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Topic: COVID-19 Research Update

Vaccination

Public health officials have been recommending that individuals who have previously been infected with SARS-CoV-2 be vaccinated even though natural infection does produce a robust immune response (Cavanaugh et al., 2021). A study has now been completed to support this recommendation, showing that COVID-19 vaccination after SARS-CoV-2 infection provides a reduced risk of reinfection compared to the immune response from infection alone.

The study was conducted in Kentucky from May to June, 2021, and Kentucky residents who were not vaccinated had 2.34 times the odds of reinfection with the virus compared with those who were fully vaccinated.

Based on these findings, the authors conclude that full vaccination provides additional protection against reinfection among persons with previous SARS-CoV-2 infection.

There were not enough individuals who were partially vaccinated in this study to determine if partial vaccination with one dose of the two-dose mRNA vaccines was sufficient to afford additional protection. Officials recommend getting fully vaccinated with two doses of an mRNA vaccine or the single dose Johnson & Johnson vaccine as it is still unknown if a single dose of mRNA vaccine provides full protection, and multiple studies have shown that partial vaccination with mRNA vaccines is less effective against the Delta variant.

A study on the effectiveness of the Moderna vaccine against the Alpha and Beta variants in real-world use in Qatar was also published (Chemaitelly et al., 2021). The researchers found that 14 days or more after a single dose of the vaccine the effectiveness against infection was 88.1% for the Alpha variant, which increased to 100% after the second dose. The effectiveness against infection for the Beta variant was 61.3% after the first dose and 96.4% after the second dose.

Effectiveness of the Moderna vaccine against any severe, critical, or fatal COVID-19 disease due to any SARS-CoV-2 infection from the Alpha or Beta variants was 81.6% after the first dose and 95.7% after the second dose.

Previous studies with the Pfizer-BioNTech vaccine have indicated that a single dose has similar efficacy against the Alpha variant (Van Beusekom, 2021). However, a single dose of vaccine has been shown to have a much lower effectiveness against the Delta variant with a reduction in effectiveness of 12 to 19 percentage points from the full two-doses, or a vaccine effectiveness of 30.7%. This lack of a robust effect is also expected to be the case with the Moderna vaccine.

Clinical Trial Data on the Johnson & Johnson Vaccine

A study of the durability of the response to the Johnson & Johnson vaccine was recently released as a preprint (Barouch et al., 2021). The level of response was measured eight months after the single-shot vaccine regimen in ten participants and six months after a two-shot regimen in ten participants. Five individuals received a placebo. There were not enough participants in the trial to compare the differences between the single and double dose regimen. Three participants were excluded from this evaluation (one due to a breakthrough infection and two who later received mRNA vaccines).

The antibody responses were stable over eight months with only a 1.8-fold reduction of the median neutralizing antibody levels. There was also an expansion of neutralizing antibodies observed over time that allowed for neutralization of emerging variants. Investigation of the T-cell responses indicated that there was also a sustained level of T-cell activation over eight months. The durability was consistent with previous adenovirus vaccines developed by the company for protection against Zika.

> **Based on the results, the researchers from Janssen state that the durability of the antibody and cellular response from the single shot Johnson & Johnson vaccine over time, as well as the increased neutralizing antibody responses to SARS-CoV-2 variants over time, support the continued use of the Johnson & Johnson vaccine for the global COVID-19 pandemic.**

A second study was also released describing the response of antibodies produced after vaccination with the single dose Johnson & Johnson vaccine to newly emerging variants (Jongeneelen et al., 2021). The largest reduction in neutralization was observed with the Beta (3.6-fold reduction) and Gamma (3.4-fold reduction) variants that were first detected in South Africa and Brazil. These variants have mutations that decrease interactions with the immune system and neutralizing antibodies that lead to a reduction in neutralization from all available vaccines and antibody treatments. Even with these decreases, the vaccines continue to be protective against severe disease and death. The decrease in neutralization for the Delta variant was 1.6-fold and 0.9-fold for the Alpha variant, suggesting that the vaccine will continue to be highly effective against these variants.

Additional information on the Johnson & Johnson vaccine was presented at a press conference from South Africa's Ministry of Health on the preliminary results from a clinical trial in South Africa, where the Delta variant is spreading at high levels (Mandavilli, 2021). The study was performed between February and May, 2021 and includes 477,234 health care workers at 122 sites who received the single shot Johnson & Johnson vaccine (Johns Hopkins, 2021).

The vaccine has an efficacy of up to 95% against death from the Delta variant, and up to 71% against hospitalization, the researchers reported.

When breakthrough infections from the Delta variant occurred, the symptoms were mild in 96% of cases, and less than 0.05% of breakthrough infections resulted in severe disease or death. The efficacy against the Beta variant was lower, which was expected. When the Beta variant was dominant, the vaccine efficacy against hospitalization was 67%. There were also two cases of the rare clotting disorder that is associated with adenovirus-based vaccines, which include the Johnson & Johnson and AstraZeneca-Oxford vaccines. Both participants made a complete recovery after the clotting episodes.

Dr. Linda-Gail Bekker, co-lead of the study and director of the Desmond Tutu H.I.V. Centre at the University of Cape Town told the *New York Times* that the "results suggest that people who have received one dose of the Johnson & Johnson vaccine don't need a booster shot."

This study is helpful because laboratory experiments had shown conflicting results on how antibodies produced in response to the vaccine responded to emerging variants and especially the Delta variant. Results are expected in the next few weeks of a trial investigating use of a two-shot regimen with the Johnson & Johnson vaccine.

Length of Protection of Moderna and Pfizer-BioNTech Vaccines

Both Pfizer and Moderna have released data that indicates the efficacy of their vaccines remains durable through at least six months after the second dose (Moderna, 2021 and Thomas et al., 2021). For the Moderna vaccine, the final analysis of the Phase 3 study data showed that the vaccine remained at 93% efficacy through six months after administration of the second dose. The Pfizer-BioNTech study indicated that the vaccine remained at 91% efficacy up to six months after the second dose. The efficacy of the Pfizer-BioNTech vaccine ranged from 86% to 100% across countries in the studies and in populations with diverse characteristics of age, sex, and race/ethnicity. **The efficacy against severe disease was 97%.** There was a slight drop from 96% protection against any symptoms in the first two months after vaccination to 84% after four months.

This level of waning is not yet of concern for the general population in the United States though it suggests that boosters may be required at some point in the future (Johnson, 2021).

Studies in Israel conducted by the Ministry of Health, where the Pfizer-BioNTech vaccine was the only administered type, showed a larger decrease in the effectiveness of the vaccine for preventing infection from the initial values of 95% measured in January to 39% in June and July (Zimmer, 2021). **However, over this same time period, the vaccine remained more than 90% effective in preventing severe disease.** There are some questions about the most recent efficacy calculations due to the small number of participants included in the evaluations. There are also differences in the level of other public health measures in place in the country and changes in the virus itself as both Alpha and Delta became widespread since the vaccine campaigns were initiated. It is difficult to interpret how these factors may be influencing the effectiveness of the vaccine in preventing infections. Because of the possibility of a reduction in

efficacy, the Israeli government has begun a program to offer booster shots for those over the age of 60.

Third Vaccine Dose for Immunocompromised Individuals

The CDC announced on August 13, 2021 that:

> **People who are moderately to severely immunocompromised should receive an additional dose of mRNA COVID-19 vaccine after the initial 2 doses.**

Based on data from the CDC, this group of individuals make up about 3% of the adult population.

This new recommendation was made because some immunocompromised individual's immune system have been found to only weakly respond to the two-dose regimen designated in the clinical trials (CDC-COVID-19, 2021). The weaker response to the two-dose regimen has led to fully-vaccinated immunocompromised individuals accounting for a large proportion of hospitalized breakthrough cases. Studies have also shown that immunocompromised people are more likely to transmit the virus to household contacts after being infected due to a weaker immune response to the vaccine.

The CDC defines immunocompromised individuals as those who have

- Been receiving active cancer treatment for tumors or cancers of the blood
- Received an organ transplant and are taking medicine to suppress the immune system
- Received a stem cell transplant within the last two years or are taking medicine to suppress the immune system
- Moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids or other drugs that may suppress your immune response

When getting the third dose, a third dose of the same mRNA vaccine (Pfizer-BioNTech or Moderna) should be used. If the mRNA vaccine product given for the first two doses is not available or is unknown, either mRNA COVID-19 vaccine product may be administered.

> **A person should not receive more than three mRNA vaccine doses.**

Preliminary studies indicate that repeated vaccination with mRNA vaccines can intensify the adverse reactions to the inert components of the vaccine while the response to the viral components wane. Therefore, unnecessary vaccination at this time may reduce the efficacy of vaccines for an individual in the future.

Because the Johnson & Johnson vaccine was authorized after the mRNA vaccines, the studies on this vaccine are behind those on the mRNA vaccines. There is not enough data at this time

to determine whether immunocompromised people who received the Johnson & Johnson vaccine also have an improved antibody response following an additional dose of the same vaccine.

At this time, The FDA's recent EUA amendment only applies to mRNA COVID-19 vaccines, as does CDC's recommendation.

Vaccine Safety Evaluations

An incredibly large number of people world-wide have received the different COVID-19 vaccines allowing for identification of the general safety profile and detection of the more rare side effects that occur in a small subset of individuals. As of July 22, 2021, 187 million persons in the United States had received at least 1 dose of one of the three authorized COVID-19 vaccines (Rosenblum et al., 2021).

Monitoring of adverse events by the Advisory Committee on Immunization Practices (ACIP) after vaccination have determined that serious adverse events with the use of the three authorized COVID-19 vaccines are rare (Rosenblum et al., 2021). To date there have been three medical conditions reported to have a temporal association with receipt of COVID-19 vaccines: thrombosis with thrombocytopenia syndrome (TTS), Guillain-Barré syndrome (GBS), and myocarditis. TTS is a syndrome characterized by clot formation in the veins or arteries (venous or arterial thrombosis) and a depletion of the cells that promote the formation of clots in other areas of the body (thrombocytopenia). GBS is an autoimmune neurologic disorder that is characterized by weakness and paralysis that starts in the legs and spreads to the arms (ascending symptoms). GBS occurs more commonly in males than in females, and incidence increases with age. Between 3,000 and 6,000 GBS cases are reported annually in the United States, and most cases are not associated with vaccination. Individuals that develop GBS might require treatment in the intensive care unit and ventilator support; although most patients recover. Myocarditis is inflammation of the muscles of the heart. TTS and GBS have been associated with the Johnson & Johnson vaccine while myocarditis is associated with the two mRNA vaccines from Pfizer-BioNtech and Moderna.

During their most recent meeting, the ACIP reviewed the previous assessment comparing the benefits of vaccination (numbers of COVID-19 cases and severe disease outcomes prevented) to the risks (numbers of cases of GBS, TTS, and myocarditis).

The benefits per million vaccine doses administered were assessed in relation to

1. The number of COVID-19 cases prevented, based on new case rates during the week of June 13 to 19, 2021
2. The number of COVID-19 hospitalizations prevented, based on rates during the week of June 19, 2021
3. The number of COVID-19 intensive care unit admissions and deaths prevented, based on the proportion of hospitalized patients who were admitted to an ICU or who died.

The risks of the Johnson & and Johnson vaccine were assessed based on the number of GBS patients reported to the Vaccine Adverse Event Reporting System (VAERS) that occurred within 42 days of COVID-19 vaccination per million doses administered through June 30, 2021 and the number of patients with TTS reported to VAERS that occurred after COVID-19 vaccination per million doses through July 8, 2021. The risks for vaccination with the mRNA COVID-19 vaccines was assessed as the number of patients reported to VAERS with myocarditis after receipt of the second dose of an mRNA COVID-19 vaccine per million doses.

As of June 30, 2021, approximately 12.6 million doses of Janssen COVID-19 vaccine had been administered in the United States, and there were 100 reports of GBS with 95% hospitalized and 10% admitted to the intensive care unit. One person had died as of the last updated report. The GBS reporting rate was 7.8 cases per million Janssen COVID-19 vaccine doses administered.

Through July 8, 2021, there were 38 cases of TTS within 15 days of vaccination that were reported to VAERS. Four of the affected individuals died. The overall TTS reporting rate was 3.0 cases per million doses administered.

With the latest data, this means that the benefit per million doses of Johnson & Johnson vaccine administered to men aged 50 to 64 years is the prevention of 1,800 hospitalizations, 480 intensive care unit admissions, and 140 deaths attributable to COVID-19 compared with 14 to 17 GBS cases and one to two TTS cases.

As of June 30, 2021, approximately 141 million second mRNA COVID-19 vaccine doses had been administered in the United States to persons over the age of 18 years, and within VAERS, there were 497 reports of myocarditis after the second dose in this group. There were no confirmed myocarditis associated deaths. The reporting rate of myocarditis overall among adults was 3.5 cases per million second doses administered. The reporting rate was highest among males between the ages of 18 and 29 years at 24.3 cases per million second doses administered.

The ACIP determined that, overall, the benefits of COVID-19 vaccination in preventing COVID-19 morbidity and mortality outweigh the risks for these rare serious adverse events in adults older than 18 years, and they also continue to recommend vaccination for children 12 and over.

There are some differences in the risk for different vaccines based on sex and age, and the ACIP emphasized the importance of informing vaccination providers and all persons receiving vaccines that some vaccines may be safer for different groups. For example, there are increased risks of GBS after the Johnson & Johnson vaccine in men aged 50 to 64 years, there are increased risks of TTS for women aged 30 to 49 after the Johnson & Johnson vaccine, and there are increased risks of myocarditis for men aged 18 to 29 years with mRNA vaccines. These groups might consider using one of the other vaccines that have lower risks of severe adverse events.

Adverse Event Reporting in Individuals between the Ages of 12 and 17 Years

As of July 16, 2021, approximately 8.9 million adolescents aged 12 to 17 years in the United States had received the Pfizer-BioNTech vaccine (Hause et al., 2021). During the time period of December 14, 2020 to July 16, 2021 the Vaccine Adverse Event Reporting System (VAERS) and v-safe (a smartphone-based safety surveillance system) were used to collect reports of adverse events and health impact assessments.

VAERS accepts reports from anyone, including health care providers, vaccine manufacturers, and members of the public. Under COVID-19 vaccine Emergency Use Authorization (EUA) requirements, health care providers must report certain adverse events after vaccination to VAERS, including death. VAERS reports are classified as serious if any of the following are reported: hospitalization or prolongation of hospitalization, life-threatening illness, permanent disability, congenital anomaly or birth defect, or death.

VAERS received 9,246 reports after Pfizer-BioNTech vaccination in this age group with 90.7% for non-serious adverse events and 9.3% for serious adverse events, including myocarditis (4.3%).

The most common conditions reported included dizziness (20.1%), syncope (fainting, 13.3%), and headache (11.1%). Among those who reported syncope, 16.3% reported a history of anxiety around needles, and 16.1% were transported to an emergency department for further evaluation.

The most commonly reported conditions and diagnostic findings among reports of serious events were chest pain (56.4%), increased troponin levels (41.7%), myocarditis (40.3%), increased C-reactive protein (30.6%), and negative SARS-CoV-2 test results (29.4%). There were 14 reported deaths after vaccination with four in individuals aged 12 to 15 years and ten aged 16 to 17 years. The cause of death was determined to be pulmonary embolism (two), suicide (two), intracranial hemorrhage (two), heart failure (one), hemophagocytic lymphohistiocytosis and disseminated Mycobacterium chelonae infection (one), and unknown or pending further records (six).

No reports of death to VAERS were determined to be the result of myocarditis.

The preliminary investigations regarding the cause of death in cases that occurred close to the time of vaccination did not indicate a pattern suggestive of a causal relationship from the vaccine. However, the cause of death for some of the cases is still pending receipt of additional information so a definitive evaluation cannot yet be made.

The CDC established v-safe, a voluntary safety-surveillance system, to monitor adverse events after COVID-19 vaccination. Individuals who enroll receive period text reminders to fill out online health surveys. If a report indicated medical attention was sought, VAERS staff members contacted the reporter and encouraged completion of a VAERS report, if indicated.

Approximately 129,000 U.S. adolescents aged 12 to 17 years enrolled in v-safe after vaccination with the Pfizer-BioNTech vaccine. They reported local (63.4%) and systemic (48.9%) reactions with a frequency similar to that reported in preauthorization clinical trials. The

most frequently reported reactions after either dose were injection site pain, fatigue, headache, and myalgia (muscle pain). During the week after the second dose, around 30% reported fever. Just under 25% reported not being able to perform daily activities the day after the second dose.

Less than 1% of adolescents aged 12 to 17 years required medical care in the week after receipt of either dose, and 56 adolescents, corresponding to 0.04%, were hospitalized.

The v-safe app does not record the reason for hospitalization, and it therefore cannot be determined whether hospitalization was related to vaccination.

Based on this evaluation, the investigators concluded that mild local and systemic reactions are common among adolescents following Pfizer-BioNTech vaccine, and serious adverse events are rare, leading to a continued recommendation for use of the vaccine in all persons over the age of twelve years.

Incidence of Cardiac Inflammation after Vaccination in Adults

A research letter in JAMA describes the clinical records of all cases of cardiac inflammation after vaccination for SARS-CoV-2 that occurred in the Providence health care system, which induces 40 hospitals in in Washington, Oregon, Montana, and Los Angeles County, California (Diaz et al., 2021). Based on vaccination records, there were 2,000,287 individuals who received at least one dose of COVID-19 vaccine. Of this group, 76.5% received more than one dose, 52.6% received the Pfizer/BioNTech vaccine, 44.1% received the Moderna vaccine, and 3.1% received the Johnson & Johnson vaccine. The median age of the individuals in the group was 57 years.

Twenty individuals had vaccine related myocarditis (1.0 per 100,000), and 37 had vaccine related pericarditis (1.8 per 100,000).

Myocarditis occurred a median 3.5 days after vaccination with a range from 3.0 to 10.8 days. In the group who experienced myocarditis, 75% were men and the median age was 36 years with a range from 26 to 48. The majority (80%) developed symptoms after the second dose, and symptoms were seen equally after the Pfizer-BioTech vaccine (55%) and the Moderna vaccine (45%). Nineteen of the 20 individuals were admitted to the hospital due to symptoms, and all were discharged after a median of two days with a range from two to three days. None of the participants needed to be readmitted to the hospital at a later date, and none died from their symptoms.

The proportion of pericarditis cases that occurred after the first dose of vaccine was higher, with 40.5% after the first dose and 59.5% after the second dose. The distribution between the types of vaccine also differed with 62% of the cases associated with use of the Pfizer-BioNTech vaccine, 32% with the Moderna vaccine, and 5% with the Johnson & Johnson vaccine. The median onset was 20 days after the most recent vaccination with a range from six to 41 days. Again, the majority of the participants affected were male (73%), and the median age was 59 years with a range from 46 to 69 years. Thirteen of the 37, corresponding to 35% were admitted to the hospital due to symptoms, but none were treated in intensive care. The median length of

stay in the hospital was one day with a range from one to two days. None of the patients died. As of the last assessment of the participants, seven individuals with pericarditis after their first dose had received a second vaccination, 19% had fully resolved symptoms, and 62% were improving.

There was a statistically significant increase in the number of myocarditis or myopericarditis cases observed in the hospital system after the vaccine became widely available, from 16.9 per month to 27.3 per month. A similar statistically significant increase was observed for pericarditis cases, which increased from 49.1 per month to 78.8 per month. This study shows a higher incidence of myocarditis than reported by the CDC from the VAERS system. The CDC detected 4.8 cases per one million people while this investigation observed one case per 100,000, or 10 cases per one million. In this study, pericarditis was found to be more common than myocarditis in older individuals.

Incidence of Local and Systemic Adverse Reactions

A systematic review and statistical analysis of 87 published studies that investigated the safety data for 19 available COVID-19 vaccines was recently published (Wu et al., 2021). Injection-site pain was the most common local reaction, and fatigue and headache were the most common systemic reactions. The frequency of vaccine-related serious adverse events was low overall and less than 0.1%. The rate of adverse events that were reported was about the same in post-authorization observational trials and clinical trials. The number of adverse events reported from post-authorization safety monitoring (e.g. the CDC VAERS Reporting system) were lower than in clinical trials and varied between countries. The proportion of reactions reported for the different types of vaccines are listed in Table 1.

Table 1. Proportion of individuals with local and systemic reactions based on type of vaccine.

	Inactivated Virus (CoronaVac, SinoPharm)	Protein Subunits (Novavax)	DNA Vaccine	RNA Vaccine (Pfizer-BioNTech, Moderna)	Non-Replicating Vector Vaccine (AstraZeneca-Oxford, J&J)	Virus-Like Particle Vaccine
Local Reactions	23.7%	33.0%	39.5%	89.4%	55.9%	100.0%
Systemic Reactions	21.0%	22.3%	29.3%	83.3%	66.3%	78.9%

A small study in France suggests that individuals who are vaccinated after having COVID-19 are more likely to have reactions to the vaccination (Tissot et al., 2021). In a study of 311 individuals, 74% patients reported at least one side effect. However when the group was analyzed based on previous COVID-19 status, 95% of participants with a history of COVID-19 reported at least one adverse event compared to 70% of those who had not previously been sick. The effects were not increased in severity, however.

Individuals with rheumatic and musculoskeletal diseases can often have a disease flare after vaccination because of the nature of the conditions (Connolly et al., 2021). Researchers at the

Johns Hopkins School of Medicine investigated if vaccination with mRNA COVID-19 vaccines led to flares of these conditions or increased levels of local or systemic reactions. They found that 11% of the 1,377 participants reported a flare that required treatment within a month of the second dose, but none of the flares were classified as severe. The reactions after vaccination were similar to those seen in the general population and included injection site pain and fatigue. Based on the results, the authors concluded that flare was an uncommon occurrence and local and systemic reactions typically did not interfere with daily activity in individuals with rheumatic and musculoskeletal diseases.

COVID-19 Illness Duration and Symptom Profile in Children

Because of the sudden and severe symptoms in older adults, the symptom profile from COVID-19 in children did not get much attention in the early part of the pandemic. Based on current evidence, between 43% and 68% of COVID-19 cases in children are asymptomatic or mild in severity with life-threatening symptoms remaining rare (Molteni et al., 2021). Some children with a SARS-CoV-2 infection later progress to the rare condition called multisystem inflammatory syndrome in children (MIS-C) that typically occurs two to four weeks after the initial infection. MIS-C is a serious condition that often requires intensive care in the hospital. The rate of Long-COVID with symptoms that persist for at least four weeks in adults is currently estimated to be around 13.3% and 4.5% for adults with symptoms that last for at least eight weeks after the initial infection. Long-COVID also occurs in children of all ages, but due to the high numbers who are asymptomatic during the initial infection, the proportion of children who have persistent symptoms of COVID-19 is not well defined. Studies have reported rates of Long-COVID in children that range between 4% and 20% (Cooney, 2021 and Radtke et al., 2021).

To better understand the symptom profile and duration, researchers from the United Kingdom investigated illness duration and symptom prevalence, duration, and burden in school aged children from five to 17 years who were tested for COVID-19 (Molteni et al., 2021). The information for those who tested positive was compared to symptomatic children who tested negative and presumably had other types of respiratory illnesses. Symptoms were collected using a mobile app called the COVID Symptom Study. Participating individuals are prompted to report daily with direct questions about specific symptoms as well as any COVID-19 tests, vaccination details, and healthcare accessed. A total of 258,790 children were entered into the study by their parents between March 24, 2020 and February 22, 2021. There were 6,975 positive COVID-19 tests reported from this group, and 1,912 had sufficient information for evaluation of illness duration. Table 2 lists the information collected on the symptom profiles of children who were ill and tested positive for COVID-19 and those who tested negative for COVID-19 and had another respiratory illness.

Overall, those with COVID-19 had a longer duration of illness compared to those with other respiratory illnesses.

Table 2. Comparison of symptom profile between children positive for COVID-19 and negative for COVID-19.

	Positive for COVID-19	Negative for COVID-19
Median duration of illness	6 days with a range between 3 and 11 days	3 days with a range between 2 and 7 days
Most common symptoms in children 5 to 11 years	Headache (62.2%) Fatigue (55%) Fever (43.7%) Sore throat (36.2%) Abdominal pain (27.7%) Persistent cough (24.7%)	Sore throat (46.6%) Headache (38.8%) Fever (30.4%) Fatigue (26.9%) Abdominal pain (24.7%)
Most common symptoms in children 12 to 17 years	Headache (62.2%) Fatigue (55%) Sore throat (51.0%) Anosmia (48.3%) Fever (34.6%) Persistent cough (26.0%)	Sore throat (60.6%) Headache (48.8%) Fatigue (37.2%) Fever (20.4%) Persistent cough (20.6%)
Hospitalization for treatment (5 to 11 years)	16 of 588 (2.7%)	7 of 585 (1.2%)
Hospitalization for treatment (12 to 17 years)	21 of 1146 (1.8%)	19 of 1134 (1.7%)
Hospitalization for treatment full group	37 of 1734 (2.1%)	26 of 1734 (1.5%)
Illness lasting 28 days or more	4.4%	0.9%
Most common symptoms of those with symptoms for 28 days or more	Fatigue (84.4%*) Headache (77.9%*) Anosmia (77.9%*) Sore throat (74.0%*)	Fatigue (65%* and 75%) Headache (30%* and 75%) Sore Throat (65%* and 35%) Persistent Cough (65% and 0%) Fever (65%* and 35%)
Illness lasting 56 days of more	1.8%	Not reported

*The values for symptoms in children who tested negative were listed as the proportion of younger children (5 to 11) and older children (12 to 17) and the group that tested positive was listed as the proportion of the entire study group

The proportion of children with COVID-19 who were admitted to the hospital for treatment was higher than that for children who tested negative for COVID-19. However, the researchers stated that the number of participants was too small to do a statistical analysis, and therefore they were not able to determine if there is a statistically significant difference between the values.

In the 4.4% of children with COVID-19 symptoms that persisted longer than 28 days, the most common symptoms throughout the entire illness were fatigue (84.4%), headache (77.9%), anosmia (loss of smell, 77.9%), and sore throat (74.0%). It was found that headache, fatigue, and sore throat were commonly present early during the illness, with a persistence of fatigue

and, to a lesser extent, headache. Anosmia was often observed only later in illness. There were also 1.8% of those who tested positive for COVID-19 who continued to have symptoms for at least 56 days after the initial infection. Older children were more likely to have symptoms that persisted to at least 28 days, but there was no difference in age in those who had symptoms that lasted at least 56 days.

Additional questions were added to the symptom list in November to include confusion, dizziness, and brain fog. In children who tested positive for COVID-19, dizziness was reported in 14.3% of younger children and 26.2% of older children during the initial infection, but it was not highly prevalent in those with symptoms that lasted at least 28 days. Confusion was reported in 2.6% of younger children and 7.1% of older children during the initial infection, but this symptom also did not often persist. Brain fog was observed in 5.9% of younger children and 11.3% of older children, and low mood was observed in 7.9% of younger children and 15.6% of older children. Due to the late inclusion of these symptoms, it was not possible to determine if they persisted at least 28 or 56 days in the current study.

Multisystem Inflammatory Syndrome in Children (MIS-C)

Researchers published follow-up information on children who were diagnosed with MIS-C early in the pandemic, allowing for an assessment of the longer-term effects six months after admission for treatment of the condition (Capone et al., 2021). The 50 individuals included in the study were all of the patients under the age of 21 admitted to Cohen Children's Medical Center for MIS-C between April 17, 2020 and June 20, 2020. The age range of individuals who were treated for MIS-C was between 9 months and 17 years with a median of 8.5 years.

Upon admission 66% of those treated had cardiac abnormalities, and 26 patients, or 52% of the total, required treatment in the intensive care unit.

Cardiac abnormalities observed in children with MIS-C

- left ventral systolic dysfunction
- left ventral diastolic dysfunction
- coronary dilation or aneurysm

Clinical improvement was rapid after admission and treatment, using institutional guidelines. Most were treated with intravenous IgG (96%) and aspirin (92%). Many also received methylprednisolone (70%), a corticosteroid, and some received a stronger anticoagulant, enoxaparin (46%). The length of stay in the hospital ranged from four to seven days with a median of five days. There were no in-hospital deaths, and no patient required ECMO support.

Cardiac abnormalities were found to improve within between one and eight days with a median of three days. Of the 26 individuals with left ventricle systolic dysfunction at admission, 69% had normalization of function by discharge, and 15% had persistent but improved function. The remaining four patients had mild dysfunction during admission and did not have an assessment done at the time of discharge from the hospital.

Two weeks after discharge from the hospital, 47% of the individuals continued to report fatigue with normal activity. Those reporting fatigue were also the individuals who had shock and myocardial systolic dysfunction at the time of admission to the hospital. **All other individuals were asymptomatic**. There was only one individual who continued to have left ventricle systolic dysfunction, and five patients (11%) who continued to have left ventricle diastolic dysfunction. Coronary abnormalities were gradually improving, and no new abnormalities were observed.

At eight weeks after discharge, 12% continued to have fatigue with regular activity. All patients had normal left ventricle systolic function and resolved coronary aneurysms and dilation. Left ventricle diastolic dysfunction persisted in four patients (9%) and qualitative coronary abnormalities were noted in five (12%) patients. There was no evidence of persistent swelling or fibrosis (scarring) in any of the individuals with prior left ventricle systolic dysfunction based on MRI assessment.

At six months after discharge, all of the individuals assessed (25 out of the 50 original patients) were asymptomatic and back to their functional baseline. Left ventricle systolic function was normal for both those with previous abnormalities during hospitalization and those who had normal readings during hospitalization. There was one individual who continued to have left ventricle diastolic dysfunction, but there was no evidence of inflammation or fibrosis based on MRI scans. The authors concluded that “Given our findings, our current practice is to allow sports participation in patients with normalization of their inflammatory markers and systolic cardiac function at eight weeks after hospital discharge.”

Neurological and Cognitive Effects of COVID-19

Researchers in the United Kingdom have performed a study of the lingering cognitive effects of COVID-19 and found them to be substantial for both those who required treatment in the hospital and those who symptoms were mild enough to convalesce at home (Hampshire et al., 2021). The amount of the deficit increased with increasing symptoms of COVID-19, but even those with mild symptoms had deficits that would be expected to affect daily functioning. Comparisons of the data showed that the deficits were not explained by differences in age, education or other demographic and socioeconomic variables, and remained in those who had no other residual symptoms.

The magnitude of the change in people who had required ventilation during hospitalization was 0.47 SD, which is

- larger than the average 10-year decline in global performance between the ages of 20 to 70 within this dataset
- larger than the deficit of the 480 people in the study who indicated they had previously suffered a stroke
- larger than the 998 who reported learning disabilities
- comparatively larger than a 7-point difference in IQ in a classic intelligence test

Based on the testing, the researchers found that the deficits were most pronounced for cognitive functions such as reasoning, problem solving, spatial planning and target detection, and simpler functions such as working-memory span as well as emotional processing were less affected.

The deficits observed in individuals who required ventilation while in the hospital have been observed previously in studies of individuals requiring intensive care. These studies suggest that cognitive deficits can last for at least five years in some individuals who were hospitalized with respiratory disease.

The magnitude of the deficits observed for those individuals who did not require treatment in the hospital was surprising to the researchers.

The magnitude of the deficit was correlated to the level of treatment received for respiratory difficulty, with increasing deficit associated with increased level of treatment. In other words, individuals who were sick at home with **no** respiratory symptoms had a lower level of deficits compared to those at home **with** respiratory symptoms not requiring medical assistance compared to those who required medical assistance for their respiratory symptoms, but did not require admission to the hospital.

The magnitude of cognitive deficit for individuals with a confirmed case of COVID-19 who remained at home while sick was 0.23 SD, which corresponds closely to level deficit observed by those in the study who had previously reported having a stroke.

The study did not include elements to determine the functional reasons for the cognitive decline, but the authors hypothesize that the correlation between the severity of respiratory symptoms and cognitive deficits may suggest a link to transient hypoxia (lack of oxygen) to important areas of the brain.

Research presented at the Alzheimer's Association International Conference on July 29, 2021 also suggests an association between worse memory scores and cognition scores due to low oxygen levels measured during a six-minute walk test (Van Beusekom, 2021). The study followed 32 participants for two months after release from the hospital for treatment of COVID-19, and it was found that 56.2% had cognitive limitations, including problems with short-term memory.

Another study of 310 participants who had been hospitalized for COVID-19 indicated that there is an increase of certain proteins associated with Alzheimer's disease and several inflammatory proteins in participants who did not have cognitive problems at the beginning of the study. The patterns of protein production observed have been associated with a breach of the blood-brain barrier and injury to neurons or another type of brain cell called glial cells.

Researchers in Norway have also published a study that examines the extent of memory problems eight months after COVID-19 infection (Søraas et al., 2021). In the study, 13,001 participants who were either tested for COVID-19 through the national program in Norway or randomly selected from the population were asked about any memory problems via a questionnaire. There were individuals who had tested positive for COVID-19 (651 individuals), participants who had been tested but were negative for COVID-19 (5,712 individuals), and those

who were randomly selected from the population of untested individuals (3,342 individuals) who sent back the follow-up questionnaire after eight months for a total of 9,705 participants. None of the participants in the study were hospitalized for treatment of their COVID-19 symptoms, and the level of symptoms reported was defined as “relatively mild”.

Proportion of each group reporting memory problems after eight months

- 11% in the SARS-CoV-2–positive group
- 4% in the SARS-CoV-2–negative group
- 2% in the untested randomly selected

In the second questionnaire, 41% of the participants in the SARS-CoV-2–positive group reported a significant worsening of health compared with one year prior. Additionally, 82% of the participants in the SARS-CoV-2–positive group who reported memory problems also reported a worsening of health. Feeling depressed, having less energy, or pain were reported relatively equally by the different groups.

Based on their findings, the authors conclude that “SARS-CoV-2 may negatively impact memory even eight months after having a mild case of the disease, and this can be associated with a worsening of health and PASC [postacute sequelae of SARS-CoV-2 infection]”. PASC is the medical term being used for Long-COVID.

The authors also highlight that their findings “are a strong impetus to reconsider the notion that COVID-19 can be a mild disease.”

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