PINNACLECARE

# Medical Intelligence Report

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# Topic: COVID-19 Research Update

## Effect of COVID-19 on Pregnancy

A systematic review of the available literature up to June 8 was performed to investigate the effects of SARS-CoV-2 infection during pregnancy (Khalil et al., 2020b). Previous investigations have reported the increased risk of infection with SARS-CoV-2 and of experiencing severe symptoms for women who are pregnant, but the outcome of pregnancy was not reported. In this review, the results from 86 studies with 2567 pregnancies were included, and statistical analysis was used to estimate the risk for both mother and child. Most of the women included as participants were in their third trimester of pregnancy, and by the end of the study period, 52.4% had delivered their babies. There was a higher than normal number of births using cesarean delivery. **There was also a higher than usual number of pre-term births (before 37 weeks), corresponding to 21.8%.** Pre-term births were due to medically induced labor in most cases reported, which was 18.4% of the total group. The most common reasons cited for induction of labor or early caesarian birth was not fetal distress, but changes in the mother's health, including severe maternal pneumonia or fear of sudden maternal decompensation.

The most commonly reported clinical symptoms in the mothers included fever (63.3%), cough (71.4%), and shortness of breath (34.4%). There were also changes in the blood-based testing that are similar to those reported in other groups of people with COVID-19, including 54% of the women with high levels of inflammatory markers (C-reactive protein or procalcitonin), 34.2% with lower-than-normal levels of a white blood cell called lymphocytes (lymphopenia), and 16% with elevated levels of an enzyme from the liver called transaminase that indicates liver damage has occurred. The number of pregnant women with COVID-19 who had chronic medical conditions was 32.5%, which is higher than the rate observed the general population. There was also a higher than normal rate of obesity with 38.2% of the participants meeting the criteria. Based on the information included in the review, 7% of pregnant women required care in the intensive care unit. Women with chronic medical conditions and those over the age of 35 were more likely to be admitted to the intensive care unit, and 3.4% of those in the intensive care unit required mechanical ventilation. **Few of the women died, and the mortality rate was around 1% with a less than 1% rate of death of the newly born babies**. In the reports that described changes to the placenta, there was abnormal inflammation in about 20% and evidence of blood-flow abnormalities in 78.6%. The rate of SARS-CoV-2 infection in the babies was low, and based on PCR-based testing 1.4% of the newborns contracted COVID-19. It is currently unclear if babies are susceptible to SARS-CoV-2 *in utero*, but there is preliminary evidence that infection before birth can occur.

The authors conclude that the increased risk of preterm birth, cesarean delivery, and potential transmission of viral infection to the newborn before or after birth are concerning outcomes due to potential long-term complications associated with them. **However, the collected information suggested that women and babies do not have a large increase in risk of serious illness associated with COVID-19**. A systematic review of pregnancy outcome in women with all coronavirus-related illnesses, including SARS and MERS, found that there was a high risk of miscarriage, preeclampsia, preterm birth, and death of the newborn. An increase in these risks, with exception of preterm birth, was not observed for SARS-CoV-2. At this time, however, only the outcome of late-term pregnancies is available.

A follow-up report included additional information that compared the outcome of pregnancies at St George's University Hospital in London, England before the SARS-CoV-2 pandemic, from October 1, 2019, to January 31, 2020 and after the start of the outbreak from February 1, 2020, to June 14, 2020 (Khalil et al., 2020a). Specific outcomes that were investigated were stillbirth, preterm birth, cesarean delivery, and neonatal unit admission. There were 1,681 births in the period before the pandemic and 1718 births after. **The incidence of stillbirth was higher during the pandemic than before (16 versus 4), but none of the deaths were associated with COVID-19.** There were no statistically significant differences over time in births before 37 weeks' gestation, births after 34 weeks' gestation, neonatal unit admission, or cesarean delivery based on this comparison. There was not enough information available to determine if there was a common factor linking the increase in the number of still births during the pandemic, but the authors surmise that general reluctance of individuals to visit a healthcare provider in the early periods of the outbreak may have contributed to missed abnormalities that would normally lead to treatment at a hospital.

Additional information has also become available from hospitals in Wuhan between December 8, 2019 and March 20, 2020 (Chen et al., 2020). Examination of the reporting system of the National Health Commission of China identified 118 women pregnant women with COVID-19, which corresponded to 0.24% of the patients in Wuhan hospitals during this time. The most common symptoms were fever (75%), cough (73%), and lymphopenia (44%). When the lungs of the women were examined with CT scans, 79% had abnormalities in both lungs. COVID-19 symptoms were classified as mild in 92% of women, and 8% were found to have hypoxia. Only one woman required noninvasive mechanical ventilation. In six of the nine women classified as having severe disease, the symptoms worsened after delivery. By the end of the study period, 94% of the women had been discharged from the hospital, including all of those classified as having severe or critical disease. Pregnancy outcomes included three cases of spontaneous miscarriage, two ectopic pregnancies, and four induced abortions due to concerns about COVID-19. Women with COVID-19 accounted for 0.56% of births in Wuhan during the study period, and 93% of the births during the study were by cesarean section. Cesarean delivery was used in 61% of the births due to concern about COVID-19 on the pregnancy, and 21% of the deliveries were preterm. None of the babies tested (8 individuals) were found to have SARS-CoV-2 infections, and there were no neonatal deaths reported.

There have been critiques of the reporting system utilized in the United States that has led to a lack of information on the effect of COVID-19 on pregnancy, pregnant women, and children born to mothers who have been sick with the virus (Caron, 2020). In order to report information on treated patients to the CDC, doctors fill out a standard case report form for people infected with

the coronavirus that includes a space to note pregnancy status, and there is also a supplemental form that can be filed with details on pregnancy. However, when healthcare providers are busy caring for sick individuals, there is little time to fill out this paperwork. In the United Kingdom, the U.K. Obstetric Surveillance System collected information quickly on COVID-19-infected pregnant women at 194 obstetric hospitals without the need for physicians to fill out paperwork. Several clinical trials have been organized in the United States to fill the gap, including the ASPIRE trial and a national registry administered by the University of California at San Francisco and Los Angeles. The registry allows pregnant women to report their own information rather than utilizing reporting from clinicians, and women can participate regardless of where they are getting care. ASPIRE is a more traditional observational clinical trial that will collect information on 10,000 women and their babies from the start of pregnancy through delivery and up to 18 months postpartum.

There was a high proportion of women who were Black, Asian, or part of another ethnic minority group included in the study by Khalil and colleagues. Other researchers have also observed this fact. A study in Philadelphia indicates that pregnant women who are Black or Latino are five times as likely as white women to have been exposed to SARS-CoV-2 (Flannery et al., 2020 and Wu, 2020). The prevalence was determined by measurement of the antibodies from 1,293 women who gave birth at Pennsylvania Hospital or the Hospital of the University of Pennsylvania between April and June. While the absolute number of positive tests for antibodies may be slightly different due to the potential inaccuracies of antibody testing, comparisons of the results made with the same test can be made. **In the entire group, the number of women found to have SARS-CoV-2 antibodies was 6.2%,** and the false positive rate is approximately 1%, which gives a corrected value of approximately 5.2% of pregnant women in Philadelphia were previously exposed to SARS-CoV-2. Based on the population of the area, this suggests an overall infection rate of the general public of approximately 1.4%.

> **The rate of positive antibody tests for Black women in the study was 9.7%, the rate for Latino women was 10.4%, and 2% of white women had a positive test for antibodies.**

The number of Black and Latino women reported to have been exposed to SARS-CoV-2 in this study is larger than that found when using testing for active infections with PCR-based tests, about 3 times more likely than white women. However, as mentioned previously, the level of this type of testing has been severely limited at times, and testing was limited to those who were visibly ill, which would have biased the results by leading to an increase in the number of people with health insurance and reliable healthcare. The testing sites in Philadelphia were also assigned by zip code, making travel to the appropriate site available mainly by car.

## SARS-CoV-2 Transmission

### Transmission from Children

There has been a heated debate recently about the return of children to school buildings for the start of school in fall. Central to the debate is the question of the extent to which children contribute to transmission of SARS-CoV-2. A study from South Korea reports on the contact tracing of 59,073 contacts of 5,706 individuals in South Korea who were the first person in their

family to test positive for COVID-19, also called the index patient, between January 20 and March 27 (Park et al., 2020). Of the 10,592 household contacts investigated, 11.8% tested positive for SARS-CoV-2. The rate of infection of contacts outside the household was smaller at 1.9%.

**The number of people who were the index patient in each age group**

- 0.5% were 0–9 years of age
- 2.2% were 10–19 years of age
- 29.7% were 20–29 years of age
- 11.7% were 30–39 years of age
- 16.5% were 40–49 years of age
- 19.4% were 50–59 years of age
- 12.9% were 60–69 years of age
- 5.9% were 70–79 years of age
- 3.5% were over 8-0 years

**The age group with the largest transmission rate to their household were children between the ages of 10 and 19.** When the index patient was between the ages of 10 and 19, 18.6% of their household contacts were found to have COVID-19 while index patients who were under the age of 10 led to a transmission rate of 5.3%. **This suggests that elementary school children would be LESS likely than middle school or high school children to spread COVID-19 between school and home.** However there is still a risk of transmission from young children.

Previous studies have been small and difficult to interpret, but Dr. Ashish Jha, director of the Harvard Global Health Institute told the *New York Times* that this study in South Korea was "very carefully done, it's systematic, and looks at a very large population…It's one of the best studies we've had to date on this issue" (Mandavilli, 2020). Other experts commented that the study was completed while interventions were in place to limit interaction in the community, which suggests that the levels observed for all groups would most likely increase as more interactions in the community occurred, including the opening of schools. **One limitation of the study is that, the contact tracers only tested children who felt ill, and there is a high proportion of children who remain asymptomatic after infection with SARS-CoV-2.** Because it has not yet been determined, there still remains a question about the role of children without symptoms in transmission of SARS-CoV-2.

Several countries have reopened schools and had varying levels of success. Some, such as Denmark and Finland, have been able to reopen, but China, Israel, and South Korea have had to stop school again after reopening due to increased transmission in the community.

### Aerosol Transmission

Initial reports suggested that SARS-CoV-2 spread mainly through infectious droplets, but there is mounting evidence of aerosol transmission from smaller, airborne particles that remain

suspended in poorly ventilated areas for over an hour (Prather et al., 2020). While droplets are typically formed when people sneeze or cough due to symptoms of an illness, aerosol particles are produced by simply breathing or speaking and can be produced by those without symptoms. Droplets can be transmitted by contact with people or contaminated surfaces while aerosols allow for inhalation of infectious particles that are suspended in the air and can be transported by air currents.

The measures used to control droplet and aerosol transmission of an infectious agent in the community differ, and experts around the world have been asking public health and government officials to add steps for the control of aerosol transmission to their plans. The CDC and WHO have both been slow to acknowledge the possibility of aerosol spread of SARS-CoV-2 because the results from available studies have not been unequivocal. However, evidence from epidemiological studies and analysis of local transmission dynamics indicate that the spread of COVID-19 is not simply occurring via droplets (Prather et al., 2020, and McAuley and Rauhala, 2020).

After the release of a commentary in the journal *Clinical Infectious Diseases* that was supported and signed by 239 clinicians, infectious-disease physicians, epidemiologists, engineers and aerosol scientists, **the WHO announced that it would issue new guidelines about transmission in settings with close contact and poor ventilation** (Lewis, 2020). In the *Clinical Infectious Diseases* commentary, the authors stated “we are concerned that the lack of recognition of the risk of airborne transmission of COVID-19 and the lack of clear recommendations on the control measures against the airborne virus will have significant consequences: people may think that they are fully protected by adhering to the current recommendations, but in fact, additional airborne interventions are needed for further reduction of infection risk.”

Part of the disconnect being observed may again be a difference in technical versus colloquial definitions as occurred in recent discussion of the terms asymptomatic and pre-symptomatic (Van Beusekom, 2020). For example, in a commentary on COVID-19 transmission published by CIDRAP, an expert on disease transmission stated that airborne transmission is typically defined as inhalation of respiratory pathogens only at a distance from the source. In the case of SARS-CoV-2, there is evidence of the generation of small, aerosol-sized particles, which remain near the source for long periods of time. This differs from the traditional definition of airborne or aerosol-based transmission, but may be similar enough to merit changes in measures to prevent transmission.

The current recommendations for maintaining good hand hygiene and maintaining a distance of six feet from others are based on studies of droplet transmission of respiratory diseases. The studies indicate that a **droplet will settle to the ground in 4.6 seconds while an aerosol particle takes 12.4 hours**. The potential for aerosol spread of SARS-CoV-2 suggests that spacing of six feet may not be sufficient to reduce transmission for indoor conditions where aerosols can remain airborne for hours, accumulate over time, and follow airflows over distances further than six feet. Experts describe the movement of airborne virus particles as similar to the particles observed when a smoker exhales cigarette smoke, and they mention that “the distance from a smoker at which one smells cigarette smoke indicates the distance in those surroundings at which one could inhale infectious aerosols” (Prather et al., 2020).

When outdoors, there are a larger number of factors that contribute to spread of infectious particles. For example, viral concentrations will be more rapidly diluted outdoors, ultraviolet radiation from the sun inactivates viruses over time, different viruses are sensitive to the temperature and relative humidity, and the presence of other particles such as dust or pollution can change how viruses travel. Little is currently known about how outdoor characteristics affect SARS-CoV-2, and recovery of virus samples is difficult because collection devices cause damage to the outer shell of the virus. Preliminary studies in mock saliva aerosols have shown that SARS-CoV-2 lost 90% of its viability in 6 minutes of exposure to summer sunlight while it was viable for 125 minutes in darkness (Lewis, 2020). There is evidence that people living in areas with higher concentrations of air pollution have been shown to have higher severity of COVID-19 (Prather, 2020). When pollution is present in the air, it can interact with viruses and modify their aerodynamic properties. Exposure to air pollution may also lead to poorer overall health leading to worse outcomes from COVID-19. As is often the case, more information is required before researchers can differentiate between the scenarios.

**To prevent the spread of aerosol-based transmission, communities will need to practice universal masking and perform regular, widespread surveillance testing to identify and isolate infected individuals who do not have symptoms**. Based on current information, masks provide a critical barrier, and reduce the number of infectious viruses in exhaled breath, especially of asymptomatic people and those with mild symptoms. Studies indicate that surgical mask material reduces the likelihood and severity of COVID-19 by substantially reducing airborne viral concentrations. A real-life example of this protection is described in detail below where two hair stylists with active COVID-19 were in contact with 139 clients. All of the stylists and clients wore masks during their appointments, and none of the clients or other stylists in the salon became sick after prolonged, indoor exposure. Use of well-fitting cloth masks has been shown to have similar aerosol filtering efficiency to that of the medical masks that were tested, meaning that supply shortages of medical grade masks would not prevent the universal use of masks.

### Use of Masks

An analysis from the *Morbidity and Mortality Weekly Report* (MMWR) of the CDC shows that face mask use was able to prevent infections of SARS-CoV-2 spreading from two stylists and 139 clients at a hair salon in Missouri (Hendrix et al., 2020). The incident occurred in May in Springfield-Green County in Missouri where stay-at-home orders had just been lifted. At a hair salon, two of the stylists tested positive for COVID-19 after having served 139 customers over the course of eight days. **In accordance with local recommendations, both the stylists and their clients wore masks, and based on testing and symptom tracking, none of the exposed customers were infected.** Additionally, none of the other stylists at the salon became ill. Based on the timing of the symptoms of the two infected stylists, it was determined that one most likely infected the other as they had several encounters when they had removed their masks to talk. The first stylist had attributed her symptoms to allergy symptoms that she normally experienced at that time of year (Wu, 2020).

Contact tracing was performed by the local county health department for all 139 clients seen after the date when the stylists developed symptoms. None of the clients reported any symptoms in response to daily phone or text messages. All of the clients were offered testing,

and 48.2% of clients volunteered to be tested while the remaining refused testing. All of those who were tested had negative PCR-based test results. The testing occurred at least five days after exposure at the salon, suggesting that viral infections would have been detectable at the time of the test. Close contacts to the stylists from outside of the salon were also followed for contact tracing, and all of the people who were in contact with the first stylist outside of the salon developed symptoms and tested positive for COVID-19, and none of those in contact with the other stylist contacts showed symptoms.

The customers ranged in age from 21 to 93 years, and the length of appointments ranged from 15 minutes to 45 minutes. When clients were asked what type of mask they wore, it was determined that 47.1% wore cloth face coverings, 46.1% wore surgical masks, 4.8% wore N95 respirators, and 1.9% did not know what kind of face covering they wore. One of the stylists wore a double-layered cotton face covering, and the other wore either a double-layered cotton face covering or a surgical mask.

> **Based on the outcome of the situation, the authors from the CDC concluded that adherence to the community's and company's face-covering policy mitigated spread of SARS-CoV-2, and broader implementation of face covering policies could mitigate the spread of infection in the general population.**

### Transmission in Correctional Facilities

Reports of the transmission of SARS-CoV-2 in individuals associated with correctional facilities in the United States have been released by analysts at the CDC in MMRW and researchers from Johns Hopkins University and the University of California, Los Angeles (Njuguna et al., 2020 and Saloner et al., 2020). There has been a wide range of responses and testing strategies in the facilities and a lack of independently collected data that may lead to inaccurate estimations of the situation. There are many facilities that are not testing prisoners and simply relying on visible symptoms for diagnosis, and others are only testing those with symptoms. There have been a few studies using mass testing that indicate that **infection rates have exceeded 65% in some facilities**.

The CDC published a study of the transmission that occurred in a correctional and detention facility in Louisiana between March 29 and May 21 (Njuguna et al., 2020). The first identified case was a staff member on March 29, and two additional staff members and 36 incarcerated individuals tested positive between April 2 and May 7. Those identified as sick were quarantined from the five dormitories where they had been living. On May 7, the Louisiana Department of Health initiated an investigation to determine how widespread COVID-19 was in the population still residing in the five dormitories. PCR-based testing was performed for 98 people in the dormitories, and 71 additional cases were identified, which corresponds to 72% of the individuals in the living areas. At the time of testing, 45% reported no symptoms and 25% had received negative test results during previous rounds of testing. **Based on this information, it was determined that use of symptoms for diagnosis or testing only at a single point in time would not have identified a large number of infected individuals**. Aside from the high number of people who did not have symptoms after infection, use of symptom reporting may be difficult if those being asked do not have an incentive to correctly report. This type of situation has also been observed in scenarios where workers are reluctant to report symptoms for fear of

losing their jobs. Use of serial testing, or multiple tests at different times, allows for increased detection in settings where individuals are in close contact with each other, including other instances such as homeless shelters, long-term care facilities, and college housing.

The researchers from Johns Hopkins and the University of California, Los Angeles collected daily counts of COVID-19 cases and presumed or confirmed deaths in all states, the District of Columbia, and the Federal Bureau of Prisons between March 31 and June 6 (Saloner et al, 2020). As of June 6, the researchers found that there had been 42,107 cases of COVID-19 and 510 deaths. Based on the collected information, the case rate, which is the rate of occurrence of new cases of COVID-19, was 5.5 times higher than that of the general United States population. During the time period of the study, the daily growth-rate of cases was 8.3% per day in prisons and 3.4% per day in the United States population. The death rate from COVID-19 was 1.3 times higher, but there are a smaller number of people over the age of 65 in the prison population, suggesting that conditions in the facilities led to **a higher rate of death for a younger overall population**.

### Transmission at Meat Packing Plants

The CDC has been able to summarize the extent of the outbreaks that occurred at 239 meat packing facilities in 23 states from the start of the pandemic until May 31 (Waltenburg et al., 2020). Overall, there were **16,233 confirmed cases of COVID-19 in workers at the facilities with 86 COVID-19 related deaths**. Some of the data was limited, and for the facilities in the 14 states with complete data, it was found that 9.1% of workers at the facilities were diagnosed with COVID-19. Some of the sites implemented facility-wide testing, and the prevalence of asymptomatic or pre-symptomatic infections among workers was found to be 14.4%. Among 9,919 cases from 21 states where information on race and/or ethnicity was reported, **87% of the diagnosed cases were among racial and ethnic minority workers**. It was reported that 56% of the diagnosed workers were Hispanic, 19% were Black, 13% were white, and 12% were Asian. The number of each ethnic or racial group within the total amount of workers shows that there was a disparity in those that became ill with 39% of the total number of workers described as white, 30% Hispanic, 25% Black, and 6% Asian. The authors conclude that Hispanic and Asian workers might be disproportionately affected by COVID-19 in this workplace setting.

### Transmission from Animal Hosts

Interest in the transmission of SARS-CoV-2 between animals stems from both the need for experiments to learn more about the virus and potential treatments as well as the possibility that animals could become a reservoir of virus that affects transmission to humans.

In order to identify animals that can be used for laboratory studies, one group of researchers has attempted to inoculate fruit bats, ferrets, pigs and chickens with SARS-CoV-2 (Schlottau et al., 2020). Transmission between animals was also investigated where animals were exposed to direct contact with animals who had previously been inoculated. PCR-based testing was used to monitor infection two days, four days, eight days, twelve days, 16 days, and 21 days after inoculation. A subset of the animals were autopsied on days four, eight, and twelve after

inoculation while the rest of the group was autopsied on day 21. The tissues from autopsy were analyzed for evidence of viral infection and antibody production.

Based on the testing, pigs and chickens were not susceptible to SARS-CoV-2. All collected samples in these animals were negative and there was no evidence of antibodies to the virus. A transient infection was detected in 78% of the fruit bats who were inoculated, and one of the three bats exposed by contact tested positive for SARS-CoV-2 infection. The bats were found to have a slight inflammatory response in their nasal cavities, but did not show signs of other symptoms. A high level of viral replication was observed in all of the ferrets who were inoculated, but no symptoms other than a mild inflammatory response in the naval cavity were observed. All three of the ferrets put into contact with inoculated animals tested positive for infection. Based on the results, the authors suggest that SARS-CoV-2 infection in ferrets resembled a subclinical human infection with efficient spread, suggesting that they might serve as a useful model for further studies. Also, the authors report that **there is little risk of transmission to chickens or pigs from infected humans in everyday life, but there is a substantial risk of transmission from contact with bats and ferrets**. Bats differ substantially from humans in immune responses, making them poor models in laboratory testing, but they may be used in tests for potential reservoir of the virus. Ferrets have the most closely related immune systems to humans, outside of primates, and their susceptibility can be useful in testing treatments and vaccines.

## Inflammatory Multisystem Syndrome in Children

The inflammatory syndrome associated with COVID-19 in children that has similarities to Kawasaki syndrome has been labeled multisystem inflammation syndrome in children, or MIS-C, in the United States and paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, or PIMS-TS, in the United Kingdom. There is a slight difference in the technical definitions of the two syndromes, but in this report, the syndrome will be referred to as MIS-C for clarity.

Based on the accumulated evidence from around the world, physicians are more confident that MIS-C is a new syndrome that is associated with previous exposure to SARS-CoV-2 (Branswell, 2020, Davies et al., 2020, and Feldstein et al., 2020). While there are similarities between the previously defined Kawasaki disease and MIS-C, reports indicate that there are important differences (Branswell, 2020). The individuals typically affected by Kawasaki disease are under the age of 5 years while the average age of children with MIS-C was eight years. In a study in New York state, 42% of the group were between the ages of 6 and 12 years. Kawasaki disease is also normally more apparent in children of Asian descent while MIS-C has been observed in children of varying ancestries. Most of those treated in the New York study were of African (40%) or Hispanic (36%) descent. It was also found that treatment to normalize blood pressure was more often required in children with MIS-C than in previous reports of Kawasaki disease with 50% of the United States' cases versus 5% of historical Kawasaki disease cases.

Another report from the United Kingdom suggests that there may be increased severity in symptoms in infants with MIS-C syndrome (Vergnano et al., 2020). The report describes the outcome of seven infants younger than a year who were diagnosed with a Kawasaki-like disease between February and March. The association of the cases to SARS-CoV-2 infection is

currently unclear because five of the seven infants did not have antibodies present to the virus upon testing. The physicians have reported the cases because they were abnormally severe and required higher than normal levels of treatment. **Six of the seven developed coronary artery aneurysms with one child dying due to ruptured aneurysm**. In historical cases of Kawasaki disease, 10 to 20% of infants develop aneurysms while 86% of this group did. The child that died was found to have markedly abnormal coronary arteries with multiple massive aneurysms but no inflammation in the upper or lower respiratory tracts that suggested ongoing respiratory infection. Significant changes in scans of the coronary arteries were also observed in studies that included older children in the United Kingdom and the United States, and severe cardiac symptoms appear to be common with MIS-C.

Together, researchers in the **United States have observed around 300 cases of MIS-C** in previously healthy children who had had COVID-19 up to four weeks previous (Branswell, 2020). Based on an editorial from Michael Levin of the Imperial College London, it is estimated that there have been **around 1,000 cases worldwide as of June 29.**

> **The occurrence of MIS-C continues to be an uncommon complication of SARS-CoV-2 infection, but there is not yet sufficient evidence to determine if there is a subgroup of children more likely to be affected.**

The number of individuals under the age of 21 who developed MIS-C was two in 100,000 while the number of individuals in that group who were diagnosed with SARS-CoV-2 is 322 in 100,000. Based on the accumulated information, physicians suggest that parents and care providers be aware of cases of fever or rash in children who live in areas where SARS-CoV-2 infections are, or were, common. Additionally, children with Kawasaki disease have a higher risk of later cardiac complications, and the physicians in the above studies suggest continued surveillance to identify potential risks in those who have recovered from MIS-C. Other long-term effects may also become apparent due to the severity of symptoms associated with the syndrome.

### Incidence of MIS-C in Adult Patients

**The was also a recent report from New York City of an adult male, aged 45, who developed a COVID-19 associated Kawasaki-like multisystem inflammatory condition similar to MIS-C** (Shaigany et al., 2020). He had cared for his wife who was sick with COVID-19 two weeks earlier and had begun to have symptoms eight days after that. His symptoms included fever, sore throat, diarrhea, bilateral lower extremity pain, eye redness, and a widespread rash. The fever persisted even after use of anti-fever medications in the emergency department where he also tested positive for SARS-CoV-2 via PCR-based testing. Further investigation showed that he had elevated levels of multiple inflammatory markers as well as troponin. Treatment involved use of anti-inflammatory medications, but treatment in the intensive care unit was not required. After use of intravenous anti-inflammatory therapy, there was an improvement in the rash, inflammation of the lips and eyes, and a reduction in the levels of the inflammatory markers. He was discharged from the hospital after nine days and had complete resolution of the skin conditions and eye inflammation as well as a normal echocardiogram. There were no symptoms associated with hypoxic respiratory failure as observed in other adults with severe COVID-19 manifestations.

## Long-Term Effects from COVID-19

There have been numerous accounts of long-term symptoms in people who had even mild cases of COVID-19. Initial reports suggested that mild to moderate cases of COVID-19 lasted around 14 days with full resolution of symptoms. As more people have been infected, this has been found to not always be the case. Online support groups have been started to help people dealing with prolonged COVID-19 symptoms (Re'em, 2020 and Gardner, 2020). Examples of some of the symptoms reported include prolonged low-grade fevers that do not respond to standard fever-reducing medications, neurological manifestations such as memory loss and changes in the ability to recall words in a primary or secondary language, exercise-induced fatigue from walking around the block that led to a relapse of symptoms, symptoms in the central and peripheral nervous systems, gastrointestinal symptoms, skin problems, cardiovascular system occurrences, and others. Most people experiencing these types of prolonged symptoms are not getting support from their doctors due to a lack of treatments, and they also are receiving little support from employers, family, and friends who often imply that the prolonged effects are due to anxiety and psychological manifestations.

An organized study from Italy assessed the prevalence and types of persistent symptoms observed in 143 individuals after discharge from the hospital (Carfi et al., 2020). In order to be included in the study, participants had to meet the WHO criteria for discontinuation of quarantine, which is no fever for three consecutive days, improvement in other symptoms, and two negative test results taken at least 24 hours apart. Participants were also tested at the start of the study, and all of those included tested negative. The mean age of participants was 56.5 years with a range from 19 to 84 years, and 37% were female. The mean length of hospital stay was 13.5 days, and while in the hospital, 15% had received non-invasive ventilation, and 5% of the participants had received mechanical ventilation. The assessment described in the report occurred a mean 60.3 days after the onset of the first COVID-19 symptoms, and 12.6% were completely free of any virus-related symptoms. **The researchers report that 32% of the participants still had one to two symptoms while 55% still had three or more symptoms**. The symptoms described during active viral infection and those that remained after are listed in Figure 1. Additionally, 44% of the participants reported that they had a worsened quality of life since having COVID-19.

Fatigue and shortness of breath (dyspnea) were the most often reported lasting symptoms. The researchers were not able to collect information that described the severity of symptoms experienced during the acute viral infection and therefore were not able to correlate this information.

There have also been a number of reports from individuals, and two physicians who became ill published their experiences (Garner, 2020 and Re'em, 2020). Paul Garner is a professor of infectious diseases at the Liverpool School of Tropical Medicine who had initial symptoms from COVID-19 in the middle of March and continued to have symptoms seven weeks later when he wrote his account. Dr. Garner was never hospitalized. During the initial infection, he experienced a lack of sense of smell, fatigue, tightness in his chest, increased heartrate, an extreme feeling of illness, and difficulty concentrating. The intensity of the symptoms waxed and waned without apparent cause, and additional symptoms appeared, including acutely painful leg

muscles, upset stomach, tinnitus, pins and needles, aching all over, breathlessness, dizziness, arthritis in the hands, and odd sensations in the skin from synthetic materials. Exertion intensified the symptoms.

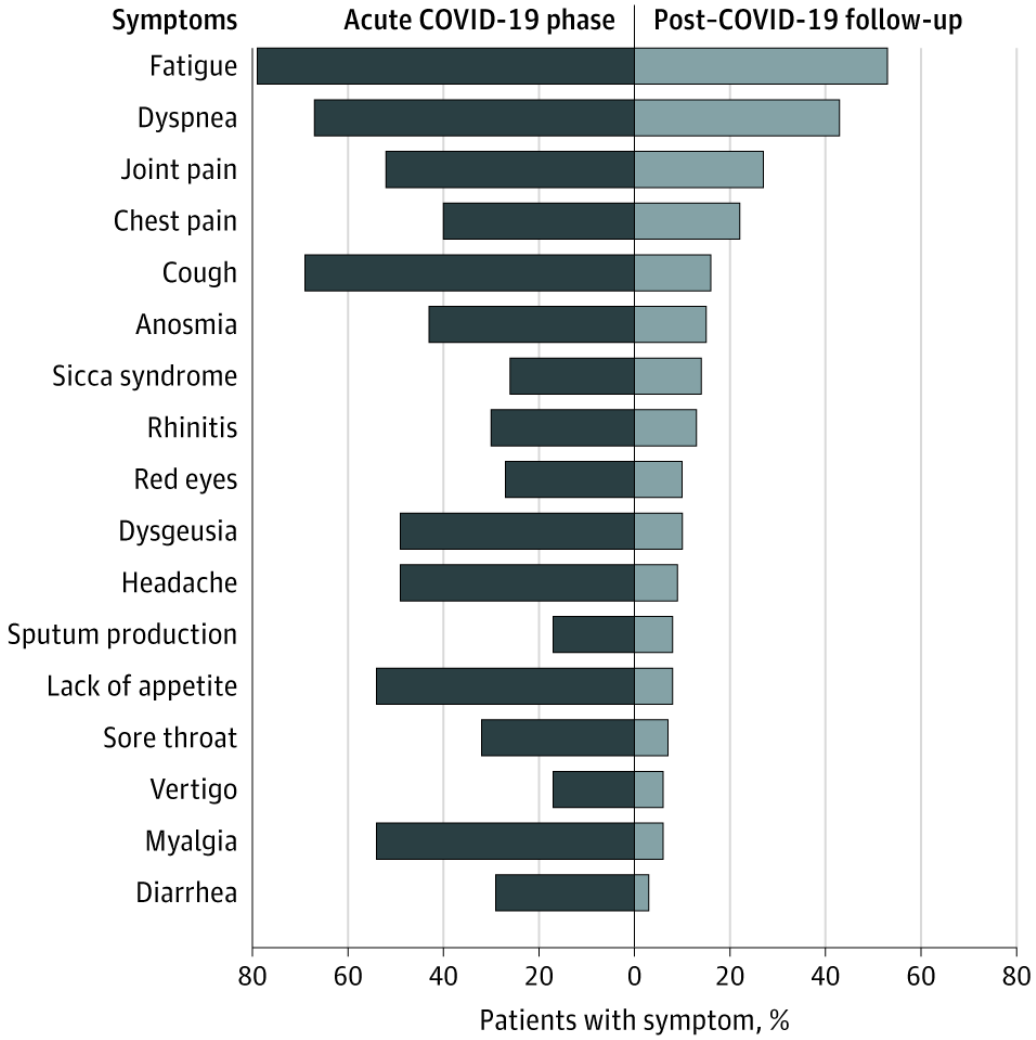


**Figure 1.** Graph of COVID19-related symptoms reported approximately two months after resolution of the active infection. The figure is reproduced from Carfi, 2020.

After several weeks, Dr. Garner described in his letter to the editor that he had returned to normal and had finally stopped having symptoms. A subsequent interview in the *The Atlantic* revealed that after feeling better he did a high-intensity workout and was bedridden for three days with off and on symptoms still occurring. Dr. Garner also mentioned how he has previously had dengue fever, which is nicknamed bone-break fever due to the intense pain associated with infections, and malaria, but COVID-19 was “like nothing else on Earth” (Yong, 2020). When asked what he thought was occurring to cause such prolonged symptoms, he stated “I honestly don’t know. I don’t understand what’s happening in my body.”

Yochai Re'em is a physician and third-year psychiatry resident at New York-Presbyterian Hospital, Weill Cornell Medical Center who first noticed symptoms from COVID-19 on March 14, including low-grade fever, profound leg pain, malaise, and loss of appetite (Re'em, 2020). As of July 8, she has had symptoms for over 100 days, and there has not been any evidence that they are resolving. The main symptoms she has been experiencing over the last four months are intermittent gastrointestinal symptoms, persistently high liver enzymes in the blood, indicating liver damage, and an odd and continuous discomfort in one leg.

The article in *The Atlantic* describes support groups on Facebook, Slack, and other social media groups with thousands of members (one called Body Politic has 3,700) who have had symptoms for months after the initial infection (Yong, 2020). Based on a non-scientific assessment of the group of symptoms described, Ed Yong, the science writer for the *Atlantic*, found that most people experienced "rolling waves of symptoms that make it hard to concentrate, exercise, or perform simple physical tasks." Many of those now affected had what has been designated "mild" symptoms because hospitalization was not required, but they do not describe their experience as mild with many being unable to return to normal tasks such as showering, reading, or grocery shopping even months after infection. The experience of this group of mainly young individuals goes against the description of the disease course initially described. One individual described that before becoming ill she expected that people with COVID-19 were "either asymptomatic or dead," but she is now on day 71 of symptoms and describes this middle ground as "hellish."

A patient-led research study has emerged from one of the early support groups on Slack called Body Politic. A number of the members of the group were also experienced in health topics and research (e.g. participatory design, neuroscience, public policy, data collection and analysis, human-centered design, health activism), and they have begun to collect and distribute data to medical professionals and other COVID-19 survivors to help improve what is known about the long-term effects from the virus. Based on the current information, about 60% of the Body Politic group is between the ages of 30 and 49, 56% were not hospitalized, and 38% were seen in the emergency department but not admitted. Akiko Iwasaki, who is an immunologist at Yale University, suggests that the prolonged symptoms may be a result of a reservoir of infectious virus that is not accessible using current testing methods; of persistent fragments of viral genes, which are not infectious that may still be triggering a violent immune overreaction; or, the possibility he favors, the virus and its components are gone and the immune system is stuck in a lingering, overactive state.

Similar effects have been reported after other large disease outbreaks, and a research study from Australia reported that 11% of people infected with Ross River virus, Epstein-Barr virus, or the bacterium that causes Q fever were diagnosed with a condition called myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). A study describing survivors of a SARS outbreak in Hong Kong stated that 40% had chronic-fatigue problems after three years and 27% met the criteria for ME/CFS. The fatigue, also called post-exertional malaise, results from a severe multi-organ crash following even light activities like a short walk.

The lingering effects are causing further complications with people's lives as it is unknown whether people with symptoms for long periods of time are still infectious. The most concerning symptom on this front is the recurrence of fevers, which is listed on the CDC and WHO

guidelines for discontinuing isolation. People with jobs that require interaction with people or that are in medical fields are asked if their fevers have resolved in order to return to work. A nurse interviewed for *The Atlantic* article has had fevers for 56 days and has not been allowed to return to work.

## Vaccine Development and Antibody Responses

The NIH has announced the establishment of a new clinical trials network specific for COVID-19 that can be used to help with enrollment for vaccine trials and trials to test the efficacy of antibody treatments for the disease (CIDRAP, 2020 and NIH, 2020). The network is called the COVID-19 Prevention Trials Network (COVPN) and can be used to "develop, manufacture, and distribute COVID-19 vaccines, therapeutics, and diagnostics." Through the COVPN, the NIH will be able to coordinate more than 100 clinical trial sites across the United States and standardize protocols to allow for comparison of different potential vaccines.

### CanSino Biologics

The Chinese company, CanSino Biologics, have published two papers describing their vaccine for SARS-CoV-2 (Zhu et al., 2020 and Zhu et al., 2020). The first was published online on May 22, 2020 and described the safety studies, or Phase 1 trials, of the adenovirus vector vaccine that expresses the spike protein of the virus. The second paper describes the Phase 2 trial, which compares the efficacy of the vaccine against a placebo. There were three groups in the trial, two different doses of the vaccine consisting of 382 participants and 126 participants that received the placebo. The vaccine was administered as a single injection, and the production of antibodies against the receptor binding domain as well as the amount of neutralizing antibodies was measured. Evaluation on day 28 indicated that 96% of participants in the lower dose group and 97% in the higher dose group were producing antibodies against SARS-CoV-2. Both groups also produced a statistically significant higher amount of neutralizing antibodies compared to the placebo group. Adverse reactions were reported by 72% and 74% of participants receiving the vaccine. There were severe reactions in 9% of the higher dose group and one severe reaction in the lower dose group.

> **Based on this trial, the authors of the peer reviewed publication conclude that at lower doses the vaccine is safe, and it induced statistically significant immune responses in the majority of recipients after a single immunization.**

Based on the results of the trial, the vaccine has been approved for use by the military in China (Reuters, 2020). The military was approved to use the potential vaccine for one year. Human testing in clinical trials will also be continued in trial sites in Canada and Brazil (New York Times, 2020).

### Oxford and AstraZeneca

Oxford reported preliminary results from a Phase 1/2 trial of their vaccine produced from an adenovirus vector that produces SARS-CoV-2 spike protein, which is called ChAdOx1 nCoV-19

(Folegatti, 2020). The trial includes 1077 participants who either received vaccination with ChAdOx1 nCoV-19 or an unrelated vaccine called meningococcal conjugate vaccine (MenACWY) that is used to vaccinate children against the bacteria that causes bacterial meningitis. The results presented here include a subset of the total participants, and are preliminary while the trial continues to collect additional data. The participants received a single injection and were assessed over 28 days. Ten of the participants who received ChAdOx1 nCoV-19 also received a booster vaccine 28 days after the first administration.

Local and systemic reactions were more common in participants receiving ChAdOx1 nCoV-19, including pain, feeling feverish, chills, muscle ache, headache, and malaise. The reactions were reduced by taking a pain reliever (acetaminophen) before the injection of the vaccine. There were no serious adverse events associated with ChAdOx1 nCoV-19. The amount of antibody against the spike protein of the virus increased up to day 28, and in participants who received a booster 28 days after the first injection, antibody levels continued to increase. A subset of 35 participants were assessed using two different tests to identify the presence of neutralizing antibodies, and the results for the first test indicated that 91% produced neutralizing antibodies while the second test showed that all 100% of the group produced neutralizing antibodies. The tests evaluate different characteristics that resulted in different outcomes. After 42 days, all of the participants who had received a booster were producing neutralizing antibodies as measured by both tests.

**Based on the preliminary results, Phase 3 trials have already begun in Britain, Brazil, and South Africa with another trial site set to open in the United States with enrollment of 30,000 additional participants (New York Times, 2020).**

### Moderna

Moderna had to delay the start of their Phase 3 trial of RNA vaccine candidate they developed for SARS-CoV-2 from July 9, but **the trial is slated to begin July 27 in coordination with the NIH and run in parallel to the Oxford and AstraZeneca Phase 3 trial mentioned above** (Grady, 2020, New York Times, 2020, and Garde, 2020). According to the company, the trial was slightly delayed in order to change the protocol of the trial, a process which is not uncommon in drug development.

The initial results of a Phase 1 trial were criticized due to a lack of data accompanying the announcement of promising results, but the results from the trial have since been published in the *New England Journal of Medicine* (Jackson et al., 2020). The phase 1 trial included 45 healthy adults who received two injections of the vaccine 28 days apart. There were three dose levels with 15 participants in each group. An increase in the amount of antibodies present was observed 28 days after the first injection as well as after the second. After the second injection, the researchers were able to detect neutralizing antibodies in all of the participants. The amount of neutralizing antibodies produced was similar to the amount seen in patients who had recovered from COVID-19. Adverse events that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site. Adverse events were more prevalent after the second dose, and three participants (corresponding to 21%) in the group with the highest dose reported one or more severe adverse events.

A Phase 2 trial of two injections of the lowest and middle dose is currently ongoing, and the Phase 3 trial is expected to utilize two injections of the middle dose, 100 micrograms. The results of the Phase 3 trial are expected to be available by the end of October, but in general, **researchers aren't sure if a single Phase 3 trial will be sufficient to prove the efficacy of any of the potential vaccines**.

**Pfizer and BioNTech**

The FDA granted fast track designation to two vaccine candidates being developed by a partnership between Pfizer and BioNTech (CIDRAP, 2020 and Herper, 2020). Both are RNA-based vaccines that involve injection of genetic material from the virus in the form of RNA, which is then thought to be produced into proteins that stimulate an immune response. Both vaccines include a region of the spike protein of SARS-CoV-2, and one has only the receptor binding domain (RBD) while the other includes the entire spike protein. The FDA designation allows for faster reviews of results from clinical trials.

**Preliminary data from a Phase 1/2 trial was released as a preprint on *medRXiv* and showed promising results.** The results from an additional trial in Germany are expected around the end of July. In the Phase 1/2 trial, 45 patients received a single injection of three different experimental doses of the vaccine or a placebo. The initial doses were to evaluate safety, and it was found that the highest dose (100 microgram) produced a fever in half of participants to receive it (6 of 12). A second dose was not administered for the 100 microgram product. After a second injection of the other dose levels three weeks later, it was found that 8.3% of the participants in the lowest dose group (10 micrograms) and 75% of those in the middle dose group (30 microgram) developed fevers. More than 50% of participants who received a second dose experienced an adverse event, such as fever or sleep disturbance, but none of the events were deemed to be serious.

Analysis of the volunteers' blood showed that antibodies were produced against COVID-19, and some of the antibodies were able to neutralize the virus in laboratory tests. **The level of antibodies produced ranged from 1.8 to 2.8 times the level observed in patients who had recovered from COVID-19.** To show that the vaccine produces immunity, it will be necessary to conduct larger studies where those who got the vaccine are at least 50% less likely to be infected with SARS-CoV-2. After review of the results from the trial, the companies have started planning a Phase 2b/3 trial that will enroll around 30,000 volunteers in order to start as quickly as possible if the FDA approves the current results.

The *Wall Street Journal* reports that the company could have several hundred million doses ready before the end of the year, and they also expect to be able to apply for regulatory approval by the end of 2020 (Pancevski, 2020). With continued production, Pfizer and BioNTech, as well as their Chinese partner Shanghai Fosun Pharmaceutical Co. Ltd., report that they would expect to have produced over 1 billion doses by the end of 2021. The estimated world population as of 2020 is 7.8 billion people. The CEO of BioNTech Dr. Ugur Sahin stated in an interview with the *Wall Street Journal*, that he feels "we will only be done with this virus when more than 90% of the global population will get immunity, either through infection or through a vaccine." **Based on his experience, Dr. Sahin said it might take up to ten years before**

**humanity achieved sufficient immunity to the disease, even if several companies launch a vaccine at the same time.**

### Inovio

Inovio was one of the first companies to announce a potential vaccine for SARS-CoV-2, but detailed results of the initial trials have not yet been published (Garde, 2020). The vaccine candidate uses DNA that codes for protective antibodies. Phase 1 trials were completed, and the company announced that 34 of 36 participants had an immunological response, but further details were not provided, including whether there was evidence of neutralizing antibodies.

### Oral and Nasal Based Vaccines

Companies are also attempting to produce vaccines that are applied to the mucous membranes in the nose, mouth, and gut to protect against SARS-CoV-2 (Wu, 2020). Vaccines delivered directly to the tissue that is infected by the virus are thought to allow for a more robust immune reaction. However, they take longer to produce. An oral polio vaccine was produced in the 1960's, and it was found to be an improvement over the injected version because polio targets cells in the gut. Antibodies produced by injected vaccines are most prevalent in the blood stream, and may take longer to be alerted to virus located in the mucosal membranes of the nose and gut. However, the efficacy of nasal and oral vaccines has been shown to vary more in different individuals than injectable vaccines. For example, Flu Mist is a nasal spray vaccine containing weakened flu viruses, and it has been shown to be more effective than flu shots in young children, but it does not produce as strong an effect in adults. There is also a possibility that the weakened viruses normally used for these applications can cause infection rather than immunity in some people. The oral polio vaccine has been shown to cause polio in a small number of cases due to mutations that occurred. To develop a weakened vaccine, it is necessary to develop a virus that is weak enough to not cause infection, but is strong enough to produce a large immune response.

### Length of Immune Response to SARS-CoV-2

As described in previous PCI COVID-19 Updates, there is growing evidence that the immune response and prevalence of antibodies against SARS-CoV-2 may be transient (Long et al., 2020 and Pollán et al., 2020). As the time from the start of different outbreaks in different areas of the world has increased, researchers are able to start to get an idea of how long the antibody response to the virus lasts. So far, the answer has been only a few months, and those with less severe symptoms have an even shorter time period before the levels of antibodies begin to decrease.

A report released on the preprint server *medRxiv* describes the antibody response of individuals from the United Kingdom (Seow et al., 2020 and Howard, 2020). The researchers did multiple antibody tests over 94 days after the onset of symptoms in 65 participants who had previously been diagnosed with COVID-19 using PCR-based testing as well as 31 healthcare workers. Over 95% of the participants had evidence of antibodies by 8 days after the start of symptoms

and they were also found to produce neutralizing antibodies. **The magnitude of the amount of neutralizing antibodies produced was correlated with the severity of disease, but the rate at which the response waned did not.** Those individuals with higher levels of antibodies retained higher levels for longer than 60 days while those with smaller peak levels had returned to baseline by the end of the study.

> **Based on the results, the authors suggest that SARS-CoV-2 seems to be similar to the seasonal coronaviruses that convey only a temporary protection from reinfection.**

The lack of antibodies in the bloodstream does not necessarily mean that white blood cells called memory cells will not produce more antibodies if there is a repeat exposure to the virus. If this occurs, individuals would likely get a milder case the second time. Each time this occurs, it reinforces the presence of the memory cells and can allow for a more robust response each time.

### Use of Unrelated Attenuated Vaccines for COVID-19

The basis behind the beneficial effect of an unrelated vaccine, such as the **measles, mumps, and rubella (MMR) vaccine and Mycobacterium bovis BCG (BCG) vaccine**, is that vaccination with a live, but weakened, virus causes an increased activation of non-specific components of the immune system. This increased activation may allow for people at higher risk for SARS-CoV-2 infection to mount a larger early response to exposure to any virus. There is also a possibility, say critics, that the increase in immune response could lead to an exacerbation of the cytokine storm associated with severe symptoms of COVID-19 (Johnson, 2020).

A small effect consisting of an improved response to other viral infections has been reported previously for the BCG vaccine, which is used outside the United States to reduce the risk of tuberculosis. The BCG vaccine was routinely administered to all newborns in Israel as part of the national immunization program between 1955 and 1982, and there was greater than 90% coverage during that time (Hamiel et al., 2020). After 1982, the vaccine was only administered to immigrants from countries with a high incidence of tuberculosis. Researchers in Israel looked at the rates of SARS-CoV-2 infection of children who were born in Israel three years before and three years after the change in policy. They found that of 72,060 test results reviewed, 3,064 positive cases were from patients born between 1979 and 1981, and 2,869 were among likely unvaccinated people born between 1983 and 1985. **There was no statistically significant difference in the proportion of positive test results in the BCG-vaccinated group and the unvaccinated group.** The effect from the vaccine may not have still been active as the participants were vaccinated as children and were now between the ages of 35 and 41-years-old. Some officials have commented on the low numbers of COVID-19 cases in areas where the BCG vaccine is more routinely given, but critics suggest that the lower numbers are due to the countries being at an earlier stage in the pandemic before widespread transmission has occurred rather than an effect from vaccination. Pakistan and other countries in this group were reported to have high rates of infections, but lower rates of death from COVID-19 (Johnson, 2020). This situation is no longer the case.

A number of groups around the world have instigated trials to determine if newly vaccinated individuals are protected from COVID-19 by vaccination from the BCG vaccine. In the United States, researchers at Texas A&M have initiated a clinical trial for healthcare workers to determine if use of the BCG vaccine will protect them from the increased risk of exposure to the virus (ClinicalTrials.gov Identifier: NCT04348370). The sites for the trial have been expanded since the start, and 1,800 volunteers are being recruited in Los Angeles, California; Bryan, Texas; and several sites in Houston, Texas.

Researchers at Tulane University in Louisiana suggest that the MMR vaccine may have a beneficial effect as well, but a booster would need to be administered as the beneficial effects wane over time (Fidel and Noverr, 2020). In previous experiments, the researchers found that vaccination with MMR led to an upregulation of non-specific components of the immune system (called myeloid-derived suppressor cells, or MDSCs) and a subsequent inhibition of septic inflammation in the lungs that occurs in acute respiratory distress syndrome, or ARDS, which is also associated with severe COVID-19. This effect was observed in several experimental models and with septic inflammation caused by multiple microbial sources.

> **The authors of the commentary emphasize that "this is strictly a preventive measure against the worst inflammatory sequelae of COVID-19 for those exposed/infected and does not represent an antiviral therapy or vaccine against COVID-19 in any manner."**

According to the researchers, use of the MMR vaccine may be useful because there are few contraindications against administration to adults of a live attenuated vaccine, such as MMR, if the recipient is immunocompetent, is not pregnant, and has not had previous allergic responses to vaccination.

Researchers have also published a commentary in the journal *Science* about the potential non-specific benefits of administering an attenuated, live vaccine, but in this case the authors focus on the live polio virus and live enterovirus vaccines (Chumakov et al., 2020). It was found that use of the oral polio virus in Bangladesh reduced the burden of bacterial diarrheal disease in infants. Studies in Finland reported that the number of middle ear infections was reduced after vaccination with oral polio vaccine, and in Denmark, the use of the oral polio virus was associated with a reduction in the hospital admissions for respiratory infections in children. The authors also cite the observation that when the measles vaccine was introduced in Africa, the overall mortality in children declined by more than 50%, which is larger than that expected from prevention of measles alone.

## Potential Treatment Updates

### Interferons

**Interferons** (IFNs) are a small protein-based molecule that participates in the control of the immune response to microbial infections (Ivashkiv, 2015). There are numerous types of interferons that have been identified that have differing roles in the cascade of events that occurs upon identification of a foreign body by the immune system. Type I IFNs, designated by Greek letters, are secreted by infected cells which leads to three effects on neighboring cells.

When a cell interacts with a type I IFN, they are alerted to potential infectious threat, and there are changes to the cell that make it more difficult for infectious agents, and especially viruses, to infect the cell. Cells also are primed to present foreign bodies for identification by white blood cells, but the production of inflammatory molecules and cytokines are kept at low levels. They also promote the initiation of steps that lead to production of antibodies by B cells and responses to antibodies by T cells.

Researchers have found that there is a correlation with low levels of type I INFs and cases of severe COVID-19 (Hadjadj et al, 2020 and Lee et al., 2020). The researchers have found that the type I IFN response plays a large role in the promotion of inflammation in severe COVID-19. Additionally, it has been discovered that type I IFN deficiencies as measured by blood tests may be indicative of a risk of severe COVID-19. It is still not clear, however if the deficiencies are due to infection by the virus or a characteristic of patients that leads to more severe symptoms.

There have been several types of IFNs that are approved by the FDA for use in treating cancer and hepatitis (Wadman, 2020). In a previous clinical trial published on the preprint server *medRxiv*, use of a daily nose drop of interferon prevented medical workers from contracting hepatitis. Researchers have found that the earlier IFNs are used, the more helpful they are in preventing or reducing the effects of viral infection. However, in the case of COVID-19, there may be a small window of time where they are beneficial after which they may worsen symptoms by contributing to the out-of-control inflammation that is a hallmark of severe COVID-19.

**Synairgen announced positive results associated with the use of its inhaled formulation of interferon beta 1a called SNG001** (Adams, 2020b). The company reported the information in a press release, and data from the study has not yet been made available. The Phase 2 trial included 101 participants who were hospitalized in the United Kingdom for COVID-19 (Synairgen, 2020). In the press release, the company reports that patients receiving SNG001 had a 79% lower risk of developing severe disease, which was defined as progressing from needing oxygen to needing ventilation, compared to placebo. Additionally patients who received SNG001 were more than twice as likely to recover from COVID-19 as those on placebo.

Additional trials are being performed using other formulations of type III interferons that help to boost the immune response to treat the earlier phase COVID-19 where viral replication drives the disease (Wadman, 2020). The trials range from use on those with mild symptoms to use as a prophylactic in people who may have been exposed. The first trial is expected to have results in August.

### Reduction of the Inflammatory Response

There has been further evidence that use of the anti-inflammatory medication tocilizumab is beneficial for treatment of individuals with severe symptoms from COVID-19. In the study, 154 participants with severe COVID-19 who required mechanical ventilation were divided into two groups (Somers et al., 2020). One group, with 78 participants, received treatment with tocilizumab, and the other did not. Participants treated with tocilizumab had a 45% reduction in the hazard of death compared to those not treated with the medication. There was an increase in bacterial infections in the group being treated with tocilizumab, 54% compared to 26%, but

there was not a difference in the fatality rate between the treatment groups in people who developed an infection.

**Overall, the authors conclude that tocilizumab was associated with lower mortality despite higher superinfection occurrence in individuals on mechanical ventilation due to COVID-19**.

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