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Topic: Update on COVID-19 Immune Response

Overview of Terms

The immune system functions to remove disease-causing germs, recognize and neutralize harmful substances from the environment, and eliminate harmful changes to tissues in the body, such as cancer cells. In general, a bacterium, virus, or other microorganism that can cause disease is called a **pathogen**, and the main focus of most immune functions is protection from pathogens. The parts of the pathogen that stimulate an immune response are called **antigens**. A single pathogen typically has multiple antigens that interact with the immune system because they are large and made up of numerous proteins and other molecules.

There are two branches of the immune system, the innate immune system and the adaptive immune system. The **innate immune system** reacts in a non-specific way to a pathogen in the body. The innate immune system is mainly localized within areas of the body where antigens and pathogens enter the body, such as the skin, respiratory tract, and gastrointestinal tract. The **adaptive immune system** targets specific pathogens to clear them from the body. The response is also referred to as **acquired immunity**.

> **The two main cellular components of the adaptive immune system are B cells and T cells, which are also called lymphocytes.**

In general, B cells function to produce antibodies, and T cells remove pathogens. Different lineages of B cells and T cells produce proteins on the cellular membrane that only interact with a single antigen. This means that large numbers of different B and T-cell lineages are needed to adequately patrol the body for pathogens. Each specific B cell and T cell is activated only when the corresponding antigen from a pathogen is present.

The proteins on the surface of B cells that interact with antigens are called **antibodies**, and some types of B cells produce antibodies that remain attached to the cell (**IgM antibodies**) while other B cells produce free antibodies that are secreted into the blood stream. The free antibodies are called **IgG antibodies**. The protein from T cells that interacts with antigens remains attached to the surface of the cell, allowing T cells to capture pathogens by binding to the antigen. There are two types of T cells, **CD8** cells, or **cytotoxic T cells**, which produce molecules to kill infected cells, and **CD4** cells, are **helper T cells**, which produce immune system components that modulate immune responses including cytokines.

What are the basic steps in an adaptive immune response?

1. A pathogen elicits an **adaptive immune response**.
2. **Antibodies**, **cytotoxic T cells**, and **helper T cells** specific to the pathogen are produced.
3. **Cytotoxic T cells** eliminate the pathogen, and **neutralizing antibodies** prevent infection of more cells.
4. **Antigen levels decline**, and T cell levels and antibody levels decline due to a lack of stimulation by the antigen.
5. **Memory cells** remain that have a heightened ability to respond to recurrence of infection with the same pathogen.

Ideally, the adaptive immune system responds to a pathogen by enacting a substantial helper T-cell, cytotoxic T-cell, and neutralizing antibody response, and all of the components contribute to clearance of the initial infection.

After the infection is cleared, the level of the immune response is reduced. However, some neutralizing antibodies may be maintained in the bloodstream. The amount of antibodies that remain is dependent on the characteristics of the specific virus. A few of each lineage of the T and B cells produced in response to an infection are retained as an immunological memory to provide a protective immunity against re-infection. These long-lived cells are called **memory cells**, and when they are exposed to the specific antigen from the virus again, they begin multiplying to quickly allow for a targeted immune response to the pathogen.

There are multiple types of immune responses that occur when an organism is exposed to a pathogen again. One is called a **sterilizing immune response**, where the adaptive immune system prevents an infection from occurring by responding to the pathogen before it can infect cells. One way of accomplishing a sterilizing immune response is though maintenance of high levels of neutralizing antibodies that keep the pathogen from interacting with cells. There are also other types of sterilizing immune responses that are effective in preventing re-infections, and one example of this type of response is observed after vaccination for hepatitis B. In this case, the immune response is completely mediated by memory cells because no antibodies are maintained in the bloodstream. This type of response if effective against the virus because hepatitis B grows slowly. There may also be a mixture of these types of responses with low levels of antibody remaining in the bloodstream with quick responses from memory cells.

Some immune responses are not sterilizing responses that completely prevent an infection from occurring. Instead, the immune response reduces the amount of virus that is produced rather than completely preventing an infection. Lower levels of viral production often result in an infection with less severe symptoms or asymptomatic infection so that while infection is not prevented, poor outcomes are avoided.

Immunity after SARS-CoV-2 Infection

More is now known about the human immune response to SARS-CoV-2 infections because more time has passed since the initial identification of the new virus, allowing for completion of more studies (Dan et al., 2021).

What has been determined about the immune response to SARS-CoV-2?

- Humans make specific **antibodies**, **CD4 cells**, and **CD8 cells** in response to SARS-CoV-2 infections.
- Robust T-cell responses are associated with reduced disease severity.
- The response of CD4 and CD8 cells is important for control and resolution of the **initial** infection.
- An ineffective response from the **innate immune system** is strongly associated with poor control of the infection and a high risk of fatal COVID-19.
- Administration of neutralizing antibodies **before** infection, which mimics a response from a previous infection, reduces the severity of the infection.
- Administration of neutralizing antibodies **after** initiation of infection has a smaller effect on the infection, which is consistent with the larger role of T cells in control and clearance of an ongoing infection.
- Neutralizing antibodies provide protective immunity against subsequent infection with SARS-CoV-2.

Developing Immunity to SARS-CoV-2

The adaptive immune response to SARS-CoV-2 begins within the first seven to ten days of the start of the infection (Jordan, 2021). Studies of the immune response to SARS-CoV-2 indicate that the intensity, character, and duration of the response of the secreted form of antibodies, or IgG antibodies, may vary greatly.

Production of IgG has been observed to peak between 50 and 60 days after infection with the duration of the response lasting up to ten months.

Individuals who produce large amounts of IgG against SARS-CoV-2 are more likely to experience severe cytokine release syndrome, and this over-reaction may be associated with an increased risk of death.

In a study of individuals in Scotland, the presence of antibodies was investigated over ten weeks starting on March 16, 2020 using leftover biological samples from testing during primary care visits or hospital care (Hughes et al., 2020). Of the 6,635 samples tested, 7.81% contained antibodies to the spike protein of SARS-CoV-2. In the samples that had evidence of antibodies, 54.17% exhibited a high neutralizing activity for the virus, which is defined as reducing infection in cell culture by greater than 90%. People who had an overall higher level of antibodies also had a larger neutralizing effect. Individuals who were being treated in the hospital also had

higher levels of antibodies overall and a higher percentage of neutralization compared to individuals who were treated in primary care practices.

This difference was interpreted by the authors as implying that disease severity is associated with a stronger and more effective antibody-mediated response, which has been proposed in previous studies as well.

There may be a difference in some of the studies because the level of antibodies were not necessarily collected at the same time after the start of the infection, and antibody levels will change over the course of the illness.

If a person produces a large number of antibodies, but few bind to critical parts of the virus, there will be little protection from infection. Antibodies that target the receptor-binding domain (or RBD) of the spike protein have been shown to be important components of the immune response to SARS-CoV-2 because they block binding of the virus to cells in the body.

Studies indicate that antibodies that target this area are critical for long-term protective immunity to COVID-19 infection and are associated with better patient survival.

Antibodies to another region of the spike protein, called the N-terminal domain (or NTD), have also been shown to have neutralizing capabilities even though it is distant from the RBD (McCallum et al., 2021). The researchers examined the memory B cells from three individuals who had recovered from COVID-19, and they found that between 65% and 77% of the antibodies from the participants interacted with the RBD of the spike protein and between 6% and 20% interacted with the NTD of the spike protein. The N-terminal domain of SARS-CoV-2 is one of the areas where mutations are frequently observed in the newly emerging variants of the virus. Changes in this area could make antibodies produced in an earlier infection less effective against a mutant virus. The researchers looked at the three-dimensional structure of the spike proteins bound to antibodies targeted to the NTD and found some of the mutations seen in the new variants would be expected to disrupt the interaction site with antibodies, making them interact less tightly or preventing binding completely.

Length of the Immune Response

There have been conflicting results over the length of immune protection after infection with SARS-CoV-2 with some reports indicating a long duration of antibody response and others reporting very short duration of antibodies in the bloodstream after resolution of illness.

A report on the immune components from 188 individuals who recovered from COVID-19 was published in the journal *Science*, and out of the total 188 samples, 43 were from at least six months after infection (Dan et al., 2021). The participants had varying degrees of severity of COVID-19, including asymptomatic, mild, moderate, and severe. Most of the participants had mild symptoms, and 93% of the study group did not require hospitalization for treatment. The remaining 7% required hospitalization, and some of these individuals were also treated in the intensive care unit. The distribution of disease severity in the participants was similar to that seen in the COVID-19 cases in the United States. The age range of the participants was from

19 to 81 years. The researchers looked at antibodies that target the spike protein of SARS-CoV-2, memory B cells that produce antibodies, and T cells that actively attack components of the virus.

The rate of individuals who begin making antibodies in response to infection with SARS-CoV-2 (also called **seroconversion**) has been found to vary between 91% and 99% depending of the study. Therefore, most people who have COVID-19 will mount an immune response.

In this study, the researchers found that the amount of IgG produced was relatively stable over six months or longer.

There was a high level of variability between individuals in regards to the amount of IgG antibody produced, but both those with high or low initial production maintained a constant level over the length of the study time period. At six to eight months after the onset of symptoms, 88% of the study population continued to have detectable IgG antibodies targeted to the spike protein of SARS-CoV-2.

The percentage of the participants with neutralizing antibodies at six to eight months after the start of symptoms was 90%.

The amount of IgG and the presence of neutralizing antibodies are measured using different tests that have different sensitivity, and therefore lower levels of neutralizing antibodies can be detected. Based on this assessment, the overall level of antibodies may decline in some individuals, but the level of neutralizing antibodies seems to remain stable. Additionally, in studies in primates, even low levels of neutralizing antibodies were found to be protective against reinfection with SARS-CoV-2.

The amount of memory B cells that target the spike protein were more abundant at six months than at one month after the onset of symptoms. The researchers saw an increase in memory B cells over the first 120 days after the start of symptoms, and then the levels plateaued at the elevated level.

The authors conclude that overall, the development of B-cell memory to SARS-CoV-2 was robust and likely to be long-lasting.

The number of SARS-CoV-2-specific CD4 and CD8 memory T cells declined over time, and the half-life, or time it takes for the amount to reduce by one half, varied from three to five months in this study group. According to the researchers, this trajectory is in line with the responses observed to other infectious diseases in humans.

The researchers also looked at differences in the immune responses based on individual characteristics.

- Men in the study had **higher** levels of IgG regardless of the level of severity of the symptoms from COVID-19
- The amount of SARS-CoV-2 memory B cells, memory CD8 T cells, or memory CD4 T cells **did not differ** between men and women.
- The level of IgG antibodies and memory B cells was **higher** in people who required hospitalization for treatment of COVID-19 compared to those with milder symptoms.
- The level of memory CD8 T cells was **lower** in individuals with more severe symptoms that required treatment in the hospital compared to people with less severe symptoms.

The relationship was less straightforward with the observed level of memory CD4 T cells, but the amount of CD4 T cells was often lower in hospitalized individuals. The differences between people with mild or severe symptoms were more difficult to detect because there was a small number of people in the study with severe symptoms.

When compared to previous studies, the increased amount of IgG antibodies and increased memory B cells in hospitalized individuals was consistent.

The reduction in T-cell levels in hospitalized individuals was in line with observations that severe cases of COVID-19 can be associated with poorer T-cell responses during the infection.

Before the pandemic, there was little information available on the timeline of IgG antibody, IgA antibodies, B-cell, CD8 T-cell, and CD4 T-cell memory after an infection. IgA antibodies are produced by mucous membranes that function to prevent the entrance of pathogens to the body. The large number of people infected over a short time period during the COVID-19 pandemic has allowed researchers to look at the interrelationships between different components of immune memory for the first time. In this study group, 64% of participants had measureable responses in all five components at one to two months after the onset of symptoms. Those without a full response were found to lack a response from CD8 and/or IgA antibodies.

When a longer time had elapsed, at five to eight months after the start of symptoms, 43% continued to have measurable response from all five components, and 95% had a measureable response from at least three of the five components.

There were variations in which immune components continued to be active in different individuals, which reiterates the overall variability in immune response between individuals to the same infectious disease.

Based on their own research and observations from previous publications, the authors proposed a possible method of long-term immunity from re-infection from SAR-CoV-2:

> With the relatively slow progression of SARS-CoV-2 to severe symptoms, maintaining a long-term lower level of neutralizing antibodies would blunt an initial infection, allowing for memory cell reactivation to prevent pneumonia or severe secondary COVID-19.

In response to the publication of the study, other experts were reassured that the activation of multiple components of the immune system would allow for a continued robust immune response even to the potential new variants (Achenbach, 2021). In order to evade natural, or even vaccine-induced, immunity, the virus would need to have a large number of transmission-enhancing mutations.

Another long-term study on the length of the immune response to SARS-CoV-2 was also published (Gaebler et al., 2021). In this study, 87 participants were assessed at 1.3 and 6.2 months after infection with SARS-CoV-2. The first assessment, at 1.3 months, was at approximately 40 days after the infection. The symptoms of the participants lasted for a median of 12 days with a range from zero to 44 days, and 11% of the participants required hospitalization for treatment of COVID-19. Additionally, 44% of the participants reported persistent long-term symptoms attributable to COVID-19, but all tested negative for COVID-19 at the assessment at 6.2 months.

Over the course of the study, the authors found a reduction of 32% in the amount of IgG antibodies targeting the spike protein of the virus, and neutralizing antibody activity decreased by five-fold over the study period. Individuals with higher antibody levels at the first assessment were found to have a larger relative decrease in the amount of antibodies. The researchers also found that individuals with persistent symptoms after the infection was cleared had higher IgG antibodies targeted to the RBD and higher total antibody levels at both assessments, suggesting that an extended immune response may play a role in individuals with continuing symptoms weeks to months after recovery from infection, or Long-COVID.

Based on their evaluation, the authors concluded that the level of antibodies targeted to the RBD, as well as the neutralizing activity, decreases 6 months after infection, but they remain detectable in the majority of individuals.

The number of memory B cells targeted to the RBD of the virus was unchanged, however. At the end of the study, or 6.2 months after the onset of symptoms, there is evidence of the memory B cells converting to long-term producers of memory B cells. This change is accompanied by “hypermutation” within the cell population that produces antibodies that have increased potency and better resistance to mutations in the RBD of the virus. This type of change is typical of the evolution of the adaptive immune response after the end of the initial infection.

Sampling of the intestines of asymptomatic individuals showed that 50% of the participants continued to have viral RNA in the small bowel at least six months after the resolution of the

infection. This process has been observed in immune complexes that retain antigens from the virus for prolonged periods of time to prolong the exposure even after the infection has been resolved. This continued exposure to antigens leads to the evolution of the immune response to produce better antibodies that are still reactive even after mutations of the virus.

Based on the results of the study, the researchers concluded that memory B-cell responses do not decay after 6.2 months, but instead continue to evolve, which "strongly suggests that individuals who are infected with SARS-CoV-2 could mount a rapid and effective response to the virus upon re-exposure."

Immunity between Mother and Infant

Researchers reported on the ability of antibodies targeted against SARS-CoV-2 to pass through the placenta of pregnant women in order to provide protection for newborns from the virus (Flannery et al., 2021). The study included 1714 women, and there were matched blood samples for 1471 mother and child pairs. In total, 6% of the 1471 women had antibodies for COVID-19.

Out of the 83 mothers who tested positive for COVID-19 antibodies, 87% of the cord blood also contained antibodies, suggesting a high number of newborns had received protection through antibodies produced by their mother.

There were eleven newborns who did not test positive for antibodies, and in 45% of cases, the mother had only produced IgM antibodies, which are those produced early in infection. The mothers of the remaining 55% of newborns without antibodies were found to have much lower amounts of IgG. Overall, the amount of IgG antibodies in the cord blood was correlated with the amount of IgG in the mother's blood. There was not a difference in antibody transfer across the placenta based on the severity of symptoms. However, there was an increase in the amount of antibodies observed with an increasing time between the onset of maternal infection and delivery.

Reinfection with SARS-CoV-2

A study of healthcare workers in the United Kingdom investigating the rate of reinfection over five months found that cases of reinfection were rare (Hall et al., 2021 and Ledford, 2021). The study enrolled healthcare workers who had had a previous SARS-CoV-2 infection and those who had not. During the study, participants were given regular SARS-CoV-2 PCR-based and antibody testing every two to four weeks and also completed fortnightly questionnaires on symptoms and exposures.

There were 44 reinfections documented out of 6,614 participants who had previously had COVID-19. There were 318 new cases of COVID-19 diagnosed by PCR-based testing and 94 positive antibody tests in the group of 14,173 participants that were negative at the start of the trial.

This corresponds to reinfection in less than 1% of participants who had had COVID-19 before.

Because individuals with COVID-19 can have long periods where they release viral DNA after the infection has resolved, there are difficulties in definitively determining if someone has been re-infected or has long-term shedding of the virus. The median interval between the participants' alleged infections in this study was more than 160 days.

To address the problem of confirming re-infection, the researchers defined infections.

A **possible reinfection** required either

- Two positive PCR tests 90 or more days apart

-or-

- A new, positive PCR-based test at least four weeks after a positive antibody test.

A **probable case** additionally required either

- Supportive quantitative serological (antibody) data

-and/or-

- Supportive viral genomic data from testing samples.

Based on these characteristics, all of the 44 cases considered for re-infection observed in the study were considered possible, and only two had enough information available to be classified as probable. There was not enough information collected in the study to determine what characteristics might be correlated with the risk of re-infection, however.

Overall, the researchers found that a previous infection reduced the risk of getting COVID-19 again by 83% based on possible cases with a 94% lower odds of symptomatic infection.

While assessment of symptom severity was not part of the study protocol, the researchers report that 30% of those with possible re-infections had symptoms while 78% of the participants with COVID-19 for the first time had a least one symptom. This result suggests that individuals with a second case of COVID-19 are less likely to have symptoms.

However, individuals who were classified as possibly re-infected often had high levels of virus in the nose and throat, suggesting they could be more contagious than people infected for the first time. As with new infections, the number of people who do not have symptoms during the infectious period of SARS-CoV-2 is high. Therefore, even if you have had the virus, you should continue to wear a mask to prevent transmission if a second infection should occur. This may be even more important in the coming weeks and months as some of the new variants, as described in more detail in another PCI update, may be more likely to re-infect individuals.

Immunity to SARS-CoV-2 via Vaccination

There are now a number of potential vaccines for COVID-19 that have been evaluated by Phase 3 clinical trials, and a number have been authorized for use in different countries. As might be expected, it has not been possible for manufacturers to produce enough vaccine to satisfy the demand to vaccinate the entire population of the world yet. Governments have set up priorities for vaccination that either attempt to preserve the most lives or slow transmission the fastest. With the emergence of new variants that are more transmissible and possibly cause more serious illness, some health organizations are looking for ways to stretch the available vaccine to get the most people inoculated quickly.

The *New York Times* has set up a "Coronavirus Vaccine Tracker" that lists the vaccines in development, those that are authorized or approved for use, and vaccines that are no longer being developed due to poor performance. It can be accessed at https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html.

Overview of Authorized or Approved Vaccines

In the United States, two vaccines have been given Emergency Use Authorization (EUA) by the FDA, the vaccines from Pfizer-BioNTech and Moderna. Some countries have given full approval for the use of certain vaccines, but no vaccine has been fully approved for use in the United States, a process with more stringent requirements than EUA. The AstraZeneca-Oxford vaccine has Phase 3 results available and has been authorized or approved in a number of countries, but is not yet available in the United States. Table 1 lists the vaccines currently available for use and where they are available (New York Times Coronavirus Tracker, 2021).

Table 1. Areas where vaccines are approved or authorized.

Manufacturer	Countries with Authorization or Approval
Pfizer-BioNTech	Bahrain, Saudi Arabia, Switzerland, Argentina, Australia, Canada, Chile, Colombia, Costa Rica, Ecuador, European Union, Iraq, Jordan, Kuwait, Lebanon, Malaysia, Mexico, New Zealand NEW, Oman, Panama, Qatar, Serbia, Singapore, Tunisia, United Arab Emirates, United Kingdom, United States with emergency use validation from the WHO
Moderna	Canada, European Union, Israel, Singapore, United Kingdom, United States, Switzerland
AstraZeneca-Oxford	Algeria, Argentina, Bangladesh, Bhutan, Brazil, Chile, Dominican Republic, Egypt, El Salvador, European Union, India, Maldives, Mexico, Morocco, Nepal, Pakistan, South Africa, United Kingdom
Sputnik V, Gamaleya Research Institute	Russia, Algeria, Argentina, Armenia, Belarus, Bolivia, Guinea, Hungary, Iran, Mexico, Nicaragua, Palestinian Authority, Paraguay, Serbia, Tunisia, Turkmenistan, United Arab Emirates, Venezuela
Sinopharm	China, Bahrain, United Arab Emirates, Egypt, Hungary, Jordan, Pakistan
Sinovac	China, Azerbaijan, Brazil, Chile, Indonesia, Turkey
Bharat Biotech	India

State of the World-Wide Vaccination Campaign

In Israel, approximately 90% of people aged 60 and older have received their first dose of vaccine (Mallapaty, 2021).

The high level of immunization in this age group has been accompanied by a 41% drop in confirmed COVID-19 infections of people over the age of 60, and a 31% drop in hospitalizations from mid-January to early February of this group

For comparison, 30% of people under the age of 59 have been vaccinated, and the number of cases dropped by 12% with hospitalizations decreasing by 5%. The country is also under a nationwide lockdown, which would contribute to decreases, but analysis of the data supplied by the government suggest that vaccines **are** contributing to the reduction of infections and hospitalizations because the change observed for the older individuals was larger and occurred sooner than in younger people. During previous lockdowns in the country when vaccines were not yet available, this trend did not occur. There is not yet evidence that enough people have been vaccinated to reduce infections in the population not vaccinated, or so-called herd immunity.

There is also early evidence from the United Kingdom that there has been a reduction in the number of healthcare workers testing positive for COVID-19 after receiving the first dose of the vaccine from Pfizer-BioNTech.

Researchers reported that those who have had one shot of the vaccine are 53% less likely to test positive than workers who have not yet been vaccinated.

Based on the results, they stressed that the trial of around 46,000 individuals was a good indication that a single dose of the vaccine could be effective at reducing transmission.

In the United States, the American Health Care Association published a press release reporting that the number of COVID-19 cases in long-term care facilities have declined by 22% between December 20 and January 10 (AHCA, 2021). The decline is thought to be due to a combination of vaccination and a decline in community transmission.

Additionally, the Center for Health Policy Evaluation in Long Term Care (CHPE) analyzed data from the federal government describing the rate of COVID-19 at 797 nursing homes that conducted their first vaccination clinic between December 18, 2020 and December 27, 2020.

Facilities that had begun vaccination of residents and staff had a 48% decline in new cases for residents three weeks after the first clinic, compared to a 21% decline among nursing homes in the same county that had not started a vaccine program yet.

The number of cases among the staff also declined by 33% in facilities that had had the first round of vaccinations compared to 18% in those that had not.

Alternative Dosing of Vaccines with Two Injections

With vaccines supplies still limited, officials and researchers are looking at ways to use the currently available vaccine to inoculate more people.

One strategy is to vaccinate as many people as possible with the first dose of the vaccine while postponing the second dose until more supplies are available. The first dose of the vaccine activates the immune system, and may provide some protection from infection from SARS-CoV-2. There is some limited evidence from the initial clinical trials that participants were less likely to become infected after their first injection when compared to those who received the placebo, but the trials were not set up to investigate this possibility, and therefore the evidence is very weak, and the length of the protection was not known.

AstraZeneca and the University of Oxford released a preprint of a study that specifically investigates the outcome of delaying the second inoculation of their vaccine, which is currently authorized for use as two shots 28 days apart (Voysey et al, 2021). The report details the outcome of additional participants and additional study sites in the Phase 3 and Phase 1/2 clinical trials.

Overall, the researchers found that there was a higher efficacy of the vaccine with a longer interval between the first and second dose, and that a single dose of vaccine is highly efficacious in the first 90 days.

The study looked at the efficacy of the vaccine to stop symptomatic COVID-19 in studies in the United Kingdom, South Africa, and Brazil. The results of the trials were analyzed when 332 participants had been diagnosed with symptomatic COVID-19 that was confirmed with a PCR-based test. The main analysis was for the efficacy of the two dose regimen evaluated 14 days after the second dose.

The efficacy of the vaccine to prevent COVID-19 in individuals who received two injections was 66.7%, and there NO hospitalizations in the vaccinated group after 21 days from the second inoculation while there were 15 in the control group.

The researchers evaluated the efficacy of the vaccine from 22 to 90 days after a single inoculation.

Using a single dose, the efficacy to prevent COVID-19 was 76%, and the level of protection did not fade over the three months of the study.

The level of antibodies against SARS-CoV-2 also remained stable over this time period.

A third group of participants received a second, booster inoculation 12 weeks or longer after the first dose of vaccine rather than 28 days after the first shot.

The researchers reported a vaccine efficacy of 82.4% in the group with a 12 week or longer interval compared to 54.9% vaccine efficacy in the group with an interval between shots of less than six weeks.

The level of antibody response was more than two-fold higher in the group with a longer interval between inoculations compared to the short interval in participants aged 18 to 55 years.

Based on the results of the study, the researchers concluded that inoculation with a single dose or a delayed second booster dose after a 3 month period is an effective strategy for reducing disease, and may be useful for rollout of the vaccine when supplies are limited in the short term.

Another study is being organized in the United Kingdom to determine if vaccines from different companies can be used as the second, booster shot according to a government sponsored press release (Department of Health and Social Care, 2021). The study will also collect data on differences in efficacy with different intervals between doses. The first shot in the study will be the vaccine developed by AstraZeneca-Oxford followed by the vaccine from Pfizer-BioNTech. The goal of the study is to determine if a more flexible vaccination program would provide protection from infection from SARS-CoV-2 while allowing for immunization to continue even with temporary supply shortages from one company.

Use of COVID-19 Vaccines in Women who are Pregnant or Breastfeeding

The Pfizer-BioNTech and Moderna vaccine have not yet been investigated with a clinical trial in pregnant or lactating women. However, there are numerous recommendations that are being reported for this potentially vulnerable group of individuals (Preston, 2021). The official

recommendation of the FDA and CDC is to discuss the options with your healthcare provider if you are pregnant or breastfeeding.

However, breastfeeding and pregnancy lead to very different exposures for a child, and pediatricians state that the risks are not the same in both scenarios.

For example, some of the potential concerns for use of a vaccine during pregnancy include if an immune response during the first weeks of pregnancy that might increase the risk of miscarriage or severe reactions, such as anaphylaxis or a high fever, in response to the shot that could affect an unborn baby. At this time, there are **no documented risks to the fetus from exposure to the vaccine**, there are no theoretical risks, and there are no risks that were indicated from animal studies of the vaccine (Mandavilli and Rabin, 2021).

The CDC has stated that, based on how the Pfizer-BioNTech and Moderna vaccines work, "they are unlikely to pose a specific risk for pregnant women."

The WHO recommends that women who are pregnant not get the vaccine "unless the benefit of vaccinating a pregnant woman outweighs the potential vaccine risks." High risk groups would be those with work exposures or chronic conditions.

However, recent studies of mortality rates for women with COVID-19 while in labor suggest that there is an increased risk of death for women with COVID-19 compared to women without COVID-19 (Jering et al., 2021). The authors of this study concluded that prevention of COVID-19 in pregnant women is important due to the higher rates of preterm birth, preeclampsia, thrombotic events, and death in women giving birth with COVID-19, and women with a higher risk of being exposed to the virus may want to consider vaccination for COVID-19.

During breastfeeding, however, the physical symptoms of the mother do not influence the infant, and the only concern is whether the molecule in question is expressed in breast milk at high enough concentrations to cause harm.

The Academy of Breastfeeding Medicine released a statement saying "During lactation, it is unlikely that the vaccine lipid would enter the blood stream and reach breast tissue. If it does, it is even less likely that either the intact nanoparticle or mRNA would transfer into milk. In the unlikely event that mRNA is present in milk, it would be expected to be digested by the child and would be unlikely to have any biological effects."

Both the WHO and the Academy of Breastfeeding Medicine recommend that those who are lactating should be offered shots just like anyone else.

There have also been many false rumors surrounding pregnancy, lactation, and fertility in connection with the COVID-19 vaccines (Lu-Culligan and Iwasaki, 2021). While there is not yet direct evidence of whether immunization affects pregnant women differently, Akiko Iwasaki, a professor of immunobiology at Yale School of Medicine and an investigator at the Howard Hughes Medical Institute stated in the New York Times, that:

For any woman who is pregnant, nursing, or trying to conceive, contracting COVID-19 is almost certainly more dangerous than getting immunized.

Duration of Vaccination Response

It has not yet been possible to estimate the duration of the response of the vaccines due to the limited time that they have been available. The results from a Phase 1 trial published in the *New England Journal of Medicine* reported an increase in the length of time observing the participants of the study from 57 days after the first vaccination with the Moderna vaccine to 119 days after the first vaccination, which corresponds to 90 days after the second dose (Widge et al., 2021).

Neutralizing antibodies continued to be detected in all the participants at day 90 after the second dose, including those aged 18 to 55 and those 56 to 70 years.

The vaccine also elicited CD4 T-cell responses 43 days after vaccination. Studies on the response of B cells to the vaccine are ongoing. Additionally, no serious adverse events were noted in the extended trial, no pre-specified trial-halting rules were met, and no new adverse events that were considered by the investigators to be related to the vaccine occurred after day 57.

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