratum in: Lancet. 2021 May 18;: PMID: 33991480; PMCID: PMC8115940.

Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, Lalloo U, Masilela MSL, Moodley D, Hanley S, Fouche L, Louw C, Tameris M, Singh N, Goga A, Dheda K, Grobbelaar C, Kruger G, Carrim-Ganey N, Baillie V, de Oliveira T, Lombard Koen A, Lombaard JJ, Mngqibisa R, Bhorat AE, Benadé G, Lalloo N, Pitsi A, Vollgraaff PL, Luabeya A, Esmail A, Petrick FG, Oommen-Jose A, Foulkes S, Ahmed K, Thombrayil A, Fries L, Cloney-Clark S, Zhu M, Bennett C, Albert G, Faust E, Plested JS, Robertson A, Neal S, Cho I, Glenn GM, Dubovsky F, Madhi SA; 2019nCoV-501 Study Group. Efficacy of NVX-CoV2373 Covid-19 Vaccine against

the B.1.351 Variant. *N Engl J Med.* 2021 May 20;384(20):1899-1909. doi: 10.1056/NEJMoa2103055. Epub 2021 May 5. PMID: 33951374; PMCID: PMC8091623.

Thompson MG, Burgess JL, Naleway AL, Tyner HL, Yoon SK, Meece J, Olsho LEW, Caban-Martinez AJ, Fowlkes A, Lutrick K, Kuntz JL, Dunnigan K, Odean MJ, Hegmann KT, Stefanski E, Edwards LJ, Schaefer-Solle N, Grant L, Ellingson K, Groom HC, Zunie T, Thiese MS, Ivacic L, Wesley MG, Lamberte JM, Sun X, Smith ME, Phillips AL, Groover KD, Yoo YM, Gerald J, Brown RT, Herring MK, Joseph G, Beitel S, Morrill TC, Mak J, Rivers P, Harris KM, Hunt DR, Arvay ML, Kutty P, Fry AM, Gaglani M. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March 2021. *MMWR Morb Mortal Wkly Rep*. 2021 Apr 2;70(13):495-500. doi: 10.15585/mmwr.mm7013e3. PMID: 33793460; PMCID: PMC8022879.

Vaidyanathan G. Coronavirus variants are spreading in India —what scientists know so far. *Nature*. Published Nay 11, 2021. Accessed May 12, 2021 at https://www.nature.com/articles/d41586-021-01274-7

Vanichkachorn G, Newcomb R, Cowl CT, Murad MH, Breeher L, Miller S, Trenary M, Neveau D, Higgins S, Post COVID-19 Syndrome (Long Haul Syndrome): Description of a Multidisciplinary Clinic at the Mayo Clinic and Characteristics of the Initial Patient Cohort, *Mayo Clinic Proceedings* (2021), doi: https://doi.org/10.1016/j.mayocp.2021.04.024.

Wen LS. Should we keep wearing masks? *The Washington Post*. Published May 18, 2021. Accessed May 19, 2021 at https://www.washingtonpost.com/opinions/2021/05/18/masks-cdc-guidance-covid-live-chat/

White EM, Yang X, Blackman C, Feifer RA, Gravenstein S, Mor V. Incident SARS-CoV-2 Infection among mRNA-Vaccinated and Unvaccinated Nursing Home Residents. *N Engl J Med*. 2021 May 19. doi: 10.1056/NEJMc2104849. Epub ahead of print. PMID: 34010526.