PINNACLECARE

Medical Intelligence Report

Date: September 30, 2021

Topic: COVID-19 Vaccine Research Update

The evidence on the protection provided by COVID-19 vaccines has become more and more complex as the pandemic has progressed. This complexity is not unexpected due to the complexity of the problem being addressed. Normally, the scientific process occurs out of the public's view with scientists, physicians, and public health officials debating the merits and shortcomings of a study at conferences and through publication of research papers. The "final" recommendation that is released is a cohesive statement that has organized supporting information.

In the case of COVID-19, the process behind the recommendations has been occurring with more public scrutiny than usual, allowing a view of the process and the methods that the stakeholders use to interpret data. This interpretation uses information that can never encompass all the various components of a problem, requiring the use of estimation and simplified model systems. It is normal for the understanding of biological processes to change as more information is collected because the processes are very complex and change with different inputs or environmental conditions. Studies of these processes are necessarily simplified at first to allow for investigation of one component at a time to determine its contribution. This makes the process slow, and the results may change as multiple components of a system that interact are tested together. Confusion can also emerge if there are previously unknown components that interfere and lead to anomalous results.

Scientists use debate to share their knowledge of a system and address remaining uncertainties, and each individual enters the discussion assured in their position that they have observed the situation correctly. In the end, there is usually a consensus of what is the most important and what is most probably correct based on all that is currently known. Those who have had their theories disproven do not always accept that their view is not supported by the compiled evidence, but the combined knowledge of the experts in a field of study will determine what the most reasonable interpretation of the combined data is.

For COVID-19 vaccines, there is evidence that is backed by experts in medicine, immunology, and public health supporting the conclusion that vaccines provide protection from both infection and illness.

Efficacy of COVID-19 Vaccines

The initial clinical trials for the COVID-19 vaccines reported the **vaccine efficacy against symptomatic disease**. This term means something different in casual conversation and scientific research. The term efficacy in conversation means "the ability to produce a desired result," and the efficacy of a vaccine would therefore seem to mean the ability to prevent infection with SARS-CoV-2. A 90% efficacy with this everyday definition would be that 10% of individuals who were vaccinated would have a breakthrough infection after vaccination, but 90% would be protected. Because accounting for the variables of human behavior during a clinical trial are nearly impossible, it is not possible to measure this type of efficacy. Therefore, the "efficacy" reported in clinical trials is **not** a description of the chance of becoming sick after getting vaccinated.

What efficacy means in a clinical trial of a vaccine:

- Researchers use the number of people in the control group (those who received a placebo and are unvaccinated) who had a symptomatic case of COVID-19 to determine the overall risk of having symptomatic infection from SARS-CoV-2.
- This baseline level of risk is compared to the number of people who had a symptomatic case of COVID-19 after receiving the vaccine, allowing for evaluation of the change in the risk of infection after treatment.

The vaccine efficacy reported in the clinical trials is the reduction in the risk of having a symptomatic case of COVID-19 after vaccination.

Based on the scientific definition, vaccine efficacy is a measurement of how much a vaccine lowers the risk of an outcome.

An efficacy of 0% means that vaccinated people are at as much risk as people who got the placebo, and an efficacy of 100% means that the risk was entirely eliminated by the vaccine (Zimmer, 2020 and Zimmer and Collins, 2021).

As reported in the initial clinical trials of the three vaccines authorized or approved for use in the United States,

- There were 94.1% fewer cases of symptomatic and confirmed COVID-19 in the vaccinated group than in the placebo group with the Moderna vaccine (Baden et al., 2021).
- There were 95% fewer confirmed COVID-19 cases in participants without evidence of prior SARS-CoV-2 infection in the vaccinated group than in the placebo group with the Pfizer-BioNTech vaccine (Polack et al., 2021).
- There were 66.9% fewer moderate to severe/critical COVID-19 cases in the vaccinated group than in the placebo group reduction with the Johnson & Johnson vaccine (FDA, 2021).

The efficacy of the vaccines, or reduction in the risk of COVID-19, is dependent both on the definition of a COVID-19 case as well as the number of unvaccinated individuals who are exposed and become ill. The number of unvaccinated individuals that become ill is therefore dependent on the level of transmission in the community as well as the infectivity of the virus at the time of the study. Efficacy is also affected by where the trial took place, how well the study group represents the general public, and a myriad of other changes that may not be easily discernable.

Effectiveness of COVID-19 Vaccines

A clinical trial includes a relatively small number of individuals compared to the general population that will eventually use the vaccine. In a clinical trial, there are specific criteria used to enroll participants in order to avoid injury to individuals who may be more susceptible to side effects in an untested vaccine and to have a group of participants with relatively similar attributes to more easily calculate how well the vaccine works. Once the overall safety is determined, the vaccine can be used in broader populations, and the ability of the vaccine to protect from illness is measured again and reported as the vaccine effectiveness.

The **effectiveness** of a vaccine has another specific scientific definition, which is the ability of the vaccine to prevent illness in real-world scenarios. Rather than a comparison between a vaccinated and control group, a random population is sampled and risk of infection is calculated from the number of the population who are vaccinated compared to those who are not (Gavi, 2020).

If the vaccine is effective, the cases of COVID-19 are more likely to be in unvaccinated individuals.

Discussions about efficacy and/or effectiveness can be further muddled when individuals are careless with their usage. Many writers use the terms interchangeably, making it difficult to determine which term is actually being discussed.

When vaccines are developed on a typical timeframe, rather than during an on-going pandemic, the effectiveness from multiple different studies would be statistically combined over a number of years to allow for a better understanding of how a vaccine performs. In each study, the effectiveness will vary based on differences in external conditions, such as the number of cases in the community and/or differences in virus strains. Researchers can assess the variations based on the known conditions to better understand if there are patterns in the performance of the vaccine.

With the current pandemic, vaccine development is still in the stage of data collection, making it difficult to observe patterns. The effectiveness of the available COVID-19 vaccines reported from different studies varies based on the prevalent conditions, and there has not been enough repetitive information to assess patterns predictably. Instead, researchers can only observe trends and use knowledge from previous experience to predict the best course of action. In the recent past, the only large scale pandemics have been from influenza, which has important differences from COVID-19, making much of the previous experience less useful.

Therefore, it is not possible to definitively report the effectiveness of any of the vaccines at this time.

In other words, there is not a single number to describe the effectiveness yet. The effectiveness of the three vaccines has been reported a number of times in different populations during different timeframes, and the vaccine effectiveness is different in every study due to external factors. The values change, but that does not mean that the studies are inaccurate or flawed. Rather, the conditions that were present when the data were collected vary.

Three examples of how the vaccine effectiveness against infection changes with the conditions at the time of the study include

- A study of a population of frontline workers with a vaccination rate of 83% who were vaccinated with the Moderna, Pfizer-BioNTech, or Johnson & Johnson vaccines, a SARS-CoV-2 infection was 80% more likely to occur in unvaccinated individuals, corresponding to a vaccine effectiveness against SARS-CoV-2 infection of 80% (Fowlkes et al, 2021). When the Delta variant was the dominant variant, a SARS-CoV-2 infection was 66% more likely to occur in an unvaccinated individual, corresponding to a vaccine effectiveness of 66%.
- A study of a population of workers at University of California San Diego Health who received either the Pfizer-BioNTech or Moderna vaccine had 76% vaccination rate by March that increased to 83% vaccinated by July. A SARS-CoV-2 infection was more than 90% more likely to occur in an unvaccinated individual between March and June. The vaccine effectiveness then decreased in July to 65% after the Delta variant became the most prevalent variant (Keehner et al., 2021).
- In a population of health care workers in South Africa who were vaccinated with the Johnson & Johnson vaccine, hospitalization due to SARS-CoV-2 infection was 71% more likely for unvaccinated individuals when the Delta variant was dominate and 67% more likely for unvaccinated individuals when the Beta variant was dominant (Reuters, 2021).

While it is not yet possible to definitively define the vaccine effectiveness for the COVID-19 vaccines, it is possible for researchers to observe trends over time. As more and more information is collected, they will be able to determine the external condition or conditions that are influencing the trend.

Importantly, the effectiveness against infection has changed over time and/or depending on the variant of SARS-CoV-2 that is more prevalent, but the effectiveness against death from SARS-CoV-2 infection has remained relatively stable for all three vaccines.

Reported vaccine effectiveness against death or hospitalization in different populations

- In populations vaccinated with the single-shot Johnson & Johnson vaccine, death was 91% to 96.2% more likely in unvaccinated individuals when Beta or Delta were the most prevalent variant, respectively (Reuters, 2021).
- In populations treated at the Mayo Clinic in Minnesota between January and July, 2021, infection with SARS-CoV-2 was 86% (Moderna) and 76% (Pfizer-BioNTech) more likely in unvaccinated individuals. During the same time period, hospitalization was 91.6% (Moderna) and 85% (Pfizer-BioNTech) more likely in unvaccinated individuals. In July, 2021 the effectiveness against infection of the Pfizer-BioNTech vaccine decreased to 42%, and the effectiveness against infection of the Moderna vaccine decreased to 76%. However, the effectiveness of the both vaccines against hospitalization were near 75% (Puranik et al., 2021).

Vaccine Effectiveness of Different Brands of Vaccine

A recent investigation by researchers affiliated with the CDC found that there are some differences in the vaccine effectiveness against hospitalization for treatment of COVID-19 between the different brands of vaccine (Self et al., 2021).

However, for all of the vaccines authorized or approved for use in the United States, hospitalization for treatment of COVID-19 was over 70% more likely for unvaccinated individuals, meaning that all FDA-approved or authorized COVID-19 vaccines provide substantial protection against COVID-19 hospitalization.

To determine the vaccine effectiveness, the researchers evaluated 3,689 individuals over the age of 18 who were treated for COVID-19 at 21 hospitals in 18 states between March 11 and August 15, 2021. Individuals who had immunocompromising conditions were **not** included in this investigation.

Based on the information between March 11 and August 15, 2021 when the Alpha and Delta variants were the most prevalent in the United States

- Unvaccinated individuals were **93%** more likely to be hospitalized than those vaccinated with the **Moderna** vaccine
- Unvaccinated individuals were **88%** more likely to be hospitalized than those vaccinated with the **Pfizer-BioNTech** vaccine
- Unvaccinated individuals were **71%** more likely to be hospitalized then those vaccinated with the **Johnson & Johnson** vaccine.

Differences in Infectiousness between Vaccinated and Unvaccinated Individuals

One important effect of vaccinating individuals is to reduce the transmission of new cases both by preventing infection and by reducing the infectivity of any breakthrough cases. Ideally, a vaccine will remove a vaccinated individual from the **chain of transmission** so that even if they become ill, they will not infect others.

With the Alpha variant, the vaccine was very efficient at reducing infectivity of individuals with breakthrough infections. So much so that vaccinated individuals were essentially non-infectious and did not require a mask to prevent transmission. The changes that have occurred to the Delta variant of SARS-CoV-2, however, made it so that individuals with breakthrough infections after vaccination are infectious.

The alteration in the virus responsible for this change is hypothesized to be the increased level of virus present in the upper airways during the SARS-CoV-2 infection. The current vaccines lead to the production of antibodies and T cells that are present in the blood stream, which are referred to as IgG antibodies. These immune system components can enter into tissues in the lungs and lower airways relatively easily, but in the upper airways much of the virus is present in mucous membranes or other structures that are not as well-accessed by blood vessels as lung tissue.

The high level of virus in the mucous membranes from the Delta variant means that it is difficult for the IgG antibodies to reach where a large amount of the viral production is occurring.

Therefore, the vaccine is not as good at lowering the amount of the Delta variant produced compared to the Alpha variant because IgG antibodies produced access the areas of viral production differently.

There are also antibodies that are found mainly in the mucous membrane of the upper airway and gut called IgA antibodies. The currently available vaccines stimulate the production mainly of IgG antibodies with a smaller level of IgA antibodies. There are experimental vaccines under investigation that are administered via a nasal spray in order to better stimulate production of IgA against SARS-CoV-2 to address this issue.

While vaccinated individuals do produce enough virus to be infectious, the amount is still lower than unvaccinated individuals.

This difference makes vaccinated individuals less infectious than unvaccinated individuals, and unvaccinated individuals continue to be the main source of transmission for COVID-19 driving the pandemic.

A study that investigated the **secondary attack rate**, or frequency that a person transmits the virus to their contacts, of SARS-CoV-2 between February 1 and May 27, 2021 allowed for the determination of the transmissibility of the **Alpha** variant (de Gier et al., 2021). The secondary attack rate was lower when the initial case was vaccinated, 11%, compared to when the initial case was not vaccinated, 31%.

The vaccine effectiveness against transmission to household-contacts was 71%, i.e. individuals who were unvaccinated were 71% more likely to infect their household contacts.

The vaccine effectiveness against transmission for each type of vaccine was also calculated, and the researchers reported a value of 58% for the AstraZeneca-Oxford vaccine, 70% for the Pfizer-BioNTech vaccine, 88% for the Moderna vaccine, and 77% for the Johnson & Johnson vaccine.

When the contact was vaccinated, the combined vaccine effectiveness against transmission was 75% for all vaccines. The breakdown of vaccine effectiveness against transmission by type of vaccine was 87% for the AstraZeneca-Oxford vaccine, 65% for the Pfizer-BioNTech vaccine, 91% for the Moderna vaccine, and 12% for the Johnson & Johnson vaccine. The value for the Johnson & Johnson was based on only 44 individuals, making the accuracy of the calculation uncertain.

A second published research article describes the vaccine effectiveness against infection and onward transmission when both the initial case and their contacts were vaccinated (Braeye et al., 2021). The study was performed between January 25 and June 24, 2021, meaning that the **Alpha** variant was the most prevalent at the time (from 33% during the first weeks to 80% by the end of the study period). There were 301,741 tests included in the study, representing the PCR-based testing results from all high-risk contacts of an infected person in Belgium. When individuals who were fully vaccinated with an mRNA vaccine were exposed to an infected unvaccinated individual, the vaccine effectiveness against infection was high, overall. When tests representing this scenario were analyzed by vaccine type, the vaccine effectiveness against infection for the Pfizer-BioNTech vaccine was 74%, the Moderna vaccine was 85%, the AstraZeneca-Oxford vaccine was 53%, and the Johnson & Johnson vaccine was 61%. The vaccine effectiveness against onward transmission was estimated at 62% for the Pfizer-BioNTech vaccine and 52% for the Moderna vaccine. There was not enough information to get an accurate value for the AstraZeneca-Oxford and Johnson & Johnson vaccines.

In those who had a breakthrough infection after exposure, the vaccine effectiveness for onward transmission was greater than 90% when both the initial individuals and their contacts were fully vaccinated with an mRNA vaccine.

A study in Guangdong, China between May and June, 2021 allowed for an investigation of the infectiousness of individuals when the **Delta** variant was more prevalent (Kang et al., 2021). The study included 167 individuals who were infected with the Delta variant in an area that had previously had an outbreak of the initial strain of the virus. This allows for a reasonably good comparison of the two strains of the virus because the population should be similar. As seen in previous studies, the researchers found a higher amount of virus present in the testing samples of participants infected with the Delta variant compared to the initial strain.

Vaccinated individuals had amounts of virus in testing samples that were three-times lower than unvaccinated individuals.

The overall secondary attack rate was 1.4% with 73.9% of transmission occurring before symptoms were apparent. The risk of being infected was higher if the contact was older, was unvaccinated or partially vaccinated, and for those who were household or close contacts.

The secondary attack rate of the Delta variant for household contacts was 22% compared to 12.4% with the original strain that circulated in early 2020.

The overall secondary attack rate was also calculated based on either the vaccination status of the initial case or the contacts. The rates are listed in Table 1.

Table 1. Secondary attack rates based on the vaccination status of either the initial case or contacts.

Initial case	Contact	Secondary Attack Rate
Fully vaccinated	Unknown population	**0.4%**
Unvaccinated	Unknown population	**1.3%**
Unknown population	Fully vaccinated	**0.9%**
Unknown population	Unvaccinated	**1.7%**

An ongoing study in England randomly selects individuals from the population for testing every few weeks, allowing for assessment of prevalence of both symptomatic and asymptomatic infection in the general public (Elliot et al., 2021). The most recent round of testing occurred when the **Delta** variant was the most prevalent strain. The researchers found that individuals who had been vaccinated had a lower amount of virus in testing samples on average than those who were unvaccinated. This differed from other studies that report similar levels of virus for both groups. The researchers suggest the difference stemmed from the larger proportion of asymptomatic cases that will be identified through the random testing when compared to testing obtained through patient-based action most often initiated after onset of symptoms (Subbaraman, 2021).

A trial of healthcare workers in the Netherlands investigated the changes in infectivity of breakthrough infections that occurred between April and July, 2021 (Shamier et al., 2021). There were 161 participants in the study, who had been vaccinated with either an mRNA or

adenoviral-based vaccine and had later tested positive for COVID-19. Genomic sequencing data was available for 126 of 161 of the participants, and 90.5% were found to be due to the **Delta** variant.

The amount of virus measured in testing samples from vaccinated and unvaccinated individuals was similar at the time of diagnosis, which has been observed in previous studies of the Delta variant, but not for other strains of SARS-CoV-2, such as Alpha. However, when the testing samples were used to infect cells in a laboratory environment, 68.6% of the samples from vaccinated participants contained sufficient infectious particles to cause an infection compared to 84.9% of the samples from unvaccinated participants.

> **This difference means that while the amount of viral RNA detected in testing samples is the same in vaccinated and unvaccinated individuals, there are less infectious virus present.**

Another important distinction between the amount of virus in the upper airways of vaccinated and unvaccinated individuals was observed in a trial from Singapore that took place while **Delta** was the dominant strain (Subbaraman, 2021). The amount of virus observed in both vaccinated and unvaccinated individuals was the same, and at high levels, in the first week of infection, but **dropped quickly after day seven in those who were vaccinated, suggesting they might be infectious for shortened periods of time**.

A combination of the available evidence suggests that vaccinated individuals with breakthrough infections from the **Delta** variant are more likely to produce infectious virus compared to infections that occur from the **Alpha** variant. However, the infectiousness of vaccinated individuals infected with the Delta variant is still **lower** than that of unvaccinated individuals due to a combination of factors, including a lower amount of infectious virus being produced and/or a reduced time period of infectiousness. Investigation of the characteristics of people who have tested positive from the Delta variant suggests that **the majority of transmission is currently fueled by unvaccinated individuals who are younger** in comparison to the start of the pandemic. However, there are also examples of local outbreaks that have been started by vaccinated individuals with breakthrough infections from the Delta variant, which warrants continued mask use of all individuals regardless of vaccination status in public areas.

Booster Doses of COVID-19 Vaccines

The discussion of booster doses of the available vaccines has been heated. On one hand, there is evidence of a reduction in the protection against infection for the Pfizer-BioNTech vaccine with time and reduction in all three vaccines to some extent against the Delta variant. However, the effectiveness against hospitalization and death from SARS-CoV-2 infection remains high with only a small reduction from initial values. Additionally, there are large numbers of individuals in the world who have not yet been vaccinated and remain at high risk for infection, hospitalization, and/or death.

Basis of the Decision for Booster Doses

The Vaccine and Related Biological Products Advisory Committee (VRBPAC) of the FDA recently met to discuss the submission by Pfizer-BioNTech to authorize a booster dose of the vaccine (VRBPAC, 2021).

The factors that the committee discussed included:

- The effectiveness of primary vaccination with the Pfizer-BioNTech vaccine over time and against circulating variants, e.g. the Delta variant.
- The effectiveness and duration of booster vaccination in preventing important COVID-19-related outcomes in individuals who have already received a primary vaccination series
- The dynamics of the pandemic in the United States
- The risks of booster vaccination in the general population or in certain subpopulations.

Pfizer has ongoing clinical trials of their currently approved vaccine (COMIRNATY), and a subset of the individuals from the Phase 1 (24 participants) and Phase 2/3 (300 participants) were chosen to receive a booster dose of the vaccine. The booster was given approximately seven to nine months after the initial two dose series for the Phase 1 participants and at approximately six months for the participants in the Phase 2/3 trial. The side effects and immune response to the third dose were evaluated.

The level of neutralizing antibodies measured one month after the booster dose was three-fold higher than the level measured one month after full vaccination with two doses.

The proportion of participants who had a large enough immune response to the booster to be considered positive was also reported. The proportion of individuals in the phase 2/3 trial who had a response to the initial two doses was 98% after one month. The proportion of participants in the Phase 2/3 booster trial with a response to the third booster dose was 99.5%.

After the booster shot, 94.4% of the participants recorded local (at the injection site) and systemic (throughout the body) reactions within seven days of receiving the dose. Of these reports, **83% of participants had a local reaction, and 77.2% reported a systemic reaction**. There were no cases of anaphylaxis immediately after the third dose. The most common local reaction was **injection site pain**, reported by 83.0% of participants. **Fatigue** (63.7%) and **headache** (48.4%) were the next most common. Pain at the injection site lasted for a mean duration of 2.6 days with a range from one to eight days. The mean duration for fatigue was 2.4 days with a range from one to 30 days and 2.1 days for headache with a range from one to eight days. Other common local or systemic reactions included **muscle pain** in between 33.3% to 39.1% of participants, **chills** in 16.7% to 29.1%, and **joint pain** in 16.7% to 25.3%. Between 33.3% and 46.7% of participants reported use of pain relievers within seven days of the booster shot.

There were 7.8% of the participants who reported an adverse event that occurred within one month of the booster dose. Severe adverse reactions were uncommon following the booster dose, with the most frequently reported severe solicited reactions being fatigue (4.5%) and muscle pain (1.4%). Lymphadenopathy (swollen lymph nodes) was reported in 5.2% of participants, which was higher than the rate observed after the initial two doses. There were no events leading to withdrawal reported through one month after booster dose administration, and no study participants died. No cases of myocarditis, pericarditis, anaphylaxis, appendicitis, or Bell's Palsy were reported up to the end of the study period.

Additional presentations to the VRBPAC were given by independent researchers about the vaccines. Based on these presentations, there have been 178 research studies investigating vaccine effectiveness against variants of concern, including 114 for the Alpha variant and 76 for the Delta variant (Sterne, 2021).

The discussion from a Viewpoint published in the Lancet was presented, which argued against the need for booster doses of vaccines.

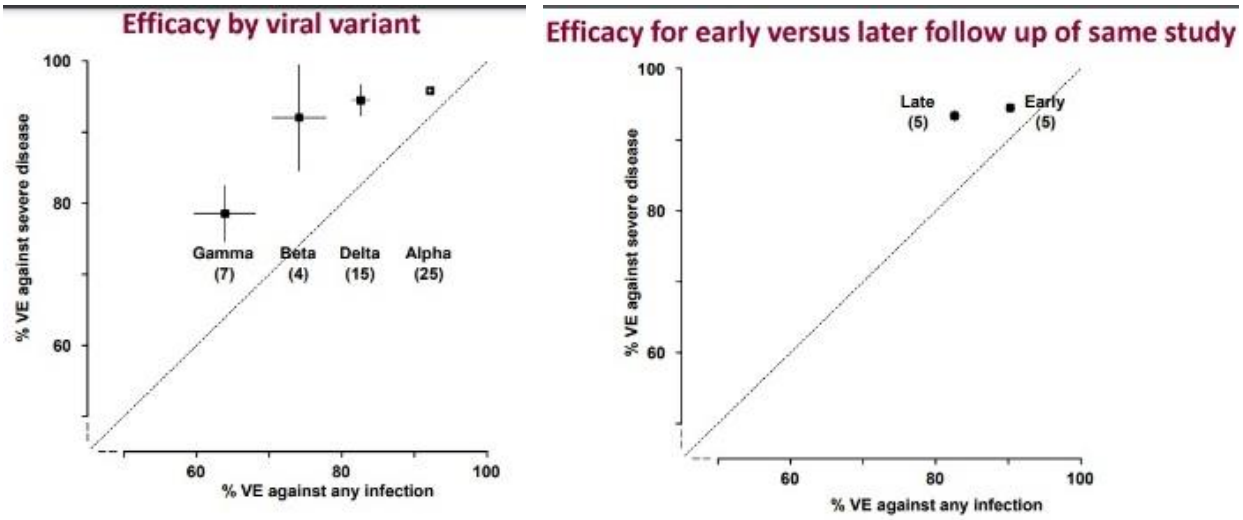

Figure 1. Plots of the vaccine effectiveness against any infection versus vaccine effectiveness against severe disease. In the plot on the left, the vaccine effectiveness is plotted for the different variants. The vaccine effectiveness against severe disease from the Alpha and Delta are both similar as seen by their location at the same vertical position in the plot. The plot on the right allows for comparison of the vaccine efficacy against infection and severe disease based on the timing of the vaccination. Early was defined as more recently relative to vaccination, and late was defined as less recently relative to vaccination. Again, the protection against severe disease is similar based on the vertical position.

Based on the information from the presentation, the effectiveness of mRNA vaccines against severe disease in settings where Delta variant is circulating also indicates that both vaccines continue to provide good protection. The vaccine effectiveness for the Pfizer-BioNTech ranged

from 75% to 96% in different geographical areas during September. The vaccine effectiveness for the Moderna vaccine ranged from 81% to 100%.

A presentation from members of the Ministry of Health in Israel and the Weizmann Institute of Science in Israel summarized the changes in vaccine effectiveness observed in Israel as the Delta variant become more prevalent (Alroy-Preis and Milo, 2021). Israel reached high levels of vaccination about three months before other countries due to a data sharing agreement with Pfizer that allowed for access to doses of the vaccine. By March, 2021 around 80% of individuals over the age of 60 were vaccinated, 60% of those between 40 and 59, and 40% of those between 16 and 39. As of August, 2021, approximately 60% of the entire population was fully vaccinated. The Delta variant became the most prevalent variant in June, 2021.

By the end of August and into September, Israel has experienced its highest levels of infection despite have more than 60% of the entire population fully vaccinated.

An increase of more than 100-fold in the number of cases occurred within 1.5 months with an increase of ten-fold in the number of active, severe cases occurred within a month. A reduction in the protection from infection by vaccination was observed in all age groups. There has also been a reduction in the protection from severe disease in individuals over the age of 60. There is not a clear indication if a reduction in protection from severe disease occurs in other groups.

Since the start of the booster campaign in Israel, over 80% of individuals over the age of 60 have received a third dose. Around 65% of those between age 50 and 59 have also received a booster, as well as approximately 50% of those 40 to 49, 40% of those 30 to 39, and 30% of those 16 to 29. Twelve days or more after the booster shot, there was an 11.4-fold decrease in the relative risk of confirmed SARS-CoV-2 infection, and a greater than ten-fold decrease in the relative risk of severe illness in individuals over the age of 60.

The booster dose was found to return the vaccine effectiveness against infection from Delta back to levels observed after the second dose against infection when Alpha was the most prevalent variant.

After the implementation of the booster campaign, the reproduction number (or number of people one sick person infects) decreased from around 1.3 to 0.96. When the reproduction number falls below one, community transmission has been halted. There was also an observable and statistically significant decrease in the number of individuals over the age of 60 who were diagnosed with COVID-19 as well as a decrease in the number of new severe cases in people over 60.

Data gathered during the rollout also allowed for analysis of the side effects associated with a third booster shot. The rate of adverse effects were reported in the number per million doses. The most common systemic adverse effects observed were weakness with lack of energy (75.3 per million doses), fever (51.6 per million doses), headache (47.4 per million doses), myalgia or muscle pain (39.7 per million doses), chills (24.0 per million doses), vomiting and nausea (13.9 per million doses), and dizziness (10.1 per million doses). The most common local adverse reactions included redness and swelling (39.4 per million doses), restriction of motion (32.8 per

million doses), lymphadenopathy (20.6 per million doses), and a nodule (10.1 per million doses). To date, only a single case of myocarditis has been reported.

An overview of the current state of the pandemic in the United States was also presented by members of the CDC (Oliver, 2021). The number of new cases in the United States has approached the levels seen during the surge last winter, which occurred before vaccines were available. There has also been a spike in hospitalizations and deaths corresponding to the surge in new cases, but the number of people affected is not as high as previous surges.

The lower levels of hospitalization and deaths are due mainly to a reduction in the number of affected individuals over the age of 65, and the rate of hospitalizations and deaths in younger groups has remained at similar levels to those observed before a vaccine was available.

The statistics collected about individuals in the United States who have been fully vaccinated indicate that over 90% of people over the age of 65 are vaccinated. This high rate of vaccination would explain the lowered hospitalization rates and decreased number of deaths. Table 2 lists the proportion of the age groups fully vaccinated as of September, 2021.

Table 2. Proportion of age groups fully vaccinated in the United States

Age Group	Proportion Fully Vaccinated
Over 75 years	**90%**
65-74 years	**95%**
50-64 years	**82%**
40-49 years	**74%**
25-39 years	**65%**
18-24 years	**62%**
16-17 years	**60%**
12-15 years	**52%**

The vaccine effectiveness has been reported from a number of different sources in the United States. Five recent reports followed changes in the vaccine effectiveness against hospitalization from February to July, 2021.

Four of the five of these reports indicate that the vaccine effectiveness against hospitalization from COVID-19 has remained above 80% even when Delta became the most prevalent variant toward the end of June.

The fifth report found a slight reduction in the vaccine efficacy against hospitalization between June and July, 2021 that decreased from 85% to 75%.

The vaccine effectiveness against infection has decreased, and five reports investigated the vaccine effectiveness against infection between March and July, 2021. This decrease is associated with the increase in the proportion of COVID-19 cases resulting from the Delta variant. There were varying degrees of change in the vaccine effectiveness against infection

measured, and the largest change reported from a single study was from 80% in June, 2021 to 40% in July, 2021. The smallest change during this time period was from 85% to 80%.

The presentation from the CDC summarized the vaccine effectiveness data both before the after Delta variant was widespread. The values presented in the FDA hearing are shown in Table 3.

Table 3. Range in vaccine effectiveness before and after the Delta variant emerged.

Characteristic	Before the Delta variant was widespread	After the introduction of the Delta variant
Vaccine effectiveness against **infection**	**72–97%**	**39–84%**
Vaccine effectiveness against **hospitalization**	**84–97%**	**75–95%**

Global studies also show that while there has been a decrease in the vaccine effectiveness against infection, the vaccine effectiveness against hospitalization for COVID-19 has only had a slight decrease. The magnitude of vaccine effectiveness can also be affected by study methods, the interval between doses, the timing of increasing levels of vaccination, and changes in the level of each variant.

There is also information available on the vaccine effectiveness based on age.

Updated data from the United States collected through COVID-NET indicates that vaccine effectiveness against hospitalization in adults over 75 years of age remains higher than 88%.

Studies performed in Canada show that vaccine effectiveness against both hospitalization and urgent care or emergency department visits remained over 82% through at least 16 weeks (around four months) after the second dose. Protection against severe disease remained stable overall in studies from Qatar with a decline noted in those over 60 years after 25 weeks.

Based on available data, the vaccine effectiveness against hospitalization in adults over 65 years of age decreased over time but remained high.

The presenters from the CDC concluded that:

- Vaccines remain effective and offer a high level of protection against hospitalization and severe disease.
- Protection against infection (including asymptomatic or mild infections) has been lower in recent months.
- The reasons for a lower effectiveness likely include both waning immunity over time and emergence of the Delta variant.

Details of the Recommendation by the FDA

Based on a review of the evidence, the VRBPAC participants determined that the FDA should authorize a booster dose of the **Pfizer-BioNTech vaccine** for certain groups (FDA, 2021b).

Specifically, a single booster dose is to be administered at least six months after completion of the primary series (first two doses) in:

- Individuals 65 years of age and older
- Individuals 18 through 64 years of age at high risk of severe COVID-19
- Individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19

The committee found that "based on the totality of the available scientific evidence, a booster dose of Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19 and that the known and potential benefits of a booster dose outweigh the known and potential risks in the populations that the FDA is authorizing for use."

The results from the clinical trial organized by Pfizer showed that "the antibody response against SARS-CoV-2 virus one month after a booster dose of the vaccine compared to the response one month after the two-dose primary series in the same individuals demonstrated a booster response." Additionally, evaluation of the Pfizer clinical trial data showed that during the study period between July and August 2021, the incidence of COVID-19 was higher among the participants who were fully vaccinated earlier, compared to participants who completed the vaccination later in the year.

The FDA determined that the rate of breakthrough infections reported during this time period translates to a modest decrease in the efficacy of the vaccine among those vaccinated earlier.

The CDC's Advisory Committee on Immunization Practices (ACIP) met after the FDA authorization and also recommended a booster for some of the same groups (Soucheray, 2021). This is the final step in the process for approving the new recommendations. During the ACIP meeting, there continued to be discussion on the specifics of the recommendations. Experts raised concerns that the vaccination campaign should focus on the prevention of hospitalizations rather than prevention of infection. There was also a heated discussion about how the decision would affect future decisions on the potential need of a booster for individuals who received the Moderna or Johnson & Johnson vaccine.

The final decision from the ACIP recommends vaccination for

- Those 65 and older
- Those 50 to 64 who have underlying medical conditions that make them prone to severe COVID-19
- Those 18 to 49 based on individual benefit and risk given underlying medical conditions

A recommendation for a fourth group, those 18 and older who worked in an occupational setting that put them at more risk for COVID-19 infections, including frontline workers, people who live in congregate settings, and caregivers for the immunocompromised, was **not** approved.

The CDC decided to go against the ACIP recommendations and has approved a booster dose for ALL four groups.

In a press conference about the decision, the Director of the CDC, Rochelle Walensky, MD, MPH, stated that even though boosters were recommended, it is not expected that booster shots will have a large effect on the trajectory of the pandemic (Soucheray, 2021b). The main group of individuals responsible for continued high transmission rates in the United States are those who are unvaccinated. There are still 18 states in the country where less than 50% of the population is vaccinated. Those states have more COVID-19 hospitalizations and deaths than the vaccinated states with the highest proportion of the population is vaccinated.

Johnson & Johnson has also recently announced clinical trial results about the use of a booster to its single shot vaccine (Johnson & Johnson, 2021). The press release from the company states that they are “engaging with the U.S. Food and Drug Administration (FDA), U.S. Centers for Disease Control and Prevention (CDC), European Medicines Agency (EMA) and other health authorities regarding boosting with the Johnson & Johnson COVID-19 vaccine.”

Mixing Vaccine Types for Different Doses

The CDC recommendations for booster shots only apply to individuals who received the Pfizer-BioNTech vaccine. The booster dose should be with the **same type of vaccine** used for the initial vaccination, which means the Pfizer-BioNTech vaccine. The recommendations were based on clinical trials which included only people who received the Pfizer-BioNTech vaccine, and only the Pfizer-BioNTech vaccine was given as a booster dose.

There have been a limited number of clinical trials investigating the results of using two different vaccine types to complete full vaccination for a vaccine requiring two doses. The majority of these investigated the use of the AstraZeneca-Oxford vaccine as the first dose with a change to an mRNA vaccine for the second dose to avoid the potential serious clotting events observed in some individuals after full vaccination with the AstraZeneca-Oxford vaccine (Vallée et al., 2021 and Singhatiraj et al., 2021). Other trials were focused on the effects of additional doses of vaccine for individuals with a poor response to vaccination due to immunocompromising conditions (Lyski et al., 2021).

The studies of use of a different type of vaccine for the second dose indicate that there is a higher rate of adverse effects from mixed doses, but there was not a statistically significant difference in the final immune response in participants who received mixed doses compared to those who received the same type of vaccine.

Because there is not a known benefit for getting a booster with another type of vaccine, and there is evidence that use of mixed doses can increase the adverse events associated with vaccination, it is not recommended at this time to mix the types of vaccine.

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