PINNACLECARE

Medical Intelligence Report

Date: April 28, 2021

Topic: COVID-19 Research Update

Excess Death Rate for 2020

Based on now available mortality data, the number of deaths due to the COVID-19 pandemic have led to the largest number of excess deaths ever recorded (Lu, 2021). Excess deaths are the numbers of deaths above the expected number of deaths in a year based on how many people are expected to die in a "normal" year. The number of excess deaths that occurred in 2020 was higher than that recorded during the 1918 flu pandemic. Since the 1918 pandemic, the death rate each year in the United States has been decreasing overall, but this year the trend was broken.

2020 had the largest single-year surge in the death rate since federal statistics became available with a 16% increase from 2019 to 2020 compared to a 12% increase during the 1918 flu pandemic.

The next largest increase in the death rate between one year and the next was 1928 when the death rate increased by 7%.

COVID-19 In-Hospital Death Rates

Researchers have studied the rate of in-hospital deaths of individuals who were admitted for at least one day at one of 209 acute care hospitals in the United States between March 1 and November 21, 2020 (Finelli et al., 2021). Of the 503,409 individuals in the study admitted to the hospital during this time, 8.5% received a positive SARS-CoV-2 test.

Overall the largest percentage of those with COVID-19 were aged 65 or older (46.8%) followed by those from 50 to 64 years (27.2%) and from 18 to 49 years (24.9%). The number of people aged 18 to 49 years increased in April, 2020, representing 20.7% of the all the hospitalized individuals, and again in June (representing 30.3%) and July (representing 29.6%). The number of individuals aged 18 to 49 years of age that were admitted to the hospital and tested positive for COVID-19 briefly exceeded those aged 50 to 64 years during the month of June.

When the mortality of individuals admitted to the hospital during the study period was evaluated, it was determined that those who had tested positive for COVID-19

had higher in-hospital mortality than patients with negative tests, 11% compared to 2.5%.

There was a large difference between the mortality rate of individuals with COVID-19 based on age, and the in-hospital mortality rate of individuals with positive COVID-19 tests increased with age from 0.2% for people younger than 18 to 20.9% for those older than 75 years. The in-hospital mortality rates were similar between men and women in individuals who were negative for COVID-19, but there was a higher mortality rate for men (12.5%) compared to women (9.6%) in people who were positive for COVID-19. The in-hospital mortality rate increased from March to April in the United States from 10.6% to 19.7% and then decreased by November to 9.3% due to statistically significant reductions in the mortality rates in the oldest age groups.

A similar study investigated the surgical risk for individuals with and without a SARS-CoV-2 infection based on the outcomes during or immediately after surgery with a specific emphasis on mortality rates (Haffner et al., 2021). The medical records of 10,940 individuals 18 years or older with and without COVID-19 who underwent surgery among all surgical specialties from April 1 through November 30, 2020 were compared. However, gynecologic, obstetrical, or minor procedures such as tracheostomy and percutaneous cardiovascular procedures were excluded.

When the entire group was analyzed as a whole, there were more than double the number of deaths reported in the cohort of patients with COVID-19, 14.8% compared to 7.1%.

Additionally, hospital acquired conditions and patient safety indicators (information on potentially avoidable safety events) were also higher in individuals who had COVID-19. The rates of complications and the median length of stay of the individuals did not differ between the two groups.

The researchers also found a difference in the surgical mortality rate in individuals with and without COVID-19 that was associated with the type of ownership of the hospital. There were more deaths of individuals with COVID-19 compared to those without COVID-19 in public (15.8% versus 4.8%) and nonprofit hospitals (14.7% versus 7.5%), but there was no statistically significant difference in private hospitals (14.1% versus 9.4%). The difference between the private hospitals was found to be due to higher mortality rates in individuals without COVID-19 as there was no difference in the mortality rates, complications, hospital-acquired conditions, or patient safety indicators among surgical patients with COVID-19 that correlated with the hospital type.

Based on the results, the authors conclude that COVID-19 was a risk factor for increased mortality during, or soon after, surgery, but there was not an association between COVID-19 and complications from surgery.

They also recommend that “surgical patients with COVID-19 should be informed of their higher in-hospital mortality risk. More important, postponing surgery should be recommended for patients with a positive preoperative COVID-19 test result when possible unless surgical intervention is absolutely necessary for life- or limb-saving measures.”

Vaccine Updates

Vaccination of the Population Prevents Spread of B.1.1.7

The vaccination campaign in Israel using the Pfizer-BioNTech vaccine began around the time that the more transmissible form of the virus, B.1.1.7, was introduced to the country (Munitz et al., 2021). To follow the progress of the vaccine campaign, a massive testing program was also initiated at the same time. Between December 6, 2020 and February 10, 2021, approximately 300,000 PCR-based tests were collected, allowing for accurate tracking of cases, and use of the samples for genomic sequencing to observe the spread of B.1.1.7.

Based on the information collected, the researchers found that the B.1.1.7 variant was 45% more transmissible than previous strains, and it became the dominant strain within 3.5 weeks after introduction.

This was similar to the increase observed in studies in England where researchers reported an increase of 56% in transmissibility. Researchers in Israel also found that the reproduction number, or the number of new infections produced by a single infected individual, increased for B.1.1.7 compared to previous variants. The previous reproduction number determined by health officials in Israel was 1.12, and the reproduction number of B.1.1.7 was found to be 1.71.

However, prioritized vaccination of the elderly allowed for prevention of spread of the more transmissible variant.

There was an increase in the number of individuals with B.1.1.7 who were aged zero to 59, but after January 13, 2021, when the vaccine campaign was active, the incidence of B.1.1.7 in people over 60 plateaued and then declined.

Before January 13, 2021, the rise in the number of people with B.1.1.7 had increased at a similar rate for all age groups. At the January 13 time point, 50% of the population who were over 60 years of age had had their first dose of vaccine for at least two weeks.

Importantly, the researchers found that while the transmission of B.1.1.7 continued to rise at a similar dramatic rate in the groups between the age of 0 to 19 and 20 to 59, the rise in the population over the age of 60 years was completely halted.

Lower Vaccine Efficacy in Individuals with Blood Cancers

Two investigations of the efficacy of vaccination of individuals with blood cancers with the Pfizer-BioNTech vaccine were recently released. In the first, researchers examined the response of 167 participants with chronic lymphocytic leukemia (CLL) (Herishanu et al., 2021). Individuals with CLL are more prone to infections from bacteria and viruses from both the treatment of CLL and the disease itself. The Pfizer-BioNTech vaccine for COVID-19 was given as directed in two doses, 21 days apart, and the level of antibodies produced was measured after administration of the second dose.

The response rate in the participants with CLL was low, with 39.5% producing antibodies.

A smaller group of participants (52 individuals) was compared to a group of 52 healthy adults, and 52% of participants with CLL produced antibodies versus 100% of the group of healthy adults.

The participants with CLL that had the largest response to vaccination were those who were not actively undergoing treatment at the time of vaccination.

The response rate was 79.2% in those who had achieved clinical remission after treatment, 55.2% in those who had not yet started treatment, and 16% in those being treated at the time of vaccination.

The researchers also evaluated the response of individuals taking different types of treatments. Those currently receiving treatment with BTK inhibitors had a response rate of 16%. The response rate of participants currently taking venetoclax, either with or without anti-CD20 antibodies, was 13.6%. Anti-CD20 antibodies are a treatment for certain types of blood cancers that reduces the amount of B cells. Because B cells are the type of immune-system cell that produce antibodies in response to infection, the reduction in B cells from anti-CD20 antibody treatment will reduce the response to vaccination. Within the total study group of 167 participants, 77 had been treated at one time with anti-CD20 therapy, including 22 individuals undergoing treatment within the last 12 months before being vaccinated.

None of the patients exposed to anti-CD20 antibodies less than 12 months prior to vaccination responded while 45.5% of those who were vaccinated more than 12 months after use of anti-CD20 therapy responded to the vaccine.

The second study investigated the effect of vaccination with the Pfizer-BioNTech vaccine in participants with multiple myeloma (Terpos et al., 2021). Individuals with multiple myeloma have a high risk of moderate to severe respiratory dysfunction associated with COVID-19 due to a combination of immunocompromised state, older age, and comorbidities, and more than 80% of individuals with multiple myeloma require hospitalization for treatment of SARS-CoV-2 infections. The 48 participants in this study were over the age of 18 with smoldering myeloma or active multiple myeloma and were eligible for vaccination. At the time of vaccination, 35 (or 72.9%) of the participants were also receiving treatment for multiple myeloma, four were in remission, and nine had smoldering myeloma.

The level of antibodies to the spike protein of SARS-CoV-2 was measured on the day before the first inoculation and on the day before the second inoculation, or 22 days after the first dose. The median level of inhibition by antibodies to SARS-CoV-2 measured for participants with multiple myeloma was 20.6% with a range from 0% to 96.7%. A healthy comparison group vaccinated at the same facility had a median level of inhibition by antibodies to SARS-CoV-2 of 32.5% with a range between 5.2% and 97.3%, which was a statistically significant difference.

However, only 12, or 25%, of the participants with multiple myeloma had antibody inhibition levels greater than 30% the day before receiving the second dose of vaccine compared to 57, or 54.8%, of the healthy comparison group.

There were 21, or 20.2%, of the healthy comparison group that were found to have antibody inhibition levels higher than 50% while only 4, or 8.3%, of the participants with multiple myeloma had greater than 50% inhibition by antibodies to SARS-CoV-2.

The four participants with the highest response were the four individuals who were in remission and not currently receiving treatment.

Only one of the nine participants (corresponding to 11.1%) with smoldering multiple myeloma reached a level of antibody inhibition over 30% while 28.2% of participants with active multiple myeloma reached this level. The single individual with a greater than 30% response was the only participant with a normal level of immunoglobulin, a measure of how well the cells from the immune system and antibody production are performing.

The authors conclude that while there have been documented accounts of strong vaccine responses in younger individuals after a single dose of the Pfizer-BioNTech vaccine, elderly multiple myeloma patients have a lower response to the first dose of the vaccine, and a second dose within the established timeframe should be required for this population.

Response to Vaccine in Recovered Individuals versus Those Who Were Never Ill

Researchers investigated the B-cell response and antibody production of individuals after receiving either the Pfizer-BioNTech or Moderna COVID-19 vaccine (Goel et al., 2021). The researchers measured the response of participants who had not been previously exposed to SARS-CoV-2 and those who had recovered from infection. Four blood samples were collected to assess the response to the vaccine; they were collected before vaccination, two weeks following the first dose, the day of second dose, and one week following the second dose.

Individuals who had not been exposed to SARS-CoV-2 required both doses of the vaccine to achieve an optimal increase in antibodies, especially for development of high neutralizing activity against the B.1.351 variant.

Memory B cells were detected after the second dose of the vaccine in those who had not previously had COVID-19, and the amount of B cells produced was found to decline slightly with age.

In participants who had recovered from COVID-19, antibody and memory B-cell responses were boosted after the first vaccine dose, and no further increase was observed after the second dose, suggesting that only a single dose may be required.

The amount of response to the vaccine observed in participants who had previously had COVID-19 was observed to be associated with the levels of pre-existing memory B cells that were produced in response to infection.

Side Effects from Vaccines

After review of the reports of adverse events associated with the Johnson & Johnson COVID-19 vaccine, the CDC has recommended that states should resume using it in their vaccination campaigns (CDC, 2021). The CDC recommended a pause in the use of the vaccine in order to determine the number of cases of a rare blood clotting condition that had occurred after vaccination and to assure that physicians were aware of the symptoms associated with the condition and how to treat it if it occurs.

Based on their evaluation, the CDC officials found that there are occurrences of a rare adverse event called **thrombosis with thrombocytopenia syndrome (TTS)** associated with the Johnson & Johnson vaccine.

> **Worldwide, nearly all of the reports of the condition associated with either the Johnson & Johnson vaccine or the AstraZeneca-Oxford vaccine have been in adult women younger than 50 years of age.**

Because of this association, the CDC recommends that women younger than 50 years of age should be aware of the rare, but increased, risk of this adverse event and that there are other COVID-19 vaccine options available for which this risk has not been seen. Regulating bodies in Europe have recommended that younger individuals use the two mRNA-based vaccines rather than the AstraZeneca-Oxford vaccine, which is authorized for use there.

As of April 23, 2021, there had been more than 8 million doses of the Johnson & Johnson vaccine administered in the United States with 15 reports of individuals who later developed TTS. TTS occurs because antibodies produced by the individual interact with proteins involved in regulating clotting. The antibodies cause proteins in the clotting system to come into contact, leading to the formation of large clots in abnormal areas in the body. The formation of these large clots also depletes clotting factors, called platelets, from other parts of the body leading to an increased bleeding risk in other tissues.

Symptoms are reported to begin between 6 and 15 days after vaccination and can include:

- Severe or persistent headaches or blurred vision
- Shortness of breath
- Chest pain
- Leg swelling
- Persistent abdominal pain
- Easy bruising or tiny blood spots under the skin beyond the injection site

In the United States, all of the individuals who have experienced the adverse event were women between the ages 18 and 59 with a median of 37 years. TTS is a rare occurrence for all women, and even more rare for those over the age of 50.

Based on the number of adverse events that have been reported and the number of doses administered, it is estimated that there are 7 events per 1 million vaccinations among women 18 through 49 years old and a rate of 0.9 per 1 million vaccinations among women 50 years and older.

The review of the reports indicates that the Johnson & Johnson vaccine's known and potential benefits outweigh its known and potential risks for those recommended to receive it.

Johnson & Johnson and Janssen have published a statement in the *New England Journal of Medicine* describing similar events in the Phase 3 trials of the vaccine (Sadoff et al,. 2021).

There were 75,000 participants in the trial, and one case of cerebral venous sinus thrombosis (CVST) in a participant who received the vaccine.

The clinical trial was paused when the adverse event was reported, and after consultation with outside experts, the trial was restarted because no clear association between the vaccine and the symptoms could be established. The participant was found to have antibodies that react to the blood clotting factor called platelet factor 4 (PF4) as has been reported in the other instances reported for both the Johnson & Johnson vaccine and the AstraZeneca-Oxford vaccine.

After the vaccine was authorized for use, the surveillance program managed by Janssen that is used to monitor safety received six reports of CVST with thrombocytopenia (low platelet levels) occurring seven to 14 days after vaccination. Based on this level of reporting, the rate of CVST is still within the range of normal occurrence of the condition in the general population, and according to their statement, the Johnson & Johnson vaccine has not been proven to be the cause of the reactions.

The Johnson & Johnson vaccine and AstraZeneca-Oxford vaccine are both adenovirus vaccines, and a link has been proposed by other researchers between this type of vaccine and the clotting reactions. However, the two vaccines use different adenoviruses from different species and attach to human cells using different proteins. The production of the spike protein also differs in that the Johnson & Johnson vaccine produces a spike protein that remains embedded in the cell surface of the cell that produces it while the AstraZeneca-Oxford vaccine produces a spike protein that is released from the cell into the bloodstream.

Other researchers have suggested that the link between the vaccines and the side effects is not due to the vaccines themselves, but to small components, such as DNA fragments or proteins, that remain after the vaccine is produced (Vogel and Kupferschmidt, 2021 and Kupferschmidt and Vogel, 2021). There have been experiments that suggest that PF4, the protein targeted by antibodies in the clotting disorder, can interact with stray DNA, proteins, or viruses if they come into contact with each other. These complexes are more likely to attract the attention of the immune system, leading to the production of antibodies. The question remains as to what part of the COVID-19 vaccines initiates this process. Currently, there is not enough information to say one way or the other, but researchers have a number of hypotheses that can be tested. For example, Gowthami Arepally, a hematologist at the Duke University School of Medicine, suggests that some individuals may simply have higher levels of PF4, that when coupled with the inflammatory response to the adenovirus, lead to formation of the complexes and antibody

production. Rolf Marschalek, a molecular biologist at Goethe University Frankfurt, suggests that the spike protein from SARS-CoV-2 may play a more direct role due to the similar timing between the production of the spike protein and emergence of the clotting disorder.

Two other vaccines, Sputnik V and the vaccine made by CanSino, are also adenovirus vaccines and are being carefully watched to see if similar clotting side effects emerge with more widespread use.

Comparison of the Risk of Blood Clots

Researchers at the University of Oxford examined the medical records of 513,284 individuals to determine the incidence of cerebral venous thrombosis (CVT) in the two weeks after being diagnosed with COVID-19, influenza, or after receiving one of the mRNA vaccines (Taquet et al., 2021).

Based on the researchers' assessment:

- The incidence after diagnosis with COVID-19 was **39 per million** people.
- There were no cases observed within two weeks of diagnosis with influenza.
- The incidence after vaccination with either the Pfizer-BioNTech or Moderna vaccine was **4.1 per million** people.
- The European Medicines Agency estimates that the incidence of CVT associated with the AstraZeneca-Oxford vaccine is **5.0 per million** people.

A similar condition called portal vein thrombosis (PVT) occurs from the same process of PF4 antibodies, but the large clots are located in the portal vein in the abdomen rather than the brain. The incidence of PVT in the two weeks after COVID-19 diagnosis was 436.4 per million people, 98.4 per million in the two weeks after diagnosis with influenza, and 44.9 per million after vaccination with either of the mRNA vaccines.

When estimating the incidence of CVT in the general population, the researchers determined the incidence of the condition across the entire health-records network. The incidence over any two-week period was 0.41 cases per million people, and the incidence two weeks after diagnosis for COVID-19 was higher than the incidence observed across the entire health records network. In individuals with COVID-19 who had CVT or PVT, the mortality was 20% and 18.8%, respectively.

The authors state that there is a high risk of serious thrombotic events associated with COVID-19, and highlighting these risks can help to communicate and contextualize the risks and benefits of vaccination.

Re-Infection with SARS-CoV-2

The rate of re-infection after COVID-19 as well as the length of time of immunity are topics of great interest to the world-at-large. While the duration of immunity can only be answered over time, researchers are conducting periodic studies to determine the re-infection rate for different groups. Two reports were released regarding re-infection, the first involved individuals who were involved in a COVID-19 outbreak at a skilled nursing facility after a vaccination campaign, and the second investigates re-infection after previous SARS-CoV-2 infection in young-adults aged 18 to 20 years of age.

The Kentucky Health Department investigated a COVID-19 outbreak at a skilled nursing facility that occurred after all residents and healthcare staff had been offered vaccination (Cavanaugh et al., 2021). There are 83 residents and 116 healthcare personnel at the facility, and 90.4% of the residents and 52.6% of the personnel received two doses of the Pfizer-BioNTech vaccine more than 14 days before the outbreak began. There were four residents and five staff members that received their second dose less than 14 days before the beginning of the outbreak. There were also ten individuals who had received only one dose at the time of the first COVID-19 case.

The index case of the outbreak was an unvaccinated staff member who tested positive on March 1, 2021 during routine antigen testing. At the time of testing, the staff member was experiencing symptoms that are associated with COVID-19.

During the outbreak, 26 residents and 20 staff tested positive for COVID-19, which included 18 residents and four staff that had been fully vaccinated before exposure from the outbreak.

The attack rate for unvaccinated residents was three-times higher than the rate for vaccinated residents (75% versus 25%). In staff members, the attack rate was 4.1-times higher in unvaccinated individuals compared to those who were vaccinated (29.6% versus 7.1%).

The estimated vaccine effectiveness against SARS-CoV-2 infection among residents was 66.2% and 75.9% in staff members.

Vaccinated residents who became ill were 86.5% less likely to have symptoms than those who were not vaccinated, and vaccinated staff members had a similar reduction in symptoms of 87.1%. The vaccine effectiveness against hospitalization was 94.4% in residents and none of the staff were hospitalized.

Overall, three residents died from COVID-19 during the outbreak, and one of the individuals who died was vaccinated.

There were four cases identified where individuals who had previously been infected with SARS-CoV-2 were re-infected. The individuals who were infected a second time were one resident and three staff members. One of the staff members had also been vaccinated. All four individuals who were re-infected experienced symptomatic illness.

The resident that was re-infected was hospitalized for treatment of severe symptoms and died.

The researchers sequenced the genome of the virus responsible for the outbreak, and it did not correspond to any of the major variants currently spreading in the United States. The designation of the variant is the R.1 lineage, and it has 14 amino acid mutations not present in the Wuhan-1 genome from the start of the pandemic. This variant is not currently designated as a variant of concern by the CDC because it has not been found to be widespread around the country.

There were four mutations within the spike protein of the virus from the skilled nursing facility, E484K, D614G, G769V, and W152L. The E484K mutation has been observed in other variants, including B.1.351 and P.1. The E484K mutation is thought to be associated with immune system escape, leading to a higher rate of re-infection. The estimate of vaccine effectiveness calculated from the information gathered during this outbreak was lower than that calculated from the real-world data collected in Israel during their nationwide vaccination campaign, which may suggest a lower effectiveness of the vaccine against R.1 variants or it may be due to differences in the size of the groups tested.

The details of this outbreak show that, overall, vaccination protects most individuals from infection and/or serious outcomes, including older individuals who are considered to be frail.

However, it also emphasizes the need for additional protections even after vaccination due to the high levels of transmission of SARS-CoV-2 in most parts of the United States and the spread of variants with different profiles that may become more transmissible, more lethal, or more able to avoid the immune response.

The authors conclude that the results from the analysis underscore the importance of the Advisory Committee on Immunization Practices' recommendation that all persons, including those who have recovered from COVID-19, be vaccinated.

Additionally, low acceptance of vaccination by staff at skilled nursing facilities will continue to increase the risk of transmission of SARS-CoV-2 to a vulnerable population, and vaccination of only the residents themselves is not sufficient protection. In the best-case-scenario, the effectiveness of the vaccine is less than 100%, and older individuals have been shown to be more likely to have a lower immune response, leading to further reduction in protection for a group more likely to be at risk for severe outcomes.

Therefore, the researchers state that vaccination of both skilled nursing facility residents and staff is essential to reduce the risk for symptomatic COVID-19, as is continued focus on infection prevention and control practices.

In the second study investigating re-infection by SARS-CoV-2, researchers evaluated COVID-19 cases in soldiers reporting to basic training camp because this group can be easily assessed due to the regimented schedule during training (Letizia et al., 2021). The researchers evaluated the re-infection rate of 3,249 United States Marine recruits, aged 18 to 20 years, as they arrived

at basic training camp. The recruits were advised to quarantine for two weeks at home before the start of the program. They were then required to participate in a mandatory two-week, supervised quarantine where they were assessed for previous SARS-CoV-2 infection through antibody testing as well as completion of questionnaires. The participants were tested for active infections at the start of the supervised quarantine, after one week, and after two weeks. They were then moved to base to begin basic training, where they received COVID-19 tests at weeks two, four, and six of training.

There were 189 individuals who had SARS-CoV-2 antibodies from a previous infection as determined during the supervised quarantine before basic training started, and 10% of these previously infected individuals tested positive for COVID-19 during the six weeks of basic training. Of the participants who had not previously been exposed to SARS-CoV-2 and did not have antibodies at the start of basic training, 1079, or 48%, of the participants tested positive for an active infection during training using PCR-based testing.

Based on this data, young-adults who have previously had COVID-19 have an 18% lower risk of infection compared to those who have not had COVID-19 before.

In participants who have previously had COVID-19, infection was more likely for individuals with lower levels of spike-protein antibodies. Those who were re-infected had viral loads approximately 10-times lower than those who were infected for the first time, suggesting a protective effect from the previous infection.

The authors conclude that although antibodies induced by a previous infection are largely protective and reduce the level of subsequent infection, they do not guarantee effective SARS-CoV-2 neutralization of the virus if exposure occurs or immunity against subsequent infection.

Budesonide for Treatment of COVID-19

Researchers investigated the effect of the inhaled corticosteroids in 2617 individuals over 65 years of age or over 50 years of age with comorbidities who had been ill with COVID-19 for less than 14 days (Yu et al., 2021). The clinical trial began on November 27, 2020 and ended March 31, 2021, and during this time, 751 participants were randomly assigned to receive the inhaled corticosteroid budesonide, 1028 were assigned to receive usual care, and 643 were assigned to other interventions that will be assessed in other reports. Previous experiments have shown that use of inhaled corticosteroids reduces expression of ACE-2 and TMPRSS2, which are used by SARS-CoV-2 for cell entry. It has not been clear whether the use of inhaled corticosteroids would improve outcomes in people not hospitalized for treatment of COVID-19.

The results that have been reported are interim results of a subset of the participants, and the results of the entire study population will be analyzed and reported when available. The results are not yet finished because the entire evaluation time (28 days) after entering the trial has not been completed for all participants.

During the trial, the time between enrollment in the trial and the time from symptom onset was a median of six days with a range from four to nine days.

Participants taking budesonide had a reduced time until recovery of three days compared to those provided usual care.

Of those included in this interim analysis, there were also fewer individuals who progressed to requiring treatment in the hospital after use of budesonide (8.5% versus 10.3%). However, as there were very few individuals assessed in the interim analysis, a complete analysis will be needed to determine if this difference is statistically significant.

There were also improvements in the daily symptom assessments in participants taking budesonide based on the daily score of how well participants felt, the scores on the WHO-5 Wellbeing Index, early sustained recovery, and the time to sustained recovery. There was not a difference in the amount of healthcare services used between the two groups in the study. Further analysis did not show an association between symptom duration prior to treatment, the severity illness of illness at the start of treatment, age of the participant, or the presence of comorbidities changed the effect of budesonide on time to first reported recovery.

Potential Source of Neurological Effects after SARS-CoV-2 Infection

A large study of samples from autopsies conducted between March and June of 2020 found that the neurological effects observed with COVID-19 did not occur due to infection of the cells in the brain (Van Beusekom, 2021).

Instead, the results of the evaluations suggest that the damage is due to inflammation triggered by SARS-CoV-2 either in other parts of the body or in the blood vessels of the brain.

The researchers found areas of brain damage due to oxygen starvation caused by broken blood vessels and blood clots. There were also a high number of activated immune cells, called microglia, in the brain that were observed to be attacking neurons. The hypoxic state, or low-oxygen state, causes microglia that have been activated by cytokines to be more likely to attack neurons.

Previous research has shown that activation of microglia leads to a permanent loss of neurons in the brain.

Most of the activated microglia were located in the brainstem and hippocampus. The brainstem is responsible for control of the heart rhythms, breathing rhythms, and levels of consciousness while the hippocampus is involved in mood and memory. The authors stated that “it is notable that some COVID-19 survivors develop neuropsychiatric symptoms, including memory disturbances, somnolence, fatigue and insomnia, and that similar symptoms are reported in both the acute and recovery phases.”

The effects observed in this study were in deceased individuals, and the effect may not be as pronounced in people who had a milder illness. However, the correlation between the regions affected and the symptoms observed in people who have recovered from the acute infection is intriguing.

Transmission of SARS-CoV-2

Transmission on Airplanes

The current CDC guidelines recommend against air travel for people who have not yet been vaccinated for COVID-19 due to the increased risk of transmission from close proximity during long periods (Dietrich et al., 2021). There have been preliminary studies suggesting that increasing the distance between travelers by leaving empty seats between household-groups may lead to a lower risk of transmission, but quantification of the effect has been difficult.

In a collaboration between researchers at Kansas State University and the CDC, a study was performed to investigate the exposure to a surrogate non-infectious virus, bacteriophage MS2, based on proximity within an airplane either at full occupancy or with the middle seat vacant.

When the middle seat was left vacant, there was a reduction in exposure by between 23% and 57%, depending on the conditions of the analysis.

A variety of plane configurations were tested. For example, a 23% reduction in the risk of exposure was observed for a single passenger who was in the same row but separated from the viral source rather than in an adjacent middle seat. This value was then extrapolated to determine the general reduction in exposure for all the passengers in the cabin when all the middle seats are left vacant, which was determined to be between 35% and 39.4%. A 57% reduction in the risk of exposure was observed when the middle seats were left vacant and the risk was evaluated for a three-row section that contained a mix of viral sources and other passengers.

Importantly, in all of the scenarios, a vacant middle seat reduces risk for exposure to SARS-CoV-2 from nearby passengers.

Therefore reducing passenger density could help reduce potential COVID-19 exposures during air travel. The values observed in this study were similar to those reported in previous studies.

When aircraft ventilation systems perform at the standards required by the FAA, most virus particles are removed within several seat rows from the source, and the recirculated portion of the air supplied to each passenger has passed through HEPA filters. However, until the air moves through the ventilation system, the airborne contaminants experience turbulent dispersion from the movement of air, leading to a spreading effect of infectious particles that is larger than what would occur from individuals moving in the aisles.

This study did not take into consideration the contribution of mask use. However, masks are more effective at reducing surface and droplet exposures, and it is now accepted that SARS-CoV-2 is transmitted through aerosol exposures in confined areas, such as aircraft. Therefore, as shown in previous studies, some virus aerosol will be emitted from an infectious and masked passenger, and increased distancing between travelers could reduce the risk of transmission.

The authors conclude that the results of this and previous studies indicate the "importance of multicomponent prevention strategies as good practices; combining the effects of masking and distancing is more protective than either by itself."

P.1 Variant of SARS-CoV-2

Researchers have been able to better characterize the P.1 variant that was first identified in Brazil (Faria et al., 2021). As reported previously, the variant acquired 17 mutations, including three relevant changes in the spike protein. These changes emerged between November of 2020 and January of 2021. Specifically, P.1 has a trio of mutations, K417T, E484K, and N501Y (the mutation observed in the B.1.1.7 variant) that are associated with increased interaction with the protein on the human cell's surface, the ACE2 receptor.

The increased interactions lead to an increase in transmission, and current estimates of P.1 suggest that it is 1.7 to 2.4-times more transmissible than earlier forms of SARS-CoV-2.

The researchers also investigated the protection gained from a previous infection with the SARS-CoV-2 variants that were common earlier in the pandemic. Based on the available information, the researchers estimate that previous infection with early versions of the virus provides 54% to 79% of the protection against infection with P.1 that is provided against earlier lineages.

This reduced level of protection means that re-infection with P.1 is more likely than with earlier versions of SARS-CoV-2.

Transmission in Schools

More details are becoming available about the risk of transmission of SARS-CoV-2 in school settings (Gettings et al., 2021). Researchers from the CDC investigated the details of COVID-19 transmission at a Georgia public school district in the Atlanta metropolitan area between December 1, 2020 and January 22, 2021.

The district includes eight elementary schools, two middle schools, and one high school, and serves approximately 8,500 students with approximately 1,400 staff members. The student body was described as 38% Hispanic, 36% non-Hispanic Black, 20% non-Hispanic White, and 60% of the students qualify for the free or reduced meal program. During the study period, in-person instruction was provided Monday through Thursday with virtual-learning only on Friday. Fully in-person or fully virtual learning was available based on parent preference, and approximately 5,300 students participated in in-person school with the most children attending elementary school in-person (63 to 89% attendance) and the least attending high school in-person (32% attendance). Mask use was mandatory on campus except during indoor or outdoor sports participation. Distance between student desks was three to six feet in the middle and high schools, but was less than three feet in the elementary school classrooms due to higher attendance rates. There were also three-sided plastic shields on all desks, hand hygiene

promotion, increased frequency of facility cleaning and disinfection, advisement of community members to perform self-screening for symptoms and remain home if symptomatic, and contact tracing for staff or students who tested positive for SARS-CoV-2 infection. Measures to improve ventilation were implemented where possible, including opening windows in classrooms and buses as well as increasing outside air intake from 15% to 30% in HVAC systems, increased HVAC filters, and ionization device installation in air handlers

During the study period, 98 index cases were identified, and 12 were excluded because their contacts could not be reached for interviews or testing within ten days of exposure. None of the individuals with samples available for genome sequencing were infected with the B.1.1.7 variant, and the majority of samples tested were the variant most prevalent at the start of the pandemic.

Of the 86 index cases evaluated in the study, 38.4% were staff, and 61.6% were students. The 86 index cases had 1,119 total contacts with a median number of contacts per case of 14. Of the contacts included in the study, 63% received testing, and 91.3% of those tested received a negative result. There were nine people who tested positive who also had possible contact with infected individuals outside of the school, and they were excluded from further analysis. The household members of 40 of the contacts from school who tested positive agreed to be tested for COVID-19 (114 people), and 28.1% of the 114 of the household members tested positive.

The researchers found that 27.9% (24 out of 59) of the index cases were associated with one or more contacts that tested positive for COVID-19, and 17.4% (15 out of 59) were associated with two or more contacts that tested positive for COVID-19. The overall secondary attack rate, or rate of infection in a group from the index case, was 8.7%. However, the secondary attack rate differed based on the setting of the exposure.

The three settings with the highest secondary attack rate were

- In indoor sports settings like basketball, wrestling, and cheerleading at 23.8%
- During interactions among staff, such as group lunches or staff meetings at 18.2%
- In elementary school classrooms at 9.5%

Along with the setting, there was an association observed between the individuals involved and the magnitude of the secondary attack rate. The secondary attack rate was higher when the index case was a staff member (13.1%) compared to when the index case was a student (5.8%).

This was especially true in elementary schools where the secondary attack rate for staff index cases was 15% compared to a secondary attack rate for student index cases of 2.7%.

In the high-school setting, 93.7% of student contacts who tested positive interacted with the index case during sports. However, in non-sports settings over all grade levels, staff members were more likely to be the index case with 87.5% of staff contacts that tested positive and

72.2% of students contacts that tested positive attributed to a staff member as the index case. The secondary attack rate was also found to be higher if the index case reported having symptoms consistent with COVID-19 (10.9% compared to 3.0%).

Overall, the lowest attack rate, 2.3%, was observed when the index case was an asymptomatic student.

References

Cavanaugh AM, Fortier S, Lewis P, et al. COVID-19 Outbreak Associated with a SARS-CoV-2 R.1 Lineage Variant in a Skilled Nursing Facility After Vaccination Program — Kentucky, March 2021. *MMWR Morb Mortal Wkly Rep*. ePub: 21 April 2021.

CDC. CDC Recommends Use of Johnson & Johnson's Janssen COVID-19 Vaccine Resume. Updated April 25, 2021. Accessed on April 26, 2021 at https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/JJUpdate.html

Dietrich WL, Bennett JS, Jones BW, Hosni MH. Laboratory Modeling of SARS-CoV-2 Exposure Reduction Through Physically Distanced Seating in Aircraft Cabins Using Bacteriophage Aerosol - November 2020*. MMWR Morb Mortal Wkly Rep*. 2021 Apr 23;70(16):595-599. doi: 10.15585/mmwr.mm7016e1. PMID: 33886531.

Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DDS, Mishra S, Crispim MAE, Sales FCS, Hawryluk I, McCrone JT, Hulswit RJG, Franco LAM, Ramundo MS, de Jesus JG, Andrade PS, Coletti TM, Ferreira GM, Silva CAM, Manuli ER, Pereira RHM, Peixoto PS, Kraemer MUG, Gaburo N Jr, Camilo CDC, Hoeltgebaum H, Souza WM, Rocha EC, de Souza LM, de Pinho MC, Araujo LJT, Malta FSV, de Lima AB, Silva JDP, Zauli DAG, Ferreira ACS, Schnekenberg RP, Laydon DJ, Walker PGT, Schlüter HM, Dos Santos ALP, Vidal MS, Del Caro VS, Filho RMF, Dos Santos HM, Aguiar RS, Proença-Modena JL, Nelson B, Hay JA, Monod M, Miscouridou X, Coupland H, Sonabend R, Vollmer M, Gandy A, Prete CA Jr, Nascimento VH, Suchard MA, Bowden TA, Pond SLK, Wu CH, Ratmann O, Ferguson NM, Dye C, Loman NJ, Lemey P, Rambaut A, Fraiji NA, Carvalho MDPSS, Pybus OG, Flaxman S, Bhatt S, Sabino EC. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. *Science*. 2021 Apr 14:eabh2644. doi: 10.1126/science.abh2644. Epub ahead of print. PMID: 33853970.

Finelli L, Gupta V, Petigara T, Yu K, Bauer KA, Puzniak LA. Mortality Among US Patients Hospitalized With SARS-CoV-2 Infection in 2020. *JAMA Netw Open*. 2021 Apr 1;4(4):e216556. doi: 10.1001/jamanetworkopen.2021.6556. PMID: 33830226.

Gettings JR, Gold JAW, Kimball A, Forsberg K, Scott C, Uehara A, Tong S, Hast M, Swanson MR, Morris E, Oraka E, Almendares O, Thomas ES, Mehari L, McCloud J, Roberts G, Crosby D, Balajee A, Burnett E, Chancey RJ, Cook P, Donadel M, Espinosa C, Evans ME, Fleming-Dutra KE, Forero C, Kukielka EA, Li Y, Marcet PL, Mitruka K, Nakayama JY, Nakazawa Y, O'Hegarty M, Pratt C, Rice ME, Rodriguez Stewart RM, Sabogal R, Sanchez E, Velasco-Villa A, Weng MK, Zhang J, Rivera G, Parrott T, Franklin R, Memark J, Drenzek C, Hall AJ, Kirking HL, Tate JE, Vallabhaneni S. SARS-CoV-2 transmission in a Georgia school district - United States,

December 2020-January 2021. *Clin Infect Dis*. 2021 Apr 17:ciab332. doi: 10.1093/cid/ciab332. Epub ahead of print. PMID: 33864375.

Goel RR, Apostolidis SA, Painter MM, Mathew D, Pattekar A, Kuthuru O, Gouma S, Hicks P, Meng W, Rosenfeld AM, Dysinger S, Lundgreen KA, Kuri-Cervantes L, Adamski S, Hicks A, Korte S, Oldridge DA, Baxter AE, Giles JR, Weirick ME, McAllister CM, Dougherty J, Long S, D'Andrea K, Hamilton JT, Betts MR, Luning Prak ET, Bates P, Hensley SE, Greenplate AR, Wherry EJ. Distinct antibody and memory B cell responses in SARS-CoV-2 naïve and recovered individuals following mRNA vaccination. *Sci Immunol*. 2021 Apr 15;6(58):eabi6950. doi: 10.1126/sciimmunol.abi6950. PMID: 33858945.

Haffner MR, Le HV, Saiz AM Jr, Han G, Fine J, Wolinsky P, Klineberg EO. Postoperative In-Hospital Morbidity and Mortality of Patients With COVID-19 Infection Compared With Patients Without COVID-19 Infection. *JAMA Netw Open*. 2021 Apr 1;4(4):e215697. doi: 10.1001/jamanetworkopen.2021.5697. PMID: 33844002.

Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, Morales Moshiashvili M, Ziv-Baran T, Shorer Y, Scarfo L, Joffe E, Perry C, Ghia P. Efficacy of the BNT162b2 mRNA COVID-19 Vaccine in Patients with Chronic Lymphocytic Leukemia. *Blood*. 2021 Apr 16:blood.2021011568. doi: 10.1182/blood.2021011568. Epub ahead of print. PMID: 33861303; PMCID: PMC8061088.

Kupferschmidt K, Vogel G. Vaccine link to serious clotting disorder firms up. *Science*. 2021 Apr 16;372(6539):220-221. doi: 10.1126/science.372.6539.220. PMID: 33859010.

Letizia AG, Ge Y, Vangeti S, Goforth C, Weir DL, Kuzmina NA, Balinsky CA, Chen HW, Ewing D, Soares-Schanoski A, George MC, Graham WD, Jones F, Bharaj P, Lizewski RA, Lizewski SE, Marayag J, Marjanovic N, Miller CM, Mofsowitz S, Nair VD, Nunez E, Parent DM, Porter CK, Santa Ana E, Schilling M, Stadlbauer D, Sugiharto VA, Termini M, Sun P, Tracy RP, Krammer F, Bukreyev A, Ramos I, Sealfon SC. SARS-CoV-2 seropositivity and subsequent infection risk in healthy young adults: a prospective cohort study. *Lancet Respir Med*. 2021 Apr 15:S2213-2600(21)00158-2. doi: 10.1016/S2213-2600(21)00158-2. Epub ahead of print. PMID: 33865504; PMCID: PMC8049591.

Lu D. 'Excess Deaths' in 2020 Surpassed Those of 1918 Flu Pandemic. *The New York Times*. Published April 23, 2021. Accessed on April 23, 2021 at https://www.nytimes.com/interactive/2021/04/23/us/covid-19-death-toll.html

Munitz A, Yechezkel M, Dickstein Y, Yamin D, Gerlic M. BNT162b2 Vaccination Effectively Prevents the Rapid Rise of SARS-CoV-2 Variant B.1.1.7 in high risk populations in Israel. *Cell Rep Med*. 2021 Apr 18:100264. doi: 10.1016/j.xcrm.2021.100264. Epub ahead of print. PMID: 33899031; PMCID: PMC8053239.

Sadoff J, Davis K, Douoguih M. Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination - Response from the Manufacturer. *N Engl J Med*. 2021 Apr 16. doi: 10.1056/NEJMc2106075. Epub ahead of print. PMID: 33861522.

Taquet M et al. Cerebral venous thrombosis: a retrospective cohort study of 513,284 confirmed COVID-19 cases and a comparison with 489,871 people receiving a COVID-19 mRNA vaccine. Version 2. *OSF*. Published April 15, 2021. Accessed on April 26, 2021 at https://osf.io/a9jdq/?show=revision

Terpos E, Trougakos IP, Gavriatopoulou M, Papassotiriou I, Sklirou AD, Ntanasis-Stathopoulos I, Papanagnou ED, Fotiou D, Kastritis E, Dimopoulos MA. Low Neutralizing Antibody Responses Against SARS-CoV-2 in Elderly Myeloma Patients After the First BNT162b2 Vaccine Dose. *Blood*. 2021 Apr 16:blood.2021011904. doi: 10.1182/blood.2021011904. Epub ahead of print. PMID: 33861315; PMCID: PMC8061093.

Van Beusekom M. COVID-19 damages brain without infecting it, study suggests. *CIDRAP News*. Published April 19, 2021. Accessed on April 20, 2021 at https://www.cidrap.umn.edu/news-perspective/2021/04/covid-19-damages-brain-without-infecting-it-study-suggests

Vogel G, Kupferschmidt K. Do preservative and stray proteins cause rare COVID-19 vaccine side effect? *Science*. Published April 22, 2021. Accessed on April 22, 2021 at https://www.sciencemag.org/news/2021/04/do-preservative-and-stray-proteins-cause-rare-covid-19-vaccine-side-effect

Yu LM et al. Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial. *medRxiv*. Published April 12, 2021. Accessed on April 15, 2021 at https://www.medrxiv.org/content/10.1101/2021.04.10.21254672v1