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Medical Intelligence Report

Date: November 19, 2021

Topic: COVID-19 Research Update

Overview of Pandemic

After a gradual decrease from the peak of the Delta-variant based surge this summer, the number of new cases of COVID-19 is increasing again in the United States (Washington Post, 2021). Nationwide as of November 12, there was a 3% increase in the last seven days. On November 19, 2021, the number of new cases had increased by 31% in the last seven days.

Forty-two states are reporting an increase in the number of cases within the last seven days.

The rapid increase in new cases was first observed in Mid-Western states and those in the Mountain West. The number of new cases rapidly starting to rise in Colorado and Arizona around November 12, 2021, and on November 19, 2021, there was an increase of 127% in new cases over the last seven days in Oklahoma. The surge in new cases is now also evident in other states around the country with Michigan and Connecticut experiencing increases between around 80% and Rhode Island and Massachusetts with increases of around 60%. There are increases of 20% or higher in areas throughout the United States.

As deaths lag behind the increases in cases, the nationwide change in the number of deaths is still decreasing with a 4% decrease over the last seven days. However, Rhode Island and South Dakota have had a 100% increase in the number of deaths from COVID-19 in the last seven days. Washington state, Maine, North Dakota, and Montana have had increases of over 60% in the number of deaths in the last seven days.

In total, the number of new deaths from COVID-19 has increased in 26 states over the last seven days.

Hospitals in Colorado are reporting the largest surge in patients in a year, and facilities are being allowed to turn away new patients due to a lack of space (Grullón Paz, 2021). As of November 12, 2021, hospitalizations due to COVID-19 had increased by 14% in the previous two weeks. In Larimer County, which includes the city of Ft. Collins, the intensive care units are at 110% capacity. The overall vaccination rate in Colorado is 62%, and 76% of the people currently hospitalized with COVID-19 are unvaccinated, and over 86% of COVID-19 patients who are in need of a ventilator and are in intensive care are unvaccinated.

Hospitalizations are climbing the most rapidly in New Hampshire, Massachusetts, Vermont, and Michigan with around a 20% increase or higher in the week before November 19, 2021.

There are 32 states where the number of individuals hospitalized for treatment of COVID-19 is rising in the last seven days, and 16 have had an increase of 10% or higher.

Vaccination is still benefiting residents of the United States, as discussed by experts interviewed for an article in STAT News (Boodman, 2021). The stark differences in the numbers of vaccinated and unvaccinated people in the United States becoming ill and requiring hospitalization can be observed in a graph from the article reproduced in Figure1.

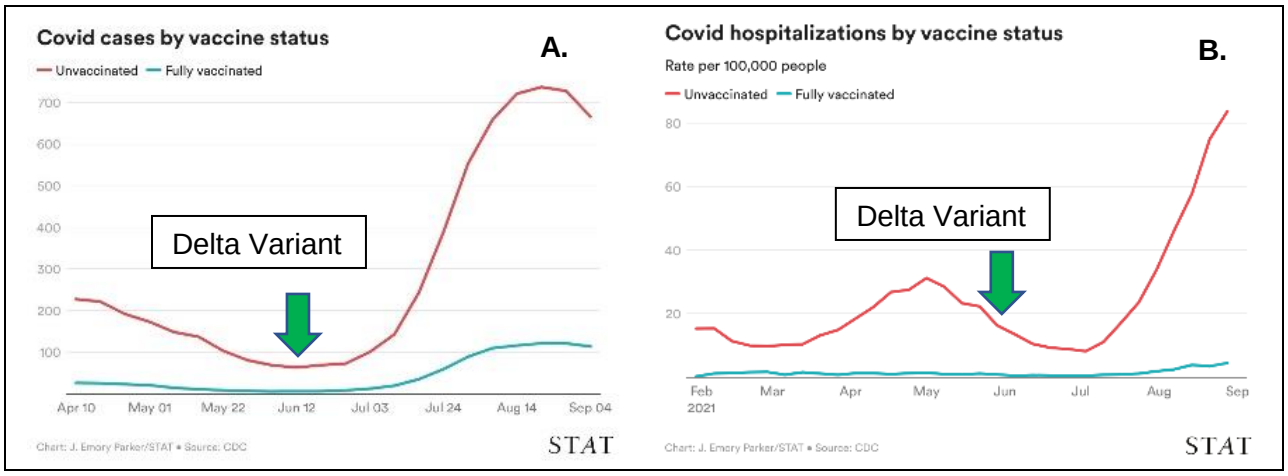

Figure 1. A. Graph of the number of COVID-19 cases per 100,000 people with unvaccinated individuals shown in red and vaccinated individuals shown in blue from February, 2021 to September, 2021. The point the Delta variant started to become dominant in the United States, in June, 2021, is shown by the green arrow. **B.** Graph of the number of hospitalization for COVID-19 per 100,000 with unvaccinated individuals shown in red and vaccinated individuals shown in blue from February, 2021 to September, 2021. The point the Delta variant started to become dominant in the United States, in June, 2021, is shown by the green arrow. Adapted from Boodman, 2021.

Also apparent from the graph is that even though vaccination has been less effective at preventing new cases recently, compared to when vaccines first became available, the number of unvaccinated individuals newly infected with SARS-CoV-2 is still vastly larger than the number of new infections for vaccinated individuals. A similar trend is seen with hospitalizations.

The number of unvaccinated people requiring hospitalization for COVID-19 is much larger than the number of vaccinated people.

There have also been reports of increases in new COVID-19 cases in the United Kingdom and Europe (Schnirring, 2021 and Schnirring, 2021b). Earlier in the month, countries in Eastern Europe and Russia were experiencing large growth in the number of new infections, but now

cases are rising in Western Europe as well. Some of the countries, such as Russia, have low levels of vaccination, but several in Western Europe, including the Netherlands with 85% coverage and Denmark with 76% coverage, have high levels of fully vaccinated individuals.

Scientists are keeping a close eye on the trajectory of new infections in the United Kingdom because there is a high level of vaccination across the country and because events in the United Kingdom have foreshadowed events in other European and North American countries (Taylor, 2021).

A key point of analysis of the current situation in the United Kingdom is that:

> **"Relative to the size of its population, the United Kingdom has around three times as many infections as the United States", but 66% fewer daily deaths.**

The divergence in the number of infections from the number of deaths between the United Kingdom and the United States is evident in the graph in Figure 2.

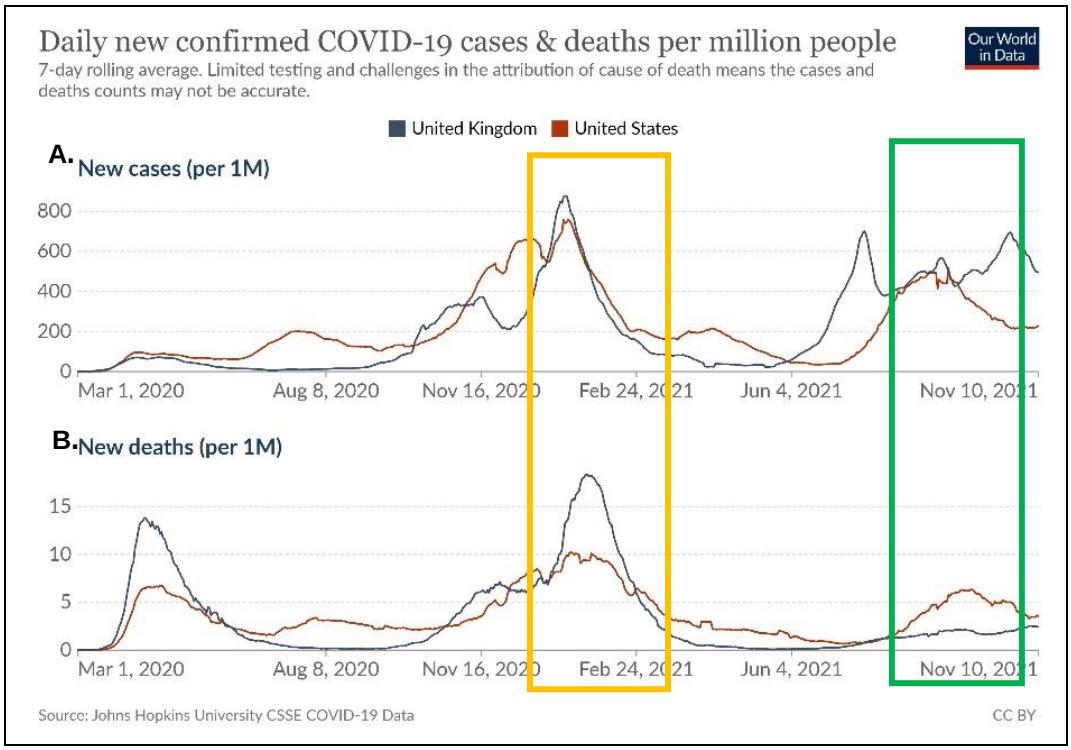

Figure 2. A. Graph of new cases per one million people in the United States (blue) and the United Kingdom (red) over the course of the pandemic. **B**. Graph of deaths from COVID-19 per one million people in the United States (blue) and the United Kingdom (red) over the course of the pandemic. Created with Our World in Data at https://ourworldindata.org/covid-cases on November 11, 2021.

The green box on the graph highlights the period of recent trends where the United Kingdom has seen large numbers of new infections but few deaths. During this time period, deaths have

still been high in the United States. This difference in the number of deaths is thought to be due to increased levels of vaccination in the United Kingdom. Vaccination has been less effective recently at preventing infection, but still provides good protection from severe COVID-19 symptoms, thus preventing hospitalization in highly vaccinated populations. In the United Kingdom, 79.5% of those aged twelve years and older have received two vaccine doses as of October 31, 2021. This is compared to the United States where 69% of the population over twelve have received two doses as of November 12, 2021.

To reach the same level of vaccine coverage, the United States will need to fully vaccinate around an additional 35 million people over the age of twelve.

The United Kingdom has lifted nearly all COVID-19 restrictions beginning in July and August, 2021 so that the main control of the spread of SARS-CoV-2 is vaccine coverage and individual public responsibility.

This combination of a high number of new cases along with the low level of COVID-19 restrictions indicates that vaccination alone cannot control the spread of the virus, but it has controlled hospitalizations.

The current situation is in contrast to the period in the orange box during the winter of 2020 and 2021, where the coverage of full vaccination in the United Kingdom was less than the United States due to the policy to get as many people as possible a single dose. The introduction of the Alpha variant also occurred at this time. During the time period in the orange box, the original, less transmissive strain of the virus was still the most prevalent strain in the United States, and vaccination efforts were targeting older adults at high risk of hospitalization and death from COVID-19.

Vaccine Updates

To better understand the long-term effectiveness of vaccination, researchers at the Veterans Health Administration looked at the number of infections and deaths from February to October, 2021 (Cohn et al., 2021). During the study period, the vaccine effectiveness against infection based on information on all the vaccines fell from 87.9% to 48.1%. The decline was the largest for the Johnson & Johnson vaccine, which decreased to 13.1%.

Even though the effectiveness against infection dropped, vaccination was still protective against death even when the Delta variant became the most prevalent strain.

From July to October, 2021, the vaccine effectiveness against death for individuals less than 65 years old was 81.7% for any of the vaccines.

The vaccine effectiveness against death in individuals UNDER 65 was

- 73% for the Johnson & Johnson vaccine
- 81.5% for the Moderna vaccine
- 84.3% for the Pfizer-BioNTech vaccine

In individuals over the age 65, the vaccine effectiveness against death was 71.6% for any of the vaccines.

The vaccine effectiveness against death in individuals OVER 65 was

- 52.2% for the Johnson & Johnson vaccine
- 75.5% for Moderna vaccine
- 70.1% for Pfizer-BioNTech vaccine

A study of real-world data from the United Kingdom found that vaccination reduces the risk of infection from the Delta variant and accelerates viral clearance in individuals with breakthrough infections (Singanayagam et al., 2021).

However, it also confirmed earlier reports that fully vaccinated individuals who have breakthrough infections due to the Delta variant are as infectious as unvaccinated individuals infected with Delta variant.

The study examined community transmission based on contact tracing of household contacts from 471 individuals who were mildly ill from the Delta variant of SARS-CoV-2 between Sep 13, 2020 and Sep 15, 2021. During the study, the COVID-19 status of 602 household contacts was recorded, and 133 participants also contributed testing samples for up to 20 days so the researchers could evaluate virus growth rates within household contacts. The risk of infection was measured by calculating the **secondary attack rate**, which is the percentage of contacts infected by the original person, or index patient.

Vaccination rates were also known for the index patients and their household contacts, allowing for an evaluation of the effect of vaccination on the secondary attack rate. Researchers reported that 62% of the household contacts had had two doses of vaccine, 19% had received one dose, and 19% had not been vaccinated. The researchers investigated individuals who were known to be infected with the **Delta** variant, and all of the 53 contacts that became infected with the Delta variant were exposed while at home rather than from non-household settings.

The secondary attack rate for all of the individuals exposed to the Delta variant was 26%, regardless of vaccination state.

The secondary attack rate for household contacts exposed to the Delta variant by an index case who was fully vaccinated was 25% while the secondary attack rate for unvaccinated index cases was 23%.

This means that vaccinated individuals with breakthrough infections are able to infect other people at a rate near to that of unvaccinated individuals.

There was also evidence of infection from fully vaccinated index cases to fully vaccinated contacts. However, all cases of COVID-19 in this study were non-severe illness that could be treated at home or were asymptomatic throughout the disease course.

The amount of virus produced was also monitored for some participants over the course of the study. Evaluation of periodic sampling showed infection with different variants caused a similar level of virus to be produced, and the level also did not vary by vaccination status. The rate that virus levels declined was faster in vaccinated individuals with an infection from the Delta variant than for all other groups measured in the study.

Based on the results from the study, the authors conclude that "although current vaccines remain effective at preventing severe disease and deaths from COVID-19, our findings suggest that vaccination alone is not sufficient to prevent all transmission of the delta variant in the household setting, where exposure is close and prolonged."

Therefore, it will be necessary to continue to protect individuals at risk for severe outcomes with both vaccination and non-pharmaceutical measures, such as masking and social distancing.

An editorial written by Annelies Wilder-Smith, MD, PhD, of the London School of Hygiene & Tropical Medicine accompanied the publication of the above study (Wilder-Smith, 2021). She highlights the finding that, unlike the Alpha variant, breakthrough infections caused by the Delta variant after vaccination easily propagate infection within households.

In other words, there is only minimal effect of vaccination in reduction of transmission of breakthrough infections.

Therefore the protection afforded to unvaccinated individuals by vaccinated ones is lower for the Delta variant than the Alpha variant because they can be infected by vaccinated people. Overall this means that a larger number of people would need to be vaccinated to reduce community transmission.

Effect of Vaccination on Severity of COVID-19 Breakthrough Infections

An evaluation of the information from the Influenza and Other Viruses in the Acutely ill (IVY) Network was conducted to investigate if prior vaccination reduces the severity of SARS-CoV-2 infections (Tenforde et al., 2021). The IVY Network includes data from 21 hospitals in the United States that are located in 18 states. The researchers evaluated medical records for 4,513 participants who had been hospitalized at facilities in the IVY Network between March 11, 2021 and August 15, 2021. This timeframe encompasses the initial vaccination campaign of older individuals up to after the Delta variant became widespread. Sequencing of test samples indicated that 33.6% of infections were caused by the **Alpha** variant, 45.9% were due to the **Delta** variant, and 20.5% were other variants. The switch from the Alpha variant to the Delta variant being the most dominate occurred in June, 2021.

The characteristics of individuals who were hospitalized for treatment of COVID-19 were compared to individuals who were hospitalized at the same time for other reasons. Individuals who had only received one dose of an mRNA vaccine were excluded, and people who had received vaccination with non-mRNA based vaccine were also excluded. There were 1,983 participants with COVID-19 and 2,530 individuals who were hospitalized for other reasons. An analysis of the individuals in this study provided an estimate of vaccine effectiveness of 85% against hospitalization for the treatment of COVID-19 even when the Delta variant is widespread.

Individuals with SARS-CoV-2 infections who were not vaccinated were more likely to be younger than individuals hospitalized for a breakthrough infection after vaccination.

The median age of participants with breakthrough infections was 67 while the median age of unvaccinated participants was 53. Participants with breakthrough infections after vaccination were also more likely to immunocompromised (40.8%) than unvaccinated participants hospitalized for COVID-19 (11%). The large proportion of participants who are immunocompromised in the group who had been vaccinated suggests that individuals with functioning immune systems were protected from hospitalization by vaccination.

Overall, vaccination was less common in individuals hospitalized for COVID-19 than in those receiving care for other conditions.

The proportion of the people hospitalized for COVID-19 who were fully vaccinated was low at 15.8%. The proportion of individuals in the hospital for treatment of other conditions who were fully vaccinated was 54.8%.

The likelihood of hospitalization due to COVID-19 was lower for vaccinated individuals for both the Alpha and Delta variants.

There was not a difference in the magnitude of the effect based on the variant causing the infection, suggesting that vaccination prevented severe disease from both variants to a similar degree.

The study identified a number of areas where full vaccination had beneficial effects for people hospitalized for treatment of COVID-19:

- Vaccinated individuals with breakthrough infections received intensive-care levels of treatment less often, 24.6% versus 40.1%
- Vaccinated individuals were less likely to require mechanical ventilation, 7.7% versus 23%.
- 93.9% of individuals who died from COVID-19 or required mechanical ventilation were unvaccinated.
- Unvaccinated individuals accounted for 91% of deaths from COVID-19 during the study.
- 6.3% of vaccinated individuals with COVID-19 died during the study while 8.6% of unvaccinated individuals died from COVID-19.
- When the severity of COVID-19 symptoms was compared based on the WHO COVID-19 clinical progression scale, disease severity was lower among vaccine breakthrough cases than unvaccinated cases.
- A larger proportion of vaccinated individuals (88%) were discharged from the hospital within 28 days of admission for treatment of COVID-19 while 77.2% of unvaccinated individuals were discharged within the same time period.
- The length of stay was found to be shorter for vaccinated individuals compared to unvaccinated individuals even when the comparisons were made based on age and immunocompromised status.

Overview of the Documented Benefits of Vaccination against SARS-CoV-2

In an editorial that was published in the same issue as the article by Tenforde and colleagues, Michael Klompus, a professor in the Department of Population Medicine at Harvard Medical School in Boston, Massachusetts, summarized what is known thus far on breakthrough infections of SARS-CoV-2 after vaccination (Klompas, 2021).

The bottom line was that fully vaccinated people remain at risk for infection with SARS-CoV-2. For example, on October 21, 2021 35% of the 519 individuals hospitalized for COVID-19 in the state of Massachusetts were fully vaccinated. There have also been numerous benefits observed as well.

However, even though there is still a risk of infection, vaccination has been found to provide numerous benefits against COVID-19:

- A study of 100,000 randomly chosen residents in England was used to determine the prevalence of COVID-19 in the population between June, 2021 and July, 2021 and showed that vaccinated individuals were 66% less likely to have COVID-19 than unvaccinated individuals.
- In a study of the Moderna vaccine, vaccinated participants were 66% less likely to be asymptomatic carriers of SARS-CoV-2 compared to unvaccinated participants who had received a placebo.
- Viral loads in vaccinated and unvaccinated individuals have been found to have similar peak levels of virus, but the amount of virus produced declines more rapidly in vaccinated individuals, suggesting that they are contagious for shorter periods.
- The virus produced by vaccinated individuals is less likely to be able to infect cells in culture than the virus produced by unvaccinated individuals, which is a test used to measure the amount of infectious virus produced during an infection.
- Vaccinated people are less likely to transmit SARS-CoV-2 to close contacts than unvaccinated people, which includes studies of both the Alpha and Delta variants.
- Vaccines decrease the severity of symptoms associated with COVID-19.
- Individuals who have been vaccinated are less likely to develop symptoms, less likely to develop severe symptoms, more likely to recover from their illness quickly, and much less likely to require hospitalization compared with unvaccinated people even when infected with the Delta variant.
- As of August 28, 2021, the age-adjusted rate of hospitalization among US adults aged 18 years or older was 83.6 per 100000 for unvaccinated persons compared with 4.5 per 100000 for fully vaccinated persons.

Comparison of Infection-Based Immunity to Vaccination-Based Immunity

A report in the CDC's *Morbidity and Mortality Weekly Report* indicates that vaccine-induced immunity was more protective than infection-induced immunity (Bozio et al., 2021). The study included information from 187 hospitals across nine states between January and September, 2021. The researchers examined medical records for 201,269 individuals who were over 18 and had COVID-19-like illness during the study period. There were 1,020 individuals with a previous infection who were identified based on a record of a previous positive PCR-based test more than 90 days before the current admission to the hospital with COVID-19-like illness. There were 6,328 vaccinated individuals identified as having admission to the hospital with a COVID-19-like illness after receiving a second dose of one of the mRNA vaccines more than 14 days before admission. Individuals with evidence of previous infection who later vaccinated were excluded from the analysis. Individuals who received the Johnson & Johnson vaccine were not included due to a small number of potential participants.

PCR-based testing showed that 5.1% of the fully vaccinated persons and 8.7% of unvaccinated, previously infected persons were positive for COVID-19.

This corresponds to a 5.5-fold increase in risk for infection with SARS-CoV-2 for individuals with a previous infection compared to individuals who were fully vaccinated.

The increase in risk did not change when the researchers compared individuals infected after the Delta variant became widespread, suggesting that the increased transmissibility of that strain did not contribute to the increase. There was also not a difference in the risk of infection between the two groups when the information was analyzed based on the amount of time elapsed from either infection or vaccination. The possible waning effects from vaccination were not evident in this study. It has been shown that the waning effect of vaccination involves protection from infection and not prevention of severe symptoms or hospitalization. The researchers postulate that as only hospitalized individuals were included in this study, a change in risk for infections over time would not be evident.

There was a large difference in the risk when analyzed based on the age of the individual.

There was a 19.6-fold increase in risk of being hospitalized with COVID-19 for previously infected, unvaccinated individuals over the age of 65 when compared to in people the same age who were fully vaccinated.

Younger previously infected and unvaccinated individuals, those 18 to 64 years old, had a lower difference in risk than older individuals, but they were still **2.57-times more likely to be hospitalized due to COVID-19** than individuals of the same age that were vaccinated.

There were also differences based on the type of vaccine received, however. Unvaccinated individuals had a 7.3-fold increase in risk for infection compared to those who received the Moderna vaccine while there was a 5.1-fold increase in risk compared to those who received the Pfizer-BioNTech vaccine. This suggests that the Moderna vaccine had a larger protective effect compared to the Pfizer-BioNTech vaccine. This is consistent with other studies that have shown a higher vaccine effectiveness against COVID-19 hospitalizations for Moderna vaccine recipients compared to Pfizer-BioNTech vaccine recipients.

Novavax Vaccine

Novavax has started the process of obtaining authorization for use of its viral protein-based vaccine (Novavax, 2021). Submissions have been made at the WHO, the European Medicines Agency, and Australia, and submission to the FDA is expected before the end of the year. The vaccine has been granted emergency use status in India, New Zealand, Indonesia, and the Philippines already, and the FDA is allowing individuals who participated in the clinical trials for the vaccine to be considered “fully vaccinated” for legal purposes.

The Novavax vaccine has been eagerly awaited because it uses conventional methods to stimulate immunity to SARS-CoV-2 through viral proteins rather than the more recently developed mRNA and viral vector vaccines. A protein-based vaccine is expected to be more

amenable to individuals who have put off vaccination due to worry about the rare side effects observed with currently available vaccines (Dolgin, 2021).

Clinical trial results about the vaccine have been available for a while, but Novavax experienced delays in authorization due to problems with manufacturing and quality-control requirements. The roll out of a protein based vaccine is inherently slower than that of an mRNA or viral-vector vaccine. The proteins for the vaccine are produced en masse in an organism, such as bacteria or cultured insect cells. This process, as well as the process for harvesting the proteins after they are made, involves numerous steps that must be optimized for each vaccine.

The Phase 3 clinical trial of the Novavax vaccine that included 30,000 participants reported that the vaccine had a more than 90% efficacy against symptomatic COVID-19 caused by non-Delta variants.

Other protein-based vaccines are being developed by Sanofi and Glaxo-Smith-Kline, and their vaccines are currently being evaluated in Phase 3 trials in Africa, Asia and Latin America. Several other smaller companies are also developing protein-based vaccines. For example, Clover Biopharmaceuticals from China has a protein-based vaccine that was found to have an efficacy of 67% against symptomatic COVID-19 from the Delta and Mu variants. This efficacy is lower than that reported from Novavax, because these variants were not yet widespread during the time of the Novavax trial.

The Novavax and Clover vaccines both lead to production of a similar level of antibodies to that reported for the mRNA vaccines, suggesting they will have a similar efficacy against the different variants.

None of the clinical trials involving protein-based vaccines have reported any major side effects, and recipients have had less severe responses directly after the shot when compared to the level of headaches, fevers, nausea, and chills elicited by the mRNA-based vaccines. One of the principal investigators of a trial for Taiwan's Medigen Vaccine Biologics Corporation reported that the "safety profile is very much like those of influenza vaccines." The different vaccines from different manufacturers contain large differences in the specific components, however, and they are not expected to have the same outcomes. Additionally, the rare side effects observed with the currently available vaccines, such as clotting disorders and myocarditis, were also not observed during the clinical trials of the vaccines. The conditions were so rare that they were not observed until they have been used in the general population.

World-wide, protein-based vaccines are expected to greatly help with the shortage of vaccines in lower-income countries. Once the method of production is elucidated, the production of the vaccines is typically fast and inexpensive, and as it is a previously used technique, there are individuals with experience in producing protein vaccines and facilities to produce them in place. Protein vaccines also are easier to distribute because they do not have strict refrigeration requirements like the currently available vaccines.

Johnson & Johnson Vaccine

Most of the studies published about vaccine effectiveness have focused on the mRNA vaccines because more people received these vaccines and because they were released earlier than the Johnson & Johnson vaccine. Researchers have published an investigation of the vaccine effectiveness of the Johnson & Johnson vaccine based on medical records in the Mayo Clinic Health System in the United States that provides services in Minnesota, Arizona, Florida, Wisconsin, and Iowa (Corchado-Garcia et al., 2021). Information on vaccination and infections between February 27, 2021 and July 22, 2021 were used in the evaluation. There were 8,889 participants in the study who received a single dose of the Johnson & Johnson vaccine as well as 88,898 unvaccinated individuals included for comparison.

The vaccine effectiveness measured in this trial was 73.6% against infection with SARS-CoV-2, which corresponds to a 3.73-fold reduction in SARS-CoV-2 infections after vaccination.

The variants that were circulating at the time of the study were Alpha and then Delta. The results were consistent with the efficacy reported in the original clinical trials even with the increased transmission of the Alpha and Delta variants.

A second study was published that examined the incidence of cerebral venous sinus thrombosis associated with the Johnson & Johnson vaccine (Ashrani et al., 2021). To determine the typical rate of the condition in the general public, the researchers evaluated the number of cases in Olmsted County, Minnesota from January 1, 2001 through December 31, 2015. Reports to the CDC Vaccine Adverse Event Reporting System (VAERS) were used to determine the number of cases of cerebral venous sinus thrombosis that occurred after an individuals received the Johnson & Johnson vaccine.

Based on the comparison, the researchers determined that the incidence of cerebral venous sinus thrombosis was higher within the 15 days after vaccination with the Johnson & Johnson vaccine than observed in the years before the pandemic.

In the 16 years used to determine the incidence in the general population, there were 39 cases of cerebral venous sinus thrombosis in Olmsted County, Minnesota where the Mayo Clinic is located. As of May 7, 2021, 38 objectively diagnosed cases of cerebral venous sinus thrombosis events had occurred within 92 days after vaccination with the Johnson & Johnson vaccine. There were 8,727,851 doses of the vaccine administered as of May 7, 2021 in the United States.

The highest risk for cerebral venous sinus thrombosis was within 15 days of vaccination, and as reported previously, women had the largest increase in risk. Women aged 30 to 49 years had the highest risk of cerebral venous sinus thrombosis after vaccination with the Johnson & Johnson vaccine, but even in this group, the overall risk was still low at 29.5 per 100,000 people in one year. In the pre-pandemic time period, men over the age of 65 had the highest risk for cerebral venous sinus thrombosis at 6.22 per 100,000 people in a year.

Specifically, the rate of cerebral venous sinus thrombosis in the post-vaccine time period was 5.1-fold higher for women when compared before the pandemic.

Treatment for COVID-19

The results of clinical trials on two new antiviral medications to treat COVID-19 were recently released (Ledford, 2021). Both are available as pills taken orally. Antivirals are medications that specifically target mechanisms of the virus and interrupt a process that is required in the viral life cycle. Many of the previous treatments used for treatment of COVID-19 were not specific to the virus and targeted bodily processes that led to exacerbation of severe symptoms, such as those that reduced the inflammatory response to infection.

Antiviral medications typically function to slow or halt the formation of new copies of the virus, allowing the immune system to clear a smaller amount of virus.

Therefore, it is important for antiviral drugs to be administered early during an infection while the amount of virus is still low.

This characteristic can also make some antivirals effective as a preventative measure for individuals who have been exposed to infection, but have not yet tested positive for infection. Researchers are still determining if the new COVID-19 medications have this characteristic. Determining its ability to be given as a prophylactic would be an important step in controlling local outbreaks in unvaccinated individuals.

Paxlovid

Pfizer announced the results from the Phase 2/3 trial of their new medication called Paxlovid in treatment of non-hospitalized adults with COVID-19 (Pfizer, 2021). The medication is an orally administered pill that contains a combination of the HIV treatment ritonavir and a new drug molecule designated as PF-07321332. PF-07321332 is a compound that inhibits the function of a viral enzyme called a protease. The SARS-CoV-2 protease is called 3CLPro, and it functions to cut new viral proteins apart in the human cell after they are produced. Halting this step of the viral lifecycle prevents the production of new virus particles, thus halting the infection of new cells. Ritonavir is added to the medication to slow the breakdown of PF-07321332 after it is ingested so that it is active in the body for a longer period of time.

The interim analysis of the Phase 2/3 study included 1,219 adults out of the originally estimated 3,000 to be enrolled in the study. Participants had a laboratory-confirmed diagnosis of COVID-19 within five days of the start of mild to moderate symptoms and also had at least one underlying medical condition that has been associated with an increased risk of developing severe illness from COVID-19.

In the study, researchers observed that participants treated with Paxlovid within three days had a reduction in the risk of hospitalization or death of 89% compared to those receiving a placebo.

Specifically, 0.8% of participants who received Paxlovid within three days of symptom onset were hospitalized within 28 days after receiving their first dose compared to 7.0% of participants who received placebo and were hospitalized or died. There were no deaths in the group receiving Paxlovid and seven deaths in the group receiving a placebo.

Individuals who began treatment within five days of symptom onset had similar outcomes, with 1% of participants who received Paxlovid requiring hospitalization within 28 days of starting the medication compared to 6.7% of participants who received a placebo. There were no deaths in the group taking Paxlovid while there were 10 deaths in the placebo group within 28 days of starting the trial.

Enrollment of new participants into the study was halted after FDA review of the interim results due to overwhelming evidence of a beneficial effect. At that time, 70% of the 3,000 expected participants, or 2,100, had been enrolled. The final analysis will be performed when the researchers finish observing all 2,100 for 28 days after receiving the trial medications. There are ongoing trials to investigate whether Paxlovid can be used as a prophylactic and what the effect is in vaccinated individuals. Pfizer applied to the FDA for an Emergency Use Authorization on November 16, 2021.

Molnupiravir

Molnupiravir was developed by Merck and Ridgeback Biotherapeutics, and the medication will be marketed as Lagevrio (Ledford, 2021). The active compound in molnupiravir is a mimic of the subunits of RNA, which becomes incorporated into the copies of the viral genome destined for new viruses. When the mimics are incorporated by viral machinery, they cause mutations that prevent an active virus from being created.

Interim results from the Phase 3 clinical trial have been reported in a press release (Merck, 2021).

> **The analysis indicates that there is a reduction in the number of people with COVID-19 that require hospitalization for treatment and a reduction in the number of deaths from COVID-19.**

Specifically, there was a 50% reduction in the risk of hospitalization or death in non-hospitalized adult patients with mild-to-moderate COVID-19. The researchers found that 7.3% of patients who received molnupiravir were hospitalized or died within the 29 days following the start of treatment, compared with 14.1% of participants who received the placebo. There were no deaths in the group receiving molnupiravir while there were eight deaths in the group receiving the placebo.

> **Based on the results of the clinical trials, regulators in the United Kingdom have granted provisional authorization of molnupiravir for adults 18 and older who have tested positive for COVID-19 and have at least one risk factor for developing severe disease.**

The medication is administered in individuals with mild to moderate COVID-19 as four pills twice a day for five days. The FDA has announced a meeting on November 30, 2021 to discuss the possible authorization for use in the United States (FDA, 2021).

Specific details on side effects from the medication have not been released by Merck, but the company reports that the rate of adverse reactions was similar between people who received molnupiravir and those who received the placebo.

Use of drugs that mimic the subunits comprising RNA have a risk of affecting the human versions of machinery that produce RNA as well as the viral forms. The subunit mimics compounds have difficulty affecting human RNA or DNA production because the machinery for that process is located in the nucleus of cells and is therefore separated from the compounds by the nuclear membrane.

Even if a small amount of molnupiravir crosses the nuclear membrane, the genome of human cells is not affected by molnupiravir because the human genome is encoded by DNA rather than RNA.

There are different subunits used in the production of DNA versus RNA, and the machinery used to maintain and copy DNA cannot utilize the subunits used for RNA.

There are some compounds in the same class of drug as molnupiravir that can be metabolized by the cell and remade into subunits compatible with the DNA-based enzymes. When this happens, the compounds can be incorporated into human DNA and cause mutations in the genome (Zhou et al., 2021). Molnupiravir causes what is considered to be a modest level of mutations in the human cells being treated cased on laboratory studies. Introduction of mutations occurs at a low rate overall, and only cells that are actively propagating into new cells could possibly be affected. Additionally, because the medication is given for only a short time (five days) at the start of SARS-CoV-2 infection, the exposure to circumstances that could cause a mutation is brief. However, due to the high number of such cells in a developing fetus, the medication is not recommended for use in pregnant individuals. The Medicines and Healthcare products Regulatory Agency in Britain reported that “studies in rats showed that (molnupiravir) may cause harmful effects to the unborn offspring, although this was at doses which were higher than those that will be given to humans, and these effects were not observed in other animals” (Perrone and Cheng, 2021).

Clinical studies of the medication have not shown molnupiravir increases the risk of mutations in humans.

Overall, most experts have supported the use of molnupiravir for treatment of COVID-19 (Service, 2021). Some have raised concerns that use of the medication may also promote mutations in the virus that could lead to development of new variants. In response to this possibility, experts acknowledged that such a scenario is theoretically possible, and while it is important to watch for such occurrences, the situation is still only hypothetical. Aris Katzourakis, a viral evolution expert at the University of Oxford, stated that the potential risk from this possibility, which has not been observed to occur, is not larger than the risk from infection in those who remain susceptible to SARS-CoV-2. Raymond Schinazi, an infectious disease expert

at Emory University, commented that if there are viable virus produced after treatment with molnupiravir, most mutations that occur are “bad for the virus.”

Laboratory studies of another drug in the same class as molnupiravir that was designed for use against the MERS coronavirus and a coronavirus that targets mice showed that mutations in the virus did emerge, but most of the mutations were damaging to the virus and led to slower growth.

The mutations were observed after virus was exposed to 30 rounds of drug treatment.

Daria Hazuda, who heads infectious disease discovery for Merck, stated that the clinical trials specifically investigating use of molnupiravir have produced no evidence of a selective bias for more virulent SARS-CoV-2. A selective bias is an evolutionary pressure that causes an organism to evolve towards a certain endpoint. For example, selective bias is the process by which HIV developed resistance to early medications. In the case of HIV, the mutations in the virus led to certain medications becoming ineffective for treatment, but there was not an increase in the virulence of the virus.

The production of molnupiravir is relatively simple and inexpensive, which is expected to make it more accessible than previous medications or vaccines (Perrone and Cheng, 2021). Merck has reportedly agreed to licensing deals with generic drugs manufacturers in India as well publically sharing information on the formulation. The company has also promised aid to companies who need technological help in producing the drug. It is hoped that this break with previous stances of large drug companies will allow for larger access by poorer countries that have currently been able to vaccinate only 1% of their populations.

It is possible, however, that the small window of time in which molnupiravir is effective may limit its usefulness in people who are diagnosed with the disease (Swaminathan, 2021). The recommendations for administering the medication within three to five days of the start of symptoms may be difficult to achieve.

In order to begin taking molnupiravir within five days of symptom onset, an individual must:

- Recognize they have symptoms indicative of COVID-19
- Secure a COVID test
- Get the test results back
- Make an appointment with a doctor
- Get a prescription from the doctor for molnupiravir
- Buy the medication

The people expected to benefit most from use of an oral treatment for the prevention of severe COVID-19 are also often the people who would have large barriers to performing all of the above steps in the time needed.

Studies in the United States investigating the use of remdesivir, which also must be given early in the disease course of COVID-19, indicate that the medicine was used half as often in Black

cancer patients as in white patients. The distribution of remdesivir was also skewed so that private hospitals, which tend to serve higher income and white patients, had earlier access when supplies were limited than public hospitals, which tend to treat ethnic and racial minorities and those with lower income.

Fluvoxamine

Fluvoxamine is a medication previously used as a treatment for depression and obsessive-compulsive disorder, but it also has properties that decrease the immune response, which made it a possible treatment for COVID-19 (Sidik, 2021). A study performed in 2019 showed that the medication reduced inflammation in mice with sepsis, a condition similar to the cytokine storm observed in severe COVID-19. The effect of fluvoxamine was studied in a platform trial called TOGETHER, investigating several already approved drugs on COVID-19. The trial included 1,497 participants who had COVID-19 and were at high risk of severe disease. The outcomes of those on fluvoxamine were compared to those taking a placebo.

There was a 90% reduction in the number of COVID-19 related deaths and a 65% reduction in the number of people requiring intensive, COVID-19-related medical care for participants who took fluvoxamine in the early stages of infection.

There was no difference in the number of people who had clearance of the virus by the seventh day, suggesting that the beneficial effects were not due to inhibition of the viral lifecycle (Van Beusekom, 2021). Previous investigations of the medication have indicated anti-inflammatory and antiplatelet properties that could lead to the improvement in outcomes with COVID-19. Antiplatelet medications prevent platelet cells in the blood from sticking together and forming a clot. There was also no statistically significant difference in the number of adverse events between those taking fluvoxamine and those receiving the placebo.

Experts interviewed by the journal *Nature* had some questions about the results from the clinical trials because they were conducted in Brazil where the protocol for treatment of COVID-19 is different from that used in the United States (Sidik, 2021). These differences make it difficult to determine if there are different definitions of “severe COVID-19” or if the setting where treatment occurs could affect the outcome. This may change the magnitude of the effect observed in individuals treated in the United States. The fact that the trial included a placebo for comparison suggests that the effect of fluvoxamine is real, however. The experts were also interested in the possibility of pairing fluvoxamine with other antiviral medications, such as those described above or monoclonal antibody treatments, because the combination of lowering the inflammatory response with reducing virus production could have a synergistic effect leading to even better outcomes.

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