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Medical Intelligence Report

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Topic: COVID-19 Research Update

Risk of Breakthrough Infections after Vaccination

The CDC has a nationwide breakthrough infection monitoring system that collects data from health department officials (CDC COVID-19 Breakthrough, 2021). As of April 20, 2021, their reporting systems indicate that more than 87 million people in the United States have been fully vaccinated, and there have been a total of 7,157 breakthrough infections reported from 45 states and territories.

This corresponds to 82 infections per million people vaccinated, or, to put it another way, 0.008% of the fully vaccinated individuals in the United States have been infected with SARS-CoV-2 after vaccination.

This number is an undercount of the actual number of infections due to continued difficulties in testing for COVID-19 and the high number of individuals who would be expected to be asymptomatic. However, even with the actual infection numbers, the overall risk of infection would still be very small based on the rarity of individuals in the community that have been identified as being infected after immunization.

The risk of transmission for vaccinated individuals, as well as unvaccinated individuals, is higher when there is a high level of transmission occurring in the community. When transmission rates are high, vaccinated individuals should continue to take precautions to reduce transmission of the virus. Additionally, new variants of SARS-CoV-2 with unknown characteristics continue to be identified, so the protection from vaccination could change.

Both vaccinated and unvaccinated individuals should wear masks in, or avoid, public areas where the risk of viral transmission is high, such as poorly ventilated, indoor locations with large groups of people in close proximity to each other.

Long-COVID

In order to better understand the long-term effects from infection with SARS-CoV-2, researchers evaluated the diagnoses, medication use, and laboratory test abnormalities of non-hospitalized individuals who are treated through the Veterans Health Administration (VHA) to determine if there were differences between those who had a COVID-19 diagnosis and those who had not (Al-Aly et al., 2021). The medical records of 73,435 users of the VHA who survived 30 days after diagnosis with COVID-19 were compared with the medical records of 4,990,835 users of the VHA who were not diagnosed with COVID-19.

Overall, after the first 30 days of illness, people with COVID-19 exhibit a higher risk of death and health resource utilization.

The risk of having long-term symptoms was evident even in individuals whose initial COVID disease was not severe enough to necessitate hospitalization, which the authors point out is the majority of those who have become ill. It was also found that the risk of long-term effects and the associated burden increases across the severity spectrum of the acute COVID-19 infection (e.g. from non-hospitalized to hospitalized and finally those admitted to intensive care). When compared to the long-term symptoms observed previously in individuals who recovered from influenza infection, the burden of symptoms in survivors of COVID-19 who required treatment in the hospital was substantially higher with both a higher magnitude of risk of occurrence as well as an increased breadth of organ involvement.

When compared to individuals who were hospitalized and recovered from influenza, individuals who recovered from COVID-19 had an increased risk of death after six months with 28.79 excess deaths per 1,000 persons.

The researchers determined that people who have recovered from COVID-19 have symptoms in a number of different systems, including the respiratory system, the nervous system, mental health disorders, metabolic disorders, cardiovascular disorders, gastrointestinal disorders, malaise, fatigue, musculoskeletal pain, and anemia. Respiratory conditions were the most commonly reported with an excess of 28.51 per 1,000 COVID-19 patients at six months compared to patients without COVID-19 followed by nervous system signs and symptoms with an excess of 14.32 per 1000 COVID-19 patients.

The specific symptoms or conditions identified and the excess number of COVID-19 patients compared to non-COVID-19 patients with symptoms are shown in Table 1.

Table 1. Conditions observed or treated during the study in individual recovered from COVID-19

Symptom or Condition Observed	Excess Number of COVID-19 Patients	Resulting Changes in Treatments or Medications
Respiratory failure, insufficiency, and arrest	3.37 per 1,000	High use of bronchodilators, cough suppressive medications and expectorants, anti-asthmatics, and glucocorticoids
Lower respiratory disease	4.67 per 1,000	High use of bronchodilators, cough suppressive medications and expectorants, anti-asthmatics, and glucocorticoids
Neurocognitive disorders	3.17 per 1,000	High use of non-opioid analgesics, opioid analgesics, antidepressants, benzodiazepines sedatives and antianxiety medication
Nervous system disorders	4.85 per 1,000	High use of non-opioid analgesics, opioid analgesics, antidepressants, benzodiazepines sedatives and antianxiety medication
Headache	4.10 per 1,000	High use of non-opioid analgesics, opioid analgesics, antidepressants, benzodiazepines sedatives and antianxiety medication
Sleep/Wake disorders (issues with quality, timing, & amount of sleep)	14.53 per 1,000	High use of non-opioid analgesics, opioid analgesics, antidepressants, benzodiazepines sedatives and antianxiety medication
Anxiety and fear-related disorders	5.42 per 1,000	High use of non-opioid analgesics, opioid analgesics, antidepressants, benzodiazepines sedatives and antianxiety medication
Trauma and stress related disorders	8.93 per 1,000	High use of non-opioid analgesics, opioid analgesics, antidepressants, benzodiazepines sedatives and antianxiety medication
Disorders of lipid metabolism, e.g. High cholesterol	12.32 per 1,000	High level of use of cholesterol lowering drugs, medication to lower blood glucose, and insulin
Diabetes	8.23 per 1,000	High level of use of cholesterol lowering drugs, medication to lower blood glucose, and insulin
Obesity	9.52 per 1,000	High level of use of cholesterol lowering drugs, medication to lower blood glucose, and insulin
Malaise and fatigue	12.6 per 1,000	Not reported
Muscle disorders	5.73 per 1,000	Not reported
Musculoskeletal Pain	13.9 per 1,000	Not reported
Anemia	4.79 per 1,000	Not reported
Hypertension	15.18 per 1,000	High use of beta blockers, calcium channel blockers, diuretics, and antiarrhythmic medication
Cardiac Dysrhythmias	8.41 per 1,000	High use of beta blockers, calcium channel blockers, diuretics, and antiarrhythmic medication

Continuation of **Table 1**. Conditions observed or treated during the study in individual recovered from COVID-19		
Symptom or Condition Observed	**Excess Number of COVID-19 Patients**	**Resulting Changes in Treatments or Medications**
Circulatory signs and symptoms	6.65 per 1,000	High use of beta blockers, calcium channel blockers, diuretics, and antiarrhythmic medication
Chest pain	10.08 per 1,000	High use of beta blockers, calcium channel blockers, diuretics, and antiarrhythmic medication
Coronary atherosclerosis	4.38 per 1,000	High use of beta blockers, calcium channel blockers, diuretics, and antiarrhythmic medication
Heart failure	3.95 per 1,000	High use of beta blockers, calcium channel blockers, diuretics, and antiarrhythmic medication
Esophageal disorders	6.90 per 1,000	Increased use of laxatives, anti-nausea medication histamine antagonists to block stomach acid as well as other antacids, and antidiarrheal agents
Gastrointestinal disorders	3.58 per 1,000	Increased use of laxatives, anti-nausea medication histamine antagonists to block stomach acid as well as other antacids, and antidiarrheal agents
Dysphagia, difficult swallowing	2.38 per 1,000	Increased use of laxatives, anti-nausea medication histamine antagonists to block stomach acid as well as other antacids, and antidiarrheal agents
Acute pulmonary embolism	2.63 per 1,000	Increased use of anticoagulants
Skin disorders	7.52 per 1,000	Not reported
Joint pain and arthritis	5.16 per 1,000	Not reported
Infections, including urinary tract infections	2.99 per 1,000	Not reported

Researchers at the CDC and Kaiser Permanente Georgia also reviewed the medical records describing health care visits that occurred in the 28 to 180 days after a diagnosis of COVID-19 at an integrated health care system to better characterize the long-term effects after the disease (Hernandez-Romieu et al., 2021). There were 3,171 participants in the study who had COVID-19 that did not require treatment in the hospital, corresponding to a mild to moderate case.

Of these individuals, 69% had one or more outpatient medical visits during the study period. When compared to those who did not have an outpatient medical visit, those who had visits were more likely to be over the age of 50, women, non-Hispanic Black, and have underlying health conditions.

Among those who had an outpatient visit, 68% of the visits were for a new primary diagnosis, and 38% had a new specialist visit.

The most commonly visited new specialists were dermatology (16%), behavioral/mental health (11%), gastroenterology (11%), and cardiology (10%).

This study did not compare the medical records of the individuals with COVID-19 with individuals without COVID-19, and further information will be needed to analyze the implications of the results. The authors point to a similar study among non-hospitalized adults with influenza in Spain during the 2009 H1N1 pandemic indicating that there were fewer outpatient visits for people after having the flu than for people after having COVID-19, suggesting that there are more long-lasting effects after infection with SARS-CoV-2.

A third group of researchers evaluated the long-term effects on individuals who were hospitalized with severe COVID-19 in three hospitals in China (Shang et al., 2021). Of the 1,174 individuals originally treated, data for 796 was later available for evaluation. The median number of days in the hospital was 21 with a range between 14 and 27, and 90.8% of the participants were classified as having a severe case while the remaining were classified as critically ill cases. A classification of critically ill means that the person was more seriously ill than someone classified as having a severe case. A total of 38 participants were admitted to the intensive care unit for treatment, and 17 required intubation and mechanical ventilation.

Six months after being discharged from the hospital, all of the participants were found to be negative for COVID-19 by PCR-based testing, and 46.4% had IgG antibodies, which are the long-term, free antibodies found in the blood stream that usually represent the main component for virus neutralization to prevent re-infection. In a previous evaluation of the same study group, the researchers found that 89.1% of the participants had detectable IgG levels 81 days after discharge from the hospital, and this study confirms a continued downward trend as the time from infection increases.

Of the individuals who had chest CT scans available for evaluation during the study, 52% had abnormal CT results six months after discharge. The types of abnormalities observed were ground glass opacity, nodules, fibrosis (scarring), and inflammation.

When the symptoms experienced by the participants were evaluated, the most common included fatigue (25.3%), sleep disorder (23.2%), shortness of breath (20.4%), muscle and/or joint pain (13.8%), cough (12.4%), digestive symptoms (10.9%), chest pains (9.9%) and impaired memory (8.7%).

In the group of participants who reported experiencing a symptom, 59.4% reported having more than one symptom.

The individuals who were more severely ill were found to be more likely to have symptoms after being discharged. For example, 11.6% of participants categorized as having had a severe case reported having a cough six months after discharge while 20.5% of participants who had been critically ill had a cough. There were 8% of participants who had a severe case of COVID-19 who experienced impaired memory six months after diagnosis, and 15.1% of those who were critically ill reported impaired memory at that time.

Based on the assessments, it was found that critical illness was an independent risk factor for memory impairment after COVID-19.

There was a slight increase in the number of women who experienced fatigue or sleep disorders compared to the men in the group (29.3% versus 21.3% and 27.3% versus 19.3%, respectively), but the difference was statistically significant. The researchers also found that women are more likely to have multiple symptoms compared to men.

Risk of Stroke after Asymptomatic COVID-19

Researchers in Singapore identified a higher than normal rate of acute ischemic stroke in adults 50 years or younger who had recovered from an asymptomatic case of COVID-19 (Tu et al., 2021). As of October 14, 2020, there had been 57,889 cases of COVID-19 in Singapore, and out of the confirmed cases, 94% were found to occur in a population of workers who lived together in dormitories. Because of the close living conditions, contact tracing and extensive testing was conducted, which identified a number of asymptomatic cases. The individuals diagnosed with COVID-19 in Singapore were enrolled in a study to observe any long-term effects from infection.

Out of the group of participants, 18 men between the ages of 31 and 50 were diagnosed with acute ischemic stroke. Seventeen had been asymptomatic during the infection with SARS-CoV-2. All had negative PCR-based tests for COVID-19 while being treated in the hospital for stroke. Twelve of the men, corresponding to 67%, had no known pre-existing risk factors for stroke, such as hypertension or high cholesterol.

There was a large range of severity of the stroke in each case. There were six individuals (corresponding to 33%) who were treated with the anti-clotting factor tissue plasminogen activator (tPA) or underwent removal of a clot (endovascular therapy) with the remaining individuals being treated with medical therapy. Ten of the men (or 56%) had a clot form in a large vessel, which can only be treated with removal of the clot rather than use of blood thinners. Thrombectomy, or blood-clot removal surgery, was performed in five of the ten individuals with large vessel occlusion.

Overall, the severity of some of the strokes and occurrence in younger men with few risk factors was striking to the researchers involved with the study.

When the incidence rate of acute ischemic stroke was calculated for the group of individuals who had asymptomatic COVID-19 in Singapore during the study period, it was found to be 82.6 cases per 100,000 people. The normal rate of acute ischemic stroke in a group of individuals of this age range based on data from 2018 was found to be 38.2 cases per 100,000.

Based on their results, the researchers found that men under the age of 50 who recovered from an asymptomatic case of COVID-19 had an annual incidence rate of stroke 2.16-times higher than the individuals of the same age without a history of COVID-19.

The median length of time after infection with SARS-CoV-2 that the strokes occurred was 54.5 days with one individual having a large vessel occlusion 130 days after testing positive for COVID-19 by antibody testing. The authors conclude that the clot forming characteristics of

COVID-19 may persist long after the acute infection has resolved. Within the group, 13 of the 18 (or 72%) had strokes with an undetermined classification, which means there was no obvious cause based on the typical origins of stroke, such as plaque in the arteries. The only characteristic that those with an unclassified stroke had in common was the presence of antibodies detected from previous infections with SARS-CoV-2.

The mechanism of clot formation in these individuals is expected to be different from that in individuals who have clot formation during an active SARS-CoV-2 infection.

Researchers postulate that during the infection, the inflammatory response and cytokine storm are factors that contribute to stroke through possible injury of the endothelial cells that line the blood vessels, which no longer occurs after the initial infection has been cleared.

Effect of SARS-CoV-2 Spike Protein on the Vascular System

Researchers have determined that when the spike protein of SARS-CoV-2 interacts with the ACE-2 receptor on human cells, that interaction alone leads to disruption of essential processes in the cell that could explain the multitude of symptoms associated with COVID-19 (Lei et al., 2021). The researchers used a modified virus that had spike protein on the outside, but was empty on the inside so that after binding to the cells, the other steps of infection did not occur. Even though most of the process of infection by SARS-CoV-2 did not happen, the cells in the experiments had the same damage occur that is observed during normal viral infection. Mainly, binding of the spike protein to the ACE-2 receptor prevented the protein from producing a signal to parts of the cell called mitochondria, which are used by the cell for the production of energy. When the signals from the ACE-2 receptor are interrupted, the mitochondria become damaged and begin to fragment, which in turn leads to further damage in the cell.

Endothelial cells are a type of cells that line the respiratory system and vascular system, which includes the circulatory system, and they produce a large amount of ACE-2 receptor on the surface of the cells.

The damage observed from binding of the spike protein alone matches the type of damage observed in organisms infected with the complete SARS-CoV-2 virus, suggesting that the protein itself may be responsible for most of the damage from COVID-19.

This discovery may explain some of the confusing aspects observed about SARS-CoV-2. For example, the spike protein from SARS-CoV-2 has a much stronger interaction with the ACE-2 receptor than SARS-CoV-1 and other coronaviruses, which might explain some of the differences observed between the different viruses.

The ability to cause damage without actually infecting the cell might also explain the damage to tissues observed throughout the body with COVID-19.

It has been difficult for researchers to explain how the virus was able to damage tissues far from the lungs where there was little, or no, evidence of viral infection. Based on this discovery,

damage to cells seems to be possible without infectious virus being present, and parts of the virus could be transported and interact with tissues far from the respiratory tract where infection initially occurred.

Vaccine Updates

The FDA has authorized the Pfizer-BioNTech COVID-19 vaccine for use in adolescents aged 12 to 15 years as of Monday, May 10, 2021 (FDA, 2021). The FDA amended the original Emergency Use Authorization (EUA) that was issued on December 11, 2020 for use of the vaccine in individuals 16 years of age and older. The dosing is the same as that used in individuals 16 years of age with two doses given three weeks apart.

The clinical trial used to support the change in the EUA includes 2,260 participants ages 12 through 15 years. The most commonly reported side effects in the adolescent clinical trial participants were similar to those in adult participants, which typically lasted one to three days and included pain at the injection site, tiredness, headache, chills, muscle pain, fever and joint pain. As with older participants, more adolescents reported these side effects after the second dose than after the first dose.

The immune response to the vaccine in adolescents was at least as good as that seen in the clinical trials involving older individuals.

There were no cases of COVID-19 in participants who received both doses of the vaccine and 16 cases in participants who received the placebo, leading to an efficacy of 100%.

Vaccine during Pregnancy

The CDC has compiled information from a number of different surveillance systems to evaluate the safety of mRNA COVID-19 vaccines in pregnant women (Shimabukuro et al., 2021). There were 35,691 women between the ages of 16 to 54 years of age included in the database who were pregnant and received a vaccine for COVID-19. Side effects from the vaccine were reported less frequently after vaccination than in non-pregnant individuals and included headache, myalgia, chills, and fever.

There were 3,958 participants who were registered in a more detailed study that allowed for evaluation of pregnancy outcome. At the time the study was published, 827 of this smaller group had a completed pregnancy. Most of those with a completed pregnancy had been vaccinated in the third trimester when development of key systems in the fetus had already occurred. There were 115 cases of pregnancy loss (or 13.9%) and 712 live births (or 86.1%). Adverse neonatal outcomes included preterm birth (in 9.4%) and small size for gestational age (in 3.2%), and no neonatal deaths were reported. There were 46 cases of spontaneous abortion after vaccination in women who were in the early stages of pregnancy.

While it is not possible to directly compare outside of a clinical trial, the proportions of adverse pregnancy and neonatal outcomes in persons vaccinated

against COVID-19 were similar to those reported in studies before the start of the pandemic, suggesting there are no major effects on pregnancy from the vaccine.

Based on the results from the examination of the databases, the researchers concluded that there are no obvious safety concerns among people who are pregnant who received mRNA COVID-19 vaccines

The American College of Obstetricians and Gynecologists updated their recommendations on vaccination soon after the release of this report (ACOG, 2021). In the recommendations, they state that no concerning safety information has been collected from Europe or the United States, and there are no negative outcomes (contraindications) that have been observed in either pregnant women or the developing fetus to suggest that there are issues with vaccination of pregnant individuals. There have been several studies that suggest an increased risk of negative outcomes for pregnant women with COVID-19, however.

"Therefore, in the interest of patient autonomy, ACOG recommends that pregnant individuals be free to make their own decision regarding COVID-19 vaccination."

To that end, they stress that while discussions with a physician may be helpful, a discussion with a physician should not be mandatory before vaccination.

The CDC also updated their recommendations for vaccination during pregnancy (CDC, 2021):

"Pregnant people are more likely to get severely ill with COVID-19 compared with non-pregnant people. If you are pregnant, you can receive a COVID-19 vaccine. Getting a COVID-19 vaccine during pregnancy can protect you from severe illness from COVID-19."

Reduction in Hospitalized Adults after Vaccination with mRNA Vaccines

In the Phase 3 clinical trials of the Pfizer-BioNTech and Moderna vaccines, the efficacy of vaccination in preventing hospitalization was determined to be between 94% and 95% (Tenforde et al., 2021). However, there were very few participants in the trials that required treatment in the hospital for COVID-19, which could influence the outcome. The CDC collected information using their surveillance networks from real-world cases of adults over the age of 65 who were admitted to the hospital between January 1, 2021 and March 26, 2021 and subsequently tested for COVID-19 to evaluate the effectiveness of the two mRNA vaccines in prevention of hospitalization.

There were 417 participants included in the study who were admitted to 24 hospitals in 14 states. There were 187 participants who tested positive for COVID-19. Nineteen of the COVID-19-positive participants, or 10%, had received at least one dose of one of the vaccines more than 14 days before illness onset. This included 18 participants who were partially vaccinated and one participant who was fully vaccinated. There were 230 participants who tested negative for COVID-19. In the COVID-19-negative group, 62 participants had received at least one dose of one of the vaccines more than 14 days before illness onset. This included 44 who were partially and 18 who were fully vaccinated.

From this information, the vaccine effectiveness against COVID-19 hospitalization was calculated to be 94% in fully vaccinated individuals over the age of 65 and 64% in partially vaccinated individuals over the age of 65.

This level of protection is similar to that reported in the Phase 3 clinical trials. The number of people vaccinated with the two types of vaccine was approximately equal, and no difference was observed between the Pfizer-BioNTech and Moderna vaccine.

Importantly, when a person had been vaccinated for less than 14 days, there was no evidence that the vaccine prevented hospitalization from COVID-19.

This highlights the continued risk for transmission of SARS-CoV-2 shortly after vaccination, before a protective immune response has been achieved.

Reduction of Transmission in Households with Vaccination

There is a high rate of transmission of SARS-CoV-2 between members of a household, also called the secondary attack rate (Harris et al., 2021). One method to determine if vaccination will reduce the transmission of SARS-CoV-2 is to evaluate the secondary attack rate in households that have vaccinated members. Researchers in England evaluated 365,447 residential households of between two and ten people with at least one case of COVID-19 between January 4, 2021 and February 28, 2021.

In households where the index case was not vaccinated, the secondary attack rate was found to be 10.1%. In households where the index case had received the AstraZeneca-Oxford vaccine 21 days or more before testing positive, the secondary attack rate was 5.72% while the attack rate in households where the index case had received the Pfizer-BioNtech vaccine 21 days or more before testing positive was 6.25%.

The risk of becoming infected from the index case was decreased by about 50% for the two vaccines when compared to those who had not been vaccinated.

The results from this study provide evidence that receipt of at least one dose of either vaccine reduces the transmission of SARS-CoV-2 from a diagnosed case to other persons in the household setting.

Single Dose of Vaccines

The *New York Times* reports that nearly 8% of the individuals who received their first dose of the Pfizer-BioNTech or Moderna vaccine did not receive their second dose within the recommended time period (Robbins, 2021). This corresponds to more than five million people as of the end of April, 2021. This leads to the problem of a large number of individuals with an unknown amount of protection from SARS-CoV-2 infection.

The number of people who have not received their second dose by the recommended time has been increasing as the vaccination effort expands to more people, and the reasons why vary widely. Some are personal reasons having to do with fear of the increased side effects sometimes observed after the second shot or a decision that they were adequately protected with only a single dose. Distribution complications are also occurring where people have arrived at their second appointment and vaccine providers do not have the right brand of vaccine currently in stock since both shots have to be from the same manufacturer. This type of administrative difficulty may lead to those with less resources, who are also typically the individuals most at risk for poor outcomes, being less likely to get fully vaccinated.

A number of studies were recently published describing different effects of single doses of the mRNA vaccines, suggesting that while there is some protection afforded, the level of effectiveness is lower and may not be useful against the variants that have started circulating.

In a commentary on the results of these studies, experts determined that with the effectiveness that has been observed in real-life examples of the available vaccines, nearly 100% of the population would need to be vaccinated with one dose or about 80% with two doses in order to reach a threshold where there were too few vulnerable people to support community transmission, or so called herd immunity (Lesham and Lopman, 2021).

> **They suggest that getting as many people one dose as soon as possible is a good strategy for averting the most deaths, but in order to stop the spread of the virus, and therefore halt the pandemic, higher population immunity and a full course of two doses will be required.**

A large study in England, called the SIREN study, investigated the effectiveness of the Pfizer-BioNTech vaccine in healthcare workers (Hall et al., 2021). Due to the decisions of officials, the second dose was delayed in order to expand the number of people who could be at least partially vaccinated as an outbreak of the B.1.1.7 variant threatened to overwhelm the healthcare system. Because the participants in this study worked in healthcare roles, they were screened for COVID-19 regardless of symptoms every two weeks as well as with monthly antibody testing. The information for this study was collected from December 7, 2020 to February 5, 2021. There were 23,324 participants from 104 sites across England with 35% identified as having had COVID-19 before vaccination.

At least one dose of vaccine was given to 20,641 (or 89%) participants by February 5, 2021, and two doses of vaccine were given to 1607 (or 8%) participants. The median length of time between first dose and second dose was 23 days with a range from 19 to 28 days. There were 977 new infections in the unvaccinated group, of which 14% were asymptomatic. In those who had one dose for at least 21 days, there were 71 new infections, and 19% were asymptomatic.

> **Vaccine effectiveness against infection at least 21 days after the first dose of Pfizer-BioNTech vaccine in the overall study population was 70% and increased to 85% after the second dose.**

During the study period, the level of B.1.1.7 in the community was estimated to be at or above 50%, suggesting that the Pfizer-BioNTech is effective against the B.1.1.7 variant.

As in England, the initial steps of the vaccination campaign in Scotland involved getting at least one dose in the largest number of individuals over the age of 50 and healthcare workers (Vasileiou et al., 2021). At the time of this study, the AstraZeneca-Oxford and Pfizer-BioNTech vaccine were the two vaccines that were mainly available, and very few individuals had received the Moderna vaccine. Therefore, this study includes only the AstraZeneca-Oxford and Pfizer-BioNTech data.

Based on the examination of health records from the national health system in Scotland between December 8, 2020 and February 15, 2021, 1,331,993 adults received the first dose of COVID-19 vaccine.

At 28 to 34 days after vaccination, the first dose of Pfizer-BioNTech vaccine was 91% effective against COVID-19 hospital admissions, and the AstraZeneca-Oxford vaccine was 88% effective against COVID-19 hospital admissions.

The effectiveness of the single dose was generally the same across age groups with 92% effectiveness for those 18 to 64 years of age, 93% effectiveness for those 65 to 79 years of age, and 83% for those over the age of 79. These values are similar to the effectiveness against hospital admission reported by health officials from Israel (78%) and England (80%) for a single dose of the Pfizer-BioNTech vaccine.

A third report from the United Kingdom describes the immunization campaign to maximize the number of people vaccinated with first doses and the effect on asymptomatic transmission (Jones et al., 2021). The study evaluated vaccinated and unvaccinated healthcare workers who participated in COVID-19 screening programs that allowed for identification of both symptomatic and asymptomatic individuals. The effectiveness of a single dose of Pfizer-BioNTech vaccine was examined during a two week span from January 18 to January 31, 2021.

During weekly asymptomatic testing, 26 out of 3,352 (0.8%) of unvaccinated participants received a positive test for COVID-19. There were 13 out of 3535 (0.4%) positive COVID-19 tests in participants who had been vaccinated but were less than 12 days from their first dose, and 4 out of 1989 (0.2%) positive COVID-19 tests in participants more than 12 days after their first dose of vaccine.

Use of the Pfizer-BioNTech vaccine led to four-fold decrease in the risk of asymptomatic SARS-CoV-2 infection 12 days after the first dose.

When symptomatic testing results were also included in the analysis, a large reduction in the risk of SARS-CoV-2 infection was also observed. There were 56 COVID-19 cases out of 3370 unvaccinated individuals (1.7%) and 8 COVID-19 cases out of 2018 individuals more than 12 days after the first dose (0.4%). This also corresponded to a four-fold reduction in risk of infection.

In another study of healthcare workers in the United Kingdom that had received a single dose of the Pfizer-BioNTech vaccine, researchers investigated the effect of vaccination on B and T-cell response and the response against the SARS-CoV-2 variants currently circulating (Reynolds et al., 2021). The 51 participants in the study were evaluated after their first dose of the vaccine, and 25 had been infected and recovered from the Wuhan-strain of SARS-CoV-2 before

vaccination while the remaining 26 participants had not been infected at the time of vaccination. Blood samples were collected at around 16 weeks after vaccination, at around 28 weeks after vaccination, and at 42 weeks after vaccination. None of the participants who had not had COVID-19 at the time of vaccination developed antibodies consistent with infection by the end of the study, suggesting that none became infected with SARS-CoV-2.

The immune response to the SARS-CoV-2 spike protein, which is part of the vaccine, was compared in individuals after infection, in those vaccinated after infection, and in participants vaccinated who had not had a prior infection. Individuals who had had a previous SARS-CoV-2 infection were found to be more likely to have a T-cell response to the vaccine (96% compared to 70%) and to have a T-cell response that was four-times larger after a single dose than those who did not have a previous infection. Vaccinated individuals with a prior infection also had a 63-fold increase in a specific IgG antibody producing cell type compared to those who had not previously had COVID-19. All of the individuals who had previously been infected produced these specific cells, and 20 out of 22 of the uninfected individuals produced the cells. The proportion of the B-cell population that was producing antibodies specific for the spike protein in previously infected individuals was between 1.90 and 50% while the proportion of the B-cell population producing antibodies to the spike protein in uninfected individuals ranged from 0.02% to 1.54%. There was also a 60-fold increase in the neutralizing antibody response in participants who had had a previous SARS-CoV-2 infection compared to those who had not been infected before vaccination.

When the antibody response of individuals who had not been previously infected with SARS-CoV-2 to the B.1.1.7 and B.1.531 variants were investigated, it was found that after a single dose of vaccine, most did not have a neutralizing antibody response to the variants.

After single dose of vaccine, 90% of uninfected, vaccinated individuals showed no detectable neutralizing antibodies against B.1.1.7 while they did have demonstrable neutralizing antibody responses to the Wuhan strain. However, all individuals who had previously had COVID-19 had a strong neutralizing response to B.1.1.7 (24/24), and all but one participant had a strong neutralizing response to B.1.351 (23/24) after a single dose. There was a reduction in the level of neutralizing ability for the variants in the previously infected individuals, but the level was above what is expected to be protective in 22 out of 24 of the participants.

Model of Future COVID-19 Cases based on Different Vaccination Coverage Rates

Researchers from the CDC used six modeling methods to assess the potential course of COVID-19 in the United States over a six-month period (April to September, 2021) using four scenarios with different vaccination coverage rates, vaccine effectiveness estimates, and the extent of implementation of other mitigation measures, such as physical distancing and mask use (Borchering et al., 2021).

The four scenarios that were considered were

1. High vaccination with moderate distancing and mask use
2. High vaccination with low distancing and mask use
3. Low vaccination with moderate distancing and mask use
4. Low vaccination with low distancing and mask use

All scenarios also included the spread of the B.1.1.7 variant, with the assumption that it was 50% more transmissible than were previously circulating SARS-CoV-2 variants.

In all four scenarios, cases were projected to increase through May, 2021 on a national level due to the increased prevalence of B.1.1.7 and decreases in mandates and compliance for distancing and mask use.

Along with the increased number of cases, a moderate increase in hospitalizations and deaths was predicted with a peak in May for all scenarios. The larger increases in cases relative to hospitalizations and deaths were attributable to higher vaccination coverage among groups with higher risk for severe COVID-19. A sharp decline was then projected in July, 2021 with a faster decline in the high-vaccination scenarios.

Moderate distancing and mask use reduced cases and deaths in both the high and low vaccination scenarios, suggesting that vaccination and mitigation strategies can complement and counterbalance each other.

The largest differences between the scenarios was the number of people hospitalized for treatment of COVID-19.

There was not a large difference in the number of deaths between the different scenarios due to the high number of high-risk individuals who have already received the vaccine for COVID-19. In all of the scenarios, a large number of new cases were projected, and there was not a large difference in the number of cases between the different responses.

In areas where there is a low rate of vaccination and low adherence to mitigation measures, the models projected large numbers of hospitalized individuals that could reach levels similar to those in the surge at the end of 2020.

With the same low vaccination rate and moderate adherence to mitigation measures, the number of excess hospitalizations projected is nearer to that with a high vaccination rate, suggesting that distancing and masking can make up for a poor vaccination rate.

The models also indicate that even moderate reductions in adherence to mitigation measures can undermine vaccination-related gains during the next two to three months.

The decrease in adherence to distancing and masking expected to occur as mandates are lifted, combined with the increased transmissibility of circulating variants are expected to cause increases in new cases, leading to additional surges in hospitalizations and deaths. All of the

models in this study attributed the projected increase in SARS-CoV-2 transmission in many parts of the United States to the relaxation of mitigation strategies and the increasing prevalence of more transmissible variants.

The authors conclude that high vaccination rates and compliance with public health prevention measures are essential to control the COVID-19 pandemic and to prevent surges in hospitalizations and deaths in the coming months.

Update on Variants of SARS-CoV-2

Increased Rate of Household Clusters with B.1.1.7

An investigation of the level of transmissibility of B.1.1.7 was performed through evaluation of the likelihood that a case gave rise to a household cluster of cases (Chudasama et al., 2021). The study was performed in England, where the level of genomic sequencing of positive COVID-19 tests allows for better tracking of the spread of variants.

Based on national data, it was found that B.1.1.7 variant cases were almost twice as likely to give rise to household clusters compared with the form of the virus that had been circulating previously.

The results from the study are consistent with previous estimates that suggest that the new variant has changes that lead to an increase in reproduction number by 73% to 81%.

Community Transmission Detected of B.1.351 in the United States

Public health officials identified two clusters of the SARS-CoV-2 variant B.1.351 in Maryland involving 17 individuals (Feder et al., 2021). None of the 17 affected individuals reported recent international travel or contact with international travelers, suggesting that there is community transmission of B.1.531 occurring in the United States. Out of the 17 individuals, two were hospitalized for treatment of COVID-19, and one died.

Contact tracing was performed before genomic sequencing had been performed, which is standard practice for all individuals diagnosed with COVID-19 in Maryland. Tracing continued until no additional cases could be identified. The index patient reported two potential exposures that may have led to infection, work and a social gathering where masks were not used while eating. No other cases were identified at the workplace, but all six attendees at the social gathering received positive COVID-19 tests with symptoms starting between one and eight days after the gathering.

One of the attendees at the gathering was identified as working at an establishment that had been reported for COVID-19 safety concerns due to several employees coming to work while displaying symptoms consistent with COVID-19. There were seven employees at this workplace, and six were found to be symptomatic and received a positive COVID-19 test. There were an additional eight contacts from the workers who were tested, and an additional five

individuals had positive tests. Two individuals linked to this workplace were hospitalized, and one died.

The authors conclude that these are the first linked clusters of B.1.351 infections identified in the United States that have no apparent connection to international travel, highlighting the importance of expanding genetic surveillance programs and continuing to follow mitigation measures to reduce transmission.

Breakthrough Infections from Variants after Vaccination

Researchers at Rockefeller University in New York City identified two individuals with infection after vaccination, and both were found to be infected with variants of SARS-CoV-2 (Hacisuleyman et al., 2021). The first individual became ill 19 days after the second dose of mRNA vaccine, and the second individual became ill 36 days after the second dose. The cases were identified through screening at the university, which entailed all employees and students at the Rockefeller University campus (approximately 1400 persons) being tested at least weekly with a saliva-based PCR test.

The first individual experienced a sore throat, congestion, and headache and tested positive later that day on March 10, or 19 days after the second dose of vaccine. Later the individual reported a loss of the sense of smell, and symptoms gradually resolved over a one-week period.

The second individual's unvaccinated partner tested positive for COVID-19 on March 3, and on March 16, the second individual began to have symptoms, including fatigue, sinus congestion, and a headache. Testing on March 17 was positive for COVID-19, and the symptoms began to resolve on March 20.

The genomes of the virus from both individuals were sequenced. Sequencing results from the first individual indicated that the virus was a variant, but it is distinct from those previously identified. **It contains some of the same mutations, but is not B.1.1.7, B.1.351, or P.1.** Specifically, the E484K mutation that is found on the spike protein was present in the virus that infected the first individual, which is the change in the protein that prevents the binding of some neutralizing antibodies in the B.1.351 and P.1 variant, leading to higher rates of re-infection and infections after vaccination. The sequence from the virus that infected the first individual was also different from the variant identified in New York, called B.1.526 that is currently being monitored by public health officials, but has not yet become widespread. Further investigation showed that the first individual had produced a high level of neutralizing antibodies, most likely in response to the vaccination. However, breakthrough infection occurred, causing symptomatic illness.

The genome of the virus from the second individual was only partially sequenced. It contained two mutations that have been found to increase the transmission of the virus, D614G and S477N, but did not include some of the hallmark mutations from B.1.1.7, B.1.351, and P.1.

> **The authors conclude that these events indicate that a potential risk of illness remains after successful vaccination from the possibility of subsequent infection with a variant form of the virus, and they also support the need for continued**

efforts to prevent and diagnose infection and to characterize variants in vaccinated persons.

SARS-CoV-2 Transmission

There were concerns about the possibility of widespread transmission occurring at the motorcycle rally in Sturgis, South Dakota on August 7 to 16, 2020. Local officials and those from the CDC urged organizers to cancel or greatly reduce the number of people involved in the event, but it is estimated that approximately 462,000 persons attended a variety of outdoor and indoor activities. The CDC has since been able to perform contract tracing to determine the outcome of the event on transmission both in surrounding areas and nationwide (Carter et al., 2021).

The CDC requested information on laboratory or clinically diagnosed COVID-19 cases detected after travel to Sturgis or Meade County, South Dakota between August 1 to 30, 2020 from the 50 state health departments as well as the health departments from Washington, DC, New York City, Chicago, and Los Angeles County. Some states reported the information as travel to South Dakota because there was reluctance from individuals to disclose attendance at the motorcycle event. Out of the 54 health departments contacted, 39 provided data, and nine reported they had no COVID-19 cases associated with the event.

There were 463 laboratory-confirmed or probable primary cases reported across the country with most laboratory-confirmed cases diagnosed within two weeks of the event and an additional 186 secondary COVID-19 cases from contacts who attended the event.

At the time of testing, 86% of those who tested positive reported having symptoms. There were 17, or 3.7%, of the primary cases who required treatment in the hospital for COVID-19, and one individual died.

Many of the cases occurred in bordering states, including Minnesota, Montana, North Dakota, Nebraska, and Wyoming, with 56% of all identified cases reported in these five states. The individuals who tested positive for COVID-19 were more likely to be male (60%) and white (84%) with a small number of individuals identified as Hispanic (5%). Just over half of all cases were between 40 and 59 years of age, and 16% were over 60 years.

From August 1 to September 15, the 14-day testing volume among Meade County residents, where Sturgis is located, increased 199%. Additionally, the 14-day test positivity increased, from 5% to 8%, indicating the event's impact on SARS-CoV-2 transmission in Meade County for both workers and county residents.

The authors conclude that there was widespread transmission of SARS-CoV-2 from the motorcycle rally in and around Sturgis, South Dakota. Based on cell phone data, attendees came from 61% of the counties in the United States.

Cases were identified in 30 of the 39 responding states and regions, and subsequent local transmission was detected in 17 jurisdictions.

The state of Minnesota reported that there was local transmission that originated from attendees of the event in one third of the counties in the state.

However, the number of confirmed cases resulting from the event are expected to be largely underestimated due to several factors, including limited testing of attendees without symptoms and those with only mild symptoms, which has limited identification of the number of cases throughout the pandemic. Additionally, those who did test positive may not have reported attendance at the rally due to the possible stigma associated from the well-publicized debate before the event. Health department officials reported a reluctance to share travel information or others who may have been exposed at the same time. There was also a lack of information from 15 health departments that did not provide data for the analysis.

Household Risk of Transmission with In-Person School

Overall, the risk of transmission of SARS-CoV-2 in schools has been found to be small when appropriate precautions are in place, and most of the cases identified from testing of students and teachers occur due to community exposure rather than in-school exposure (Lessler et al., 2021). However, researchers report that “Even if transmission in classrooms is rare, activities surrounding in-person schooling, such as student pick-up and drop-off, teacher interactions, and broader changes to behavior when school is in session could lead to increases in community transmission.” The risk of severe disease and death is low in students, but the size of the risk to school staff and family members of students is still unknown.

Researchers have utilized the COVID-19 Symptom Survey, which is organized through Facebook in partnership with Carnegie Mellon University, to access information on symptoms related to COVID-19, testing, and schooling experience. In this study, researchers evaluated information collected between November 24, 2020 and December 23, 2020 as well as January 11, 2021 to February 10, 2021.

> **Evaluation of the information from the survey showed that living in a household with a child attending full-time, in-person school was associated with a substantial increase in the odds of reporting COVID-19-like illness or a positive COVID-19 test.**

The strength of the association between likelihood of COVID-19 symptoms and having a child in school increased with grade level. The magnitude of the effect was smaller when children were attending in-person school on a part-time basis, but there was a still statistically significant increase.

There was also an association between the number of mitigation measures implemented by the school and the risk of COVID-19 outcomes among adult household members. There were 14 mitigation measures reported by people completing the survey, and the most common included student mask-mandates for 88% of respondents, followed by teacher mask mandates in 80%, entry restrictions for individuals other than staff and students in 66%, and extra space between desks in 63%.

On average, each measure implemented is associated with a 9% decrease in the odds of COVID-19-like illness in adults in the household, an 8% decrease in the odds of loss of taste or smell, and a 7% decrease in the odds of a recent positive SARS-CoV-2 test.

Comparisons between the contributions of different mitigation measures allowed for a ranking in the mitigation measures that were most effective at reducing risk of COVID-19 illness in the household.

The assessment of the ranked order of mitigation measures showed that

- Symptom screening is associated with a greater risk reduction than the average reduction of the complied measures.
- Teacher mask mandates and cancelling extra-curricular activities are also associated with larger reductions than average.
- Closing cafeterias, play-grounds, and use of desk shields are associated with smaller reductions in risk reductions, or increases in risk in some cases.

While the initial analysis showed that part-time, in-person school led to a lower risk of COVID-19-like illness in household members than full-time attendance, when the number of mitigation measures used at a school were accounted for, this association was no longer observed. This suggests that the mitigation measures are an important contribution to reducing the risks associated with in-person school.

The researchers also observed that when seven or more mitigation measures were in place at a school, the association between in-person schooling and COVID-19-like illness disappeared.

Schools with seven or more mitigation measures in place had similar measures in place with over 80% reporting a combination of student and teacher mask mandates, restricted entry to the school, extra space between desks, and no supply sharing along with over 50% of those with seven or more mitigation measures reporting formation of student cohorts, reduced class size, and daily symptom screening.

The authors conclude that there is a clear association between in-person schooling and the risk of COVID-19-related illness in adult household members, and that this association disappears when more than seven school-based mitigation measures are in place at a school.

The information available in the survey did not allow for an evaluation of the risk to staff at the schools participating in in-person schooling because survey participants only entered information about their own households. The researchers were able to assess the risk to school staff who reported that they worked “outside the house” during the study period, and working outside the home was associated with an increase in COVID-19-related illness. The magnitude

of the risk was similar to that observed in other occupations that required working outside the home, such as healthcare and office work.

Probability of Detection of Infection with PCR-Based Testing

In a recent study, researchers determined that the peak probability of testing positive for COVID-19 with a PCR-based test is four days after exposure with the probability decreasing to 50% by ten days after exposure (Hellewell et al., 2021). The more frequently testing occurs, the higher the probability that symptomatic cases will be detected before symptom onset and the higher probability that someone who remains asymptomatic will be detected within seven days of exposure. However, the detection depends both on the speed at which the results are returned as well as the frequency of the testing.

Examples of changes in testing delays and frequency:

- If it takes one day to receive the results from the test, an increase in testing frequency from every four days to every two days allows for an increase in the probability of detection of asymptomatic cases from 76% to 95%.
- If testing occurs every two days but the time to receive the test results change, the probability of detecting a symptomatic infection before symptom onset is 58% with a one-day delay and 42% with a two-day delay.

When there is a longer delay for the test results, the infection must be identified earlier to allow for the longer time between the test being administered and the person being notified. This could lead to a reduced probability of detection asymptomatic infections overall because there is a smaller window of time when an asymptomatic infection can be detected due to the typically lower amounts of virus produced. There is less of a trade off when detecting symptomatic infections. The researchers give the example that the probability of detecting a symptomatic case prior to symptom onset is similar when using a two-day testing frequency with a two-day notification delay (probability of 42%) compared to a four-day testing frequency with a one-day notification delay (probability of 40%).

The highest probability of detecting infections was found to be testing every other day if the tests were returned in one day. With these conditions, PCR-based testing would detect 57% of symptomatic cases prior to the onset of symptoms and 94% of asymptomatic cases within 7 days of exposure.

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