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Medical Intelligence Report

Date: July 7, 2020

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Topic: COVID-19 Research Update



CDC Broadens Guidance on Those with Increased Risk from COVID-19

The CDC updated its guidance on individuals that may be at an increased risk for contracting COVID-19 or for experiencing severe symptoms (CDC, People, 2020). They have created two risk categories, people at increased risk for severe illness and people who need extra precautions.

People at Increased Risk for Severe Illness	People Who Need Extra Precautions
<ul style="list-style-type: none"> • People with medical conditions • Older adults 	<ul style="list-style-type: none"> • Racial and ethnic minority groups • People experiencing homelessness • Women who are pregnant or breastfeeding • People with disabilities • People with developmental and behavioral disorders

People at Increased Risk for Severe Illness

One of the changes to the category of people at increased risk of severe illness removed the specific age designation previously listed as it has been determined that there is a continual increase in risk that begins between the ages of 18 and 29 (CDC, Older Adults, 2020). The risk for severe illness continues to increase with age as depicted in Figure 1. People over the age of 65 are the most likely to die from the infections, with 8 out of 10 deaths from COVID-19 in the United States occurring in this age group. However, as discussed below, those **who become ill in all age-groups have been shown to have long-lasting and debilitating effects after recovering from COVID-19.**

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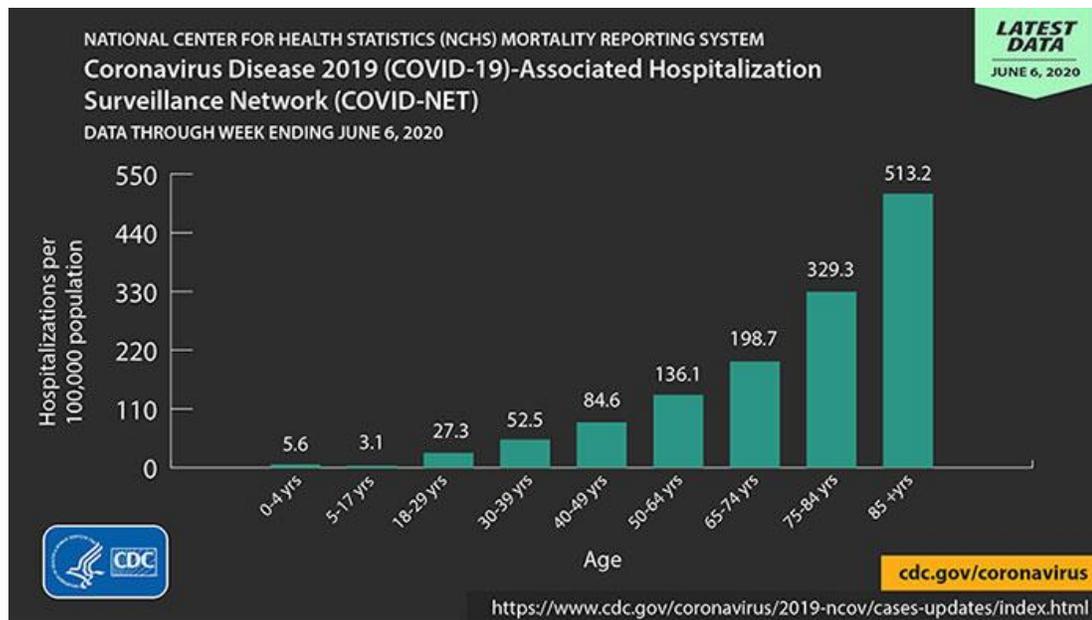


Figure 1. Graph with the number of hospitalizations for COVID-19 based on age. The risk increases with increasing age with an initial increase evident for those between 18 and 29 years.

The change in the CDC guidelines coincides with an increased rate of diagnosis of younger people with SARS-CoV-2 infections (Bosman and Mervosh, 2020). In Arizona, nearly 50% of the cases have been in individuals between the ages of 20 and 44. The median age of people testing positive in Florida has dropped from 65 years in March to 35 years as of June 25. This increase underscores the fact that younger people can be infected by the virus, and as they are more likely to interact with others in their community, they can be a big driver of transmission. The increase in the number of younger people being diagnosed is in part a consequence of increased access to testing, but **the coinciding increases in hospitalizations in areas where the number of cases has dramatically increased indicate that there is also an increase in the transmission rates.** Based on current information, Dr. Robert Redfield, the director of the CDC, stated that earlier in the outbreak many of the cases occurring in younger people went undiagnosed, and he added that “our best estimate right now is that for every case that was reported, there actually were 10 other infections.”

The list of medical conditions that have been associated with more severe outcomes from COVID-19 was also updated (CDC, People of Any Age, 2020). The CDC emphasizes that **people of any age with these conditions are at increased risk.** One noteworthy change was the addition of obesity as a risk factor, which is defined as those with a BMI of 30 or higher.

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**Conditions associated with an increased risk of severe illness from COVID-19:**

- Chronic kidney disease
- COPD (chronic obstructive pulmonary disease)
- Immunocompromised state (weakened immune system) from solid organ transplant
- Obesity (body mass index [BMI] of 30 or higher)
- Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- Sickle cell disease
- Type 2 diabetes mellitus

In an interview with STAT News, the incident manager for the CDC's COVID-19 response Jay Butler asserted that "younger people are in no way completely immune to the effects of SARS-CoV-2 nor are they at zero risk of severe manifestations, and among young people, that risk is elevated in those with underlying illness or health conditions, including things like diabetes or obesity" (Branswell, 2020).

Children with medical conditions have also been found to be at increased risk even though healthy children seem to have a reduced risk from SARS-CoV-2. Specifically, increased risk was observed in children who have medically complex conditions; who have neurologic, genetic, and metabolic conditions; or who have congenital heart disease.

People Who Need Extra Precautions

There are also a number of conditions listed by the CDC that may lead to an increased risk of infection or severe symptoms, but there is insufficient evidence to establish a correlation (CDC, People, 2020). The CDC recommends that people with the conditions listed below take extra precautions to reduce the risk of infection with SARS-CoV-2.

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**List of conditions that require extra precautions:**

- Asthma (moderate-to-severe)
- Cerebrovascular disease (conditions that affect blood vessels and blood supply to the brain)
- Cystic fibrosis
- Hypertension (high blood pressure)
- Immunocompromised state (weakened immune system)
- Neurologic conditions, such as dementia
- Liver disease
- Pregnancy
- Pulmonary fibrosis (having damaged or scarred lung tissues)
- Smoking
- Thalassemia (a type of blood disorder)
- Type 1 diabetes mellitus

Risk of COVID-19 Associates with Pregnancy

A report in the Morbidity and Mortality Weekly Report (MMWR) from the CDC shows that there is an increased risk for severe illness in women who are pregnant, which is a finding that has not been reported previously (Ellington et al., 2020 and Branswell, 2020). **Importantly, 31.5% of pregnant women with SARS-CoV-2 infection have required hospitalization while only 5.8% of non-pregnant women required hospitalization for treatment of COVID-19.**

Additionally, pregnant women were 50% more likely to be admitted to the intensive care unit and had a 70% increase in the risk of requiring mechanical ventilation compared to those who were not pregnant. **The risk of death was NOT elevated with pregnancy** compared to women who were not pregnant. The outcomes for the babies were not reported in this article.

The number of pregnant women admitted to the hospital after testing positive for SARS-CoV-2 may be elevated compared to their non-pregnant counterparts due to a lower threshold for admittance of those who were pregnant, and testing is more likely for pregnant women due to the increased medical care associated with pregnancy. However, the increase in the number of pregnant women admitted to the intensive care unit or put on mechanical ventilation would not be affected by this bias and suggests an increased risk of severe symptoms associated with pregnancy. Similar associations have been reported in other countries as well.

As with other instances of SARS-CoV-2 infection, analysis of those who tested positive showed that pregnant women who are Hispanic and Black were more likely to have COVID-19 than white women. It was found that among pregnant women with laboratory-confirmed SARS-CoV-2 infection 46% were Hispanic, 22% were Black, and 23% were white. Based on the statistical information from 2019, the proportion of women giving birth in the United States was 24% Hispanic, 15% Black, and 51% white.

There is also evidence that the symptoms associated with COVID-19 may differ for pregnant women compared to those who are not pregnant. Pregnant women had a higher likelihood of being asymptomatic than non-pregnant women with a positive test for SARS-CoV-

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2. There was also a lower percentage of pregnant women who had fever, muscle aches, chills, headache, and diarrhea compared to non-pregnant women.

Risk of COVID-19 for Minorities

Additional information has been reported that indicates there is a higher rate and more severe outcomes from SARS-CoV-2 infection in people who belong to ethnic or racial minorities. As previously described, people of African descent who now live in the United States are more likely to be hospitalized for treatment of COVID-19, and emerging studies suggest that Latinos have a higher rate of testing positive for SARS-CoV-2 than other racial or ethnic groups (CIDRAP, 2020).

The New York Times recently reported on statistical information that was only made available by the United States CDC after the newspaper filed a lawsuit (Oppel et al., 2020).

Based on the newly released information, “Black and Latino people have been disproportionately affected by the coronavirus in a widespread manner that spans the country, throughout hundreds of counties in urban, suburban and rural areas, and across all age groups.”

Analysis of the information shows that Latino and Black residents of the United States have been three times as likely to become infected compared to white residents. A large disparity in infection rate was also observed with Native Americans in Arizona compared to white people living there.

In Fairfax County, which is located near Washington D.C., it has been found that 43% of Black and Latino workers are employed in service or production jobs that cannot be done remotely as reported in census data from 2018. On the other hand, about 25% of white workers in the county held jobs that require them to be onsite. Additionally, due to the high prices for housing, Latino families are twice as likely to reside in a crowded dwelling, which is defined as less than 500 square feet per person, as white people, according to the American Housing Survey. **These conditions have led to an infection rate for Latino individuals in Fairfax County who are between the ages of 40 and 59 that is five times higher than white people in the same age group.** There is a higher mortality rate as well, and it was calculated that 25% of the Latino people who died from COVID-19 were under the age of 60 while 6% of white people who have died are under the age of 60.

The information from the CDC highlights the fact that differences in housing conditions and types of employment are driving an increased number of infections in minorities in the United States. As Dr. Mary Bassett of Harvard University and a former New York City health commissioner states, “a big determinant of who dies is who gets sick in the first place” and “infections have been far more prevalent among people who can’t work from home.”

In earlier examinations of the CDC data, severe cases of COVID-19 were found to be associated with underlying health conditions. However, the new information expands the association and suggests that other factors, such as living and employment environments are correlated with infection risk. One of the reasons that the initial data may have been skewed is

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that severe cases are more likely to be reported due to hospitalization of individuals. As mentioned above, current estimates suggest that the number of actual cases of COVID-19 may have been up to ten times the number of reported cases, and the CDC is not able to determine the racial and ethnic characteristics of unreported cases. Dr. Jennifer Nuzzo from the Johns Hopkins School of Public Health states that the additional data released in response to the New York Times lawsuit means that the previous association between COVID-19 and underlying health conditions or poor health in minority individuals is more tenuous.

In order to obtain complete information from the CDC, the New York Times filed a Freedom of Information Act lawsuit requesting the race, ethnicity, and county of residence of every person who tested positive, which was about 1.5 million people at the time. The information was originally missing for hundreds of thousands of individuals. The CDC blames the lack of information on the reporting system used to collect information. The main onus is on state and local health officials to report detailed information, but these groups are often overwhelmed by the volume of cases and lack the resources to investigate everyone who falls ill.

Hospitalization Rates in Atlanta, Georgia

A recent analysis of people in Atlanta diagnosed with COVID-19 published in the MMWR from the CDC showed that residents who are Black were more likely to require hospitalization than white residents (Killerby et al., 2020). The report indicates that 79% of those hospitalized identified as being Black. The information on hospitalization rates was collected from six hospitals in the Atlanta metropolitan area. Other characteristics that were found to be associated with an increased rate of hospitalization included older age (over 65 year), diabetes, lack of insurance, male sex, smoking, and obesity (BMI over 30). Hypertension was not found to be associated with hospitalization in this study. The authors describe the disparity as arising from the difficulty in separating similar conditions that are associated with hypertension. When the data was evaluated based on underlying conditions, the researchers found that **diabetes had the highest association with hospitalization** compared to other medical conditions.

One important distinction from previous reports is that when the influence of underlying medical conditions is removed from the analysis the association between an increased rate of hospitalization for Black individuals was still present. This result indicates that **underlying conditions alone do not account for the higher rate of hospitalization among Black individuals**. Other factors that have been identified that may contribute to the high rate of hospitalization include differences in health care access, social determinants of health, or the possibility of bias. Based on the information obtained in the analysis, the authors suggest that measures to prevent infection with SARS-CoV-2 should be emphasized for persons at highest risk for hospitalization with COVID-19. They also point out that there may be potential barriers for people who fall into these high-risk categories to adhere to measures that reduce the likelihood of infection.

SARS-CoV-2 Infection Rate in Latinos in the United States

In a recent study conducted by the Johns Hopkins University School of Medicine and published in JAMA, researchers found that 40% of the Latinos in the Baltimore/Washington D.C. region

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who were tested for SARS-CoV-2 received a positive result (CIDRAP, 2020 and Martinez et al, 2020). During the time period between March 11 and May 25, 37,727 people were tested in the five hospitals and 30 outpatient clinics that are part of the Johns Hopkins Health System. From this group, 16.3% (corresponding to 6,162 individuals) tested positive for SARS-CoV-2. The positivity rate for Latino individuals was 42.6%, which was higher than that found for both the Black individuals tested (17.6%), the white individuals tested (8.8%), or those who identified themselves as another race or ethnicity (17.2%). Of those who tested positive, 35.9% of the entire group were admitted to the hospital. The admission rate was lowest for Latino individuals at 29.1% compared to white individuals (40.1%) and Black individuals (41.7%). Comparisons of characteristics of the hospitalized group indicate that Latinos hospitalized with COVID-19 were younger (a greater proportion aged 18 to 44 years), more likely to be male, and had lower rates of hypertension, congestive heart failure, pulmonary disease, and chronic obstructive pulmonary disease than white or black patients. Because of the limited information available to the researchers, they were not able to determine the cause of the increase in the number of Latino individuals testing positive for SARS-CoV-2, but there were two possibilities that they suggest may be likely based on knowledge of the region's population, either a higher disease prevalence, differences in access to health care (eg, reluctance in seeking care), or both.

Similar trends have been observed in California and other areas around the United States, which are attributed to the increased exposure due to employment and domestic environments (Hubler et al, 2020). **The CDC reports that Latino individuals are 18% of the United States population, but they account for 34% of the COVID-19 cases.** There are a large number of Latino residents with COVID-19 in California, Florida, and Texas, which is not surprising based on the demographics of these regions. However, Latinos have also been shown to have a higher level of SARS-CoV-2 infections in regions where they make up a lower percentage of the overall population. For example, in North Carolina, the Latino population is 10% of the total population, but they represent 46% of the SARS-CoV-2 infections. The large outbreak currently occurring in Yakima County, Washington is also has a disproportionately large number of Latino individuals. Politico has reported that Latinos account for roughly 34% of reported coronavirus cases nationally, which is currently the highest of any racial and ethnic minority group, and they make up a **disproportionate share of the cases in nearly every state.**

The stark increase in cases is very visible in California where Latinos account for 39% of the population, but 57% of new cases at the end of June were in Latino individuals. Generally, California has been able to implement and maintain limits on social interactions based on cell phone data collected in the region, and **infection rates in affluent neighborhoods with high numbers of Latino residents have remained low.** This situation suggests that the increased infection rates are based on employment in industries that have not shut down during the outbreak, such as manufacturing, food-processing plants, farm hands, hospital orderlies, food preparers, supermarket workers. In San Francisco, researchers tested around 4,000 people in a four block area of the Mission District. Of those tested, 40% were Latino and 41% were white. However, less than 1% of the white people tested were positive for SARS-CoV-2. Latinos who lived in California were found to have lower infection rates than other racial and ethnic groups early in the timeline of the pandemic (April), but the proportion of Latinos infected quickly **increased** when community lockdowns went into place.

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Race and Income as a Risk-Factor COVID-19

A federal analysis of Medicare billing was released on June 22, and it shows that income is correlated with risk for COVID-19 (Goldstein, 2020). Based on the assessment, the investigators found that Black Americans are more likely to test positive for the virus and to be hospitalized for treatment. Out of every 100,000 United States residents on Medicare, 731 Black people were infected, compared with 380 Hispanics, 281 whites, and 256 Asians. There was a similar pattern observed with people requiring hospitalization for COVID-19, and 332 out of 100,000 Black individuals on Medicare required treatment in a hospital, compared with 124 Hispanics, 95 Asians, and 88 whites.

It was also found that people who have an income under the threshold to also qualify for Medicaid were four times more likely to have been infected or hospitalized with the coronavirus compared to wealthier individuals using Medicare.

CDC Recommendations for COVID-19 Testing

On June 13, the CDC consolidated and updated their recommendations on testing for SARS-CoV-2 (CDC, CDC Releases, 2020 and CDC, Overview of Testing). Previously, the recommendations had been spread throughout the CDC website, and the changes allow for easier access and the most relevant information. There were not any major changes to the content, but the recommendations are more specifically described.

Diagnosis of active infection with the virus should be performed with tests that detect RNA from the virus using PCR-based methods, which are the most common type of diagnostic tests, or with antigen-based tests that detect other components from the virus that are present in respiratory fluids.

Antigen-based tests allow for the reliable detection of virus components such as proteins, but these types of tests are not yet widely available. Becton, Dickinson and Company, or BD, received Emergency Use Authorization from the FDA on July 6 to begin using an antigen-based test that uses a machine that is already in place in many laboratories and provider offices around the country (BD, 2020).

The length of time before the results of a test are available is dependent on the platform used, and some tests can be read at the point of care within a few minutes while others must be sent to external laboratories. The accuracy of a test is not necessarily dependent on the time it takes for the results, but there have been reports that some specific brands of tests, e.g. those from Abbott Laboratory, are less reliable when a negative result is reported. **Generally, positive results from diagnostic testing are the most accurate while negative tests should be evaluated based on known exposures and symptoms to determine if a second test should be performed.** The possibility of getting a false negative result from two diagnostic tests is low, and negative results on two tests suggest that an individual is not currently infected.

Antibody testing is not currently recommended for diagnostic purposes, and antibody, or serological testing, is not authorized by the FDA for diagnosis of COVID-19. For medical treatment, antibody testing may be used to determine if current symptoms are part of a post-

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infectious syndrome, such as Multisystem Inflammatory Syndrome in Children, which becomes evident after recovery from the viral infection. Researchers and healthcare workers also use serological testing to develop models of viral spreading and to test blood samples for use as a treatment, e.g. convalescent plasma. The use of antibodies tests to ascertain immunity from previous infection is not recommended because the tests have a high rate of false positive results, and it is not currently known what conditions produces immunity from SARS-CoV-2. Antibody protection from the seasonal coronaviruses that cause colds every year are short-lived and last only a few months while antibodies from SARS and MERS have been detected for longer. It is not possible to predict how the body will react to SARS-CoV-2 based on this evidence, and only time will allow scientists and healthcare workers to determine if and how long immunity lasts after recovering from COVID-19. Two reports were published on preliminary results of antibody testing of large populations, which are described in detail below.

As testing has become more available, the recommendations for who should be tested have expanded. There are two broad categories of testing for active infections with PCR-based tests being performed at this time, diagnostic and surveillance. **Diagnostic testing occurs in individuals with symptoms or a known exposure to someone who is sick. Surveillance testing is conducted among asymptomatic individuals without a known exposure to SARS-CoV-2 for early identification, to detect areas where high levels of transmission is occurring, or to characterize disease trends.**

The CDC recommends consultation with your healthcare provider to determine if symptoms are compatible with COVID-19 because there is a wide variation in symptoms between individuals. Early in the pandemic, testing for influenza was used to rule out SARS-CoV-2 infection, but it has since been determined that it is possible to have both viruses at the same time, called co-infection, and a positive test for the flu does not exclude the possibility of infection with another virus. Testing of asymptomatic individuals should be performed for those who have had close contact with someone known to have COVID-19. **Close contact is defined as being within six feet of someone for 15 minutes or more or if there is direct contact with respiratory fluids, such as a cough in the face.** The CDC also recommends testing of all babies whose mothers had COVID-19 at the time of their birth. Testing of asymptomatic individuals may also be warranted when there are circumstances that have been linked to a superspreading event, such as workers in meat packing plants, nursing homes, correctional facilities, or large groups where social distancing was not followed.

Testing is now also recommended for determination of the resolution of infection. As the number of available tests has increased, the CDC recommends using serial testing, which means multiple tests at different times, to determine when isolation is no longer required to prevent transmission of SARS-CoV-2. When testing is limited, the CDC recommended isolation until individuals have had a normal temperature for 72 hours without use of medication, there is an improvement in respiratory symptoms, and at least seven days have passed since symptoms first appeared. If testing is available, isolation can be ended after resolution of fever without the use of fever-reducing medications, an improvement in respiratory symptoms, and two negative results from an approved PCR-based COVID-19 test.

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Testing Frequency for Surveillance Programs

A recent preprint report from researchers at the Harvard School of Public Health in Boston, Massachusetts found that more frequent testing is of higher importance in gauging the extent of a local outbreak using surveillance-based testing than tests with a higher sensitivity to detect the virus (Nature, 2020 and Larremore et al., 2020).

Based on their results, the authors conclude that **surveillance testing of asymptomatic individuals can be used to limit the spread of SARS-CoV-2**. The needs for successful surveillance testing are different from those of diagnostic testing of people with symptoms. Cost is less important for diagnostic testing because fewer people will be tested in this manner. Also, quick turnaround times are less important because those with symptoms can isolate in the interim until the results are available. With surveillance programs, a delay of a day can meaningfully reduce the effectiveness because people without symptoms can spread SARS-CoV-2. Having tests that detected lower amounts of RNA, which occurs early and at the end of the infection, did not help increase the effectiveness of surveillance, and increasing the sensitivity of detection can lead to increases in price for the testing.

The frequency of testing and speed at which the results are reported are more important than detecting very low levels of viral RNA early in the infection period. When testing frequency was increased in the model, surveillance programs were able to limit viral spread by reducing both the number of people who each person infects and the total number of infections that occur. A reduction in the amount of time before the results were returned also led to better containment of transmission. Models were examined where results were returned immediately, within a day, and within two days. Delays in receiving testing results led to less effective control of viral spread, and there were only small benefits from improving the detection of very low levels of viral RNA.

Community Transmission in the United States

Community transmission has been increasing dramatically in some parts of the United States. **On July 6, the New York Times reported that over the last 14 days, there has been an 84% increase in the number of new cases in the United States** (Oppel et al., 2020).

Increased Incidence and Reemergence of Shortages

The increased number of cases in certain regions of the United States have led to a return of shortages of tests, medical supplies, and strain on the healthcare system. On a worldwide level, the WHO COVID-19 Situational report for June 23 showed that there is exponential growth in the number of new cases (JHU, 2020). The length of time for the number of cases to increase has dramatically shortened.

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**The timeline of the COVID-19 pandemic's worldwide trajectory:**

- Zero cases to 1 million cases : approximately **100 days**
- 1 million to 2 million cases: **12 days**
- 2 million to 3 million cases: **13 days**
- 3 million to 4 million cases: **12 days**
- 4 million to 5 million cases: **11 days**
- 5 million to 6 million cases: **10 days**
- 6 million to 7 million cases: **8 days**
- 7 million to 8 million cases: **8 days**
- 8 million to 9 million cases: **6 days**

In the United States, the CDC is reporting the highest daily incidence of new cases so far in the pandemic with 37,667 new cases on June 26 and 44,703 new cases reported on June 29. The five day average during the last days of June had four of the five highest number of new cases recorded during the pandemic. The Johns Hopkins Center for Health Security reports in their situation report that “the United States’ daily incidence has nearly doubled since June 9, up from 20,338 new cases per day to 38,006 (7-day average).” The number of new cases is rising in 23 different states in the United States. The outbreaks have been found to stem from gatherings at churches, college athletes returning to campus, bars, strip clubs, casinos, fraternity rush parties, and continued transmission in industries where workers are in close contact, such as apple packaging facilities and a vegetable packaging facility (Mervosh et al., 2020).

The overall increase in cases may be partly due to increased levels of testing in the United States, but the concurrent increase in the number of hospitalizations and changes in the rate of positive tests being reported indicate that transmission has increased.

However, using other methods to assess the extent of transmission and sickness that do not rely on testing makes it evident that certain regions of the country have transmission rates that are higher than the local infrastructure can provide for.

For example, the rate of positive tests is higher than 10% in Arizona, South Carolina, and Alabama. The WHO recommends a positive test rate of around 5%, and at this level, it is estimated that most of the cases in a community would be identified. Higher positive testing rates suggest that there are additional cases in the community that are not being recognized.

Some hospitals in Texas, Arizona, and Florida are reporting that all of the available space to treat patients is full, and in Yakima County in the state of Washington, patients are being transferred to other areas due to a lack of available capacity to treat people with COVID-19. The Governor of Texas has suspended elective surgeries in counties around San Antonio, Dallas, Houston and Austin where the number of hospital admissions has risen by 66%, 136% and 426%, respectively, since the end of May (Sun and Achenbach, 2020 and Tozzi et al., 2020). In Florida, 75% of available hospital beds in the state were reported to be full as June 18, and numerous individual hospitals reported there was no availability at all at their facilities. Two of the hospitals in Palm Beach reported all intensive care unit beds were filled (Czachor, 2020).

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The number of deaths per day has been falling since the number of cases in New York and surrounding areas began to fall, but experts warn that due to the manner COVID-19 progresses, there is a lag of several weeks between the increase in the number of infections and the number of deaths. After symptoms first appear, most people do not develop serious symptoms that require treatment at a hospital for about five days, and after being admitted to the hospital, the amount of time before needing mechanical ventilation or care in an intensive care unit is an additional five days or so. People have required ventilation for weeks at a time, and death may not occur from COVID-19 for more than 2 months after a confirmed diagnosis.

Shortages are again being reported for testing supplies and medical supplies to treat sick individuals. In Arizona, testing sites have not been able to keep up with demand (Kliff, 2020). At one site in Phoenix, all 1,000 testing slots per day are normally taken within seven minutes of the phone lines opening. The largest medical laboratory in the state received 12,000 tests on June 19, which is twice the number that can be processed in one day with all their machines running every day and all day. Even testing from hospitalized individuals in Arizona may take more than a day before the results are available, and treatment with SARS-CoV-2 specific treatments cannot be initiated until a positive test is received.

The bottlenecks being reported are similar to those reported earlier in the pandemic, including a lack of the machines needed to run more tests, difficulties hiring workers to staff laboratories and test sites, and a fragmented system that makes it hard for hospitals and doctor's offices to coordinate with facilities that could handle excess volume. There are also still worldwide shortages of supplies for collecting samples. The laboratories in Arizona ordered more machines to run tests in May, but they are not expected to arrive until July. When a surge happens, the demand at labs for testing has been shown to double or triple within a matter of days, and there is no system in place to accommodate the sudden increase and not enough time to seek partnerships with others to meet the demand. While on a nationwide scale there have been improvements in resources, there is also not a system to identify shortages and shift needed supplies to new areas where outbreaks are occurring.

There has been criticism of public officials who explained that the initial lockdown in the United States was in part needed to allow for preparations to be put in place to manage future outbreaks because it appears that those preparations have not occurred (Joseph, 2020). There is a lack of contact tracing ability throughout the country and a lack of needed guidance and resources. Epidemiologists in Arizona have said that health authorities were using the time bought by the lockdowns, but that the enforcement of social distancing was not for long enough to build the capacities needed or to train new people for roles as contact tracers.

A shortage in medical supplies is also of great concern, and there have been reports about shortages of medical oxygen that is vital for treating respiratory symptoms associated with COVID-19 (Schnirring, 2020). The WHO estimated that for treatment of 1 million new cases of COVID-19 there is a worldwide requirement for 20,000 cubic meters of oxygen each day, or the equivalent of 88,000 large cylinders. A shortage of the machines to concentrate oxygen from the atmosphere is being seen in many countries. Additionally, personal protective equipment is still being reused due to lack of resources in hospitals. In Kentucky, one nurse reported he had been wearing his N95 mask for two weeks until it finally broke, and a replacement was not expected for three days (Tozzi et al., 2020). The White House Supply Chain Task Force has projected that there will be a shortage of protective gowns in June and July. The supply of

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surgical masks, nitrile gloves, and face shields is expected to meet the demand through July, and estimates suggest that there will be sufficient N95 masks up until October. Further projections past these estimates were not provided, and the recent increase in cases may reduce the supply more quickly than anticipated.

Transmission at Hospitals in the United States

A report from the Wall Street Journal details the difficulty hospitals in the United States are having in preventing spread in the people who work there (Gold and Evans, 2020). While this type of spread is most likely occurring around the country, the article focuses on the University of Illinois Hospital in Chicago, which saw its first COVID-19 patient in the beginning of March. **By the middle of June it was estimated that more than 260 workers at the hospital had tested positive for the coronavirus while nationwide there have been 5,142 reported cases of COVID-19 that are thought to have been acquired in hospitals by patients between May 14 and June 21.** There has not been publicly reported in-house infection rates of the staff of hospitals by the CDC. It has been difficult to monitor cases that are acquired in the hospital due to a two-week long incubation time in some individuals, transmission from those without symptoms, and a lack of tests or inaccurate tests that kept officials from identifying contagious patients. This type of situation requires a heavy reliance on personal protective equipment, which was not available at sufficient levels for months, and some areas are still experiencing shortages.

Hospitals are now beginning to reopen as well, and postponed procedures are being allowed. There is a real concern over the risks of delayed treatments, as evidenced by the three-fold increase in cardiac arrest outside of hospitals in New York City from March 1 to April 25 that is attributed to people not coming to the emergency room when they were experiencing symptoms (Van Beusekom, 2020). It has been estimated that 42% fewer people went to emergency departments in April of 2020 compared to April, 2019 (Keshavan, 2020). The number of deaths that have occurred when emergency medical service personnel are present has doubled, which suggests that people are waiting until circumstances are dire before calling the paramedics. The National Cancer Institute has estimated an additional 10,000 deaths in the United States over the next decade due to delays in diagnosis from the pandemic.

Misleading Claims from High-Ranking Officials

Public health experts have been sending out a single, overlaying message about COVID-19 from the start of the pandemic, “Until there is an effective vaccine, we need to use the measures we have — masks, some distancing, and reasonable steps to reduce infection — to try to keep the virus in check” (Herper, 2020). However there has been a disturbing trend of some government officials to provide misleading information to downplay the seriousness of the ongoing SARS-CoV-2 pandemic. This includes claims that the majority of coronavirus cases are not serious, which has been labeled as not true by numerous health experts (Wagner, 2020 and Facher, 2020). There have also been claims that the virus will disappear from the population as occurs with influenza, which has also been refuted by public health experts and by the continued increase in new cases being reported throughout the country.

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Experts in the United States and other countries have also brought attention to the sense of resignation about the current state of affairs being touted by officials who seem to suggest that there is little that can be done to stem the transmission of the virus. However, countries around the world with similar demographics, such as Italy, Spain, and Germany, have controlled their outbreaks even after having large outbreaks and high rates of COVID19-related deaths. The basis of their approach has been increasing the availability and speed of testing, isolating people when they are sick to prevent further transmission, avoiding crowds and close contact with other people, frequent hand-washing, and use of face masks to reduce transmission (Sun and Achenbach, 2020).

Government officials have attempted to get the media and the public to focus on encouraging signs while using statistics that are different from those used by researchers and highlighting only portions of reports in a manner that makes the information seem more positive. For example, it was stated at one meeting of officials that only 12 states have had an increase in the number of cases, which does not agree with information from multiple other sources. Other groups reported that 23 states were seeing an increase at the time of the meeting, and more recent reports show that 39 states are currently experiencing increased rates of new cases (NPR, 2020). CNN reported that only two states (Connecticut and Rhode Island) were reporting a decline in the number of cases as of June 28 with 36 states reporting increased incidence (Maxouris and McLaughlin, 2020). On July 5, 13 states reported new highs in their seven-day case averages, with Montana, Delaware and Alaska experiencing the biggest percentage change from their past records. West Virginia also set a record number of daily cases, with 130 (Hawkins et al., 2020).

The increase in new cases is being attributed by some as a result of increased levels of testing or due to the release of a large number of results on a certain day (a test dump). These explanations as to why the number of new cases has been rising are not supported by examination of the number of people requiring treatment for COVID-19 and the recent increases in the positive testing rate observed around the country. The Johns Hopkins University Coronavirus Resource Center reports the seven day average of the positive testing rate for each state, and the averages, as of June 30, of some of the states that have experienced large outbreaks are listed below. Updated information on testing in individual states can be accessed at the JHU website, <https://coronavirus.jhu.edu/testing/individual-states>.

Table 1. Seven day average of the positive testing rate as of June 30 for states with large outbreaks.

State	Positive Testing Rate
Arizona	24.4%
Texas	14.1%
Florida	14.3%
Louisiana	7.9%
North Carolina	7.7%
California	5.9%
New Mexico	3.3%
Illinois	2.7%
New York	1.1%

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At the height of the outbreak in New York, the positive testing rate was at 50% due to a lack of available testing resources. Available tests were used to test the population that was highly likely to be infected, leading to a very high positivity rate (Nuzzo, 2020). Laboratories in the state were able to do around 20,000 tests a day with a peak of more than 10,000 new cases confirmed each day. Currently, laboratories in the region are able to process more than 50,000 tests a day and the positivity rate is below 2% with around 600 to 700 new cases a day. Increased testing does not lead to an increase in the number of positive tests if enough tests are being conducted to capture all of the individuals who are sick. This threshold is around the 5% positivity rate recommended by the WHO. In the middle of May, the positivity rate in Florida was reported to around 4%, suggesting that testing had been at a level able to identify the sick individuals in the state (Cunningham and Firozi, 2020). The positive rate is now up to around 14%, which suggests that increased testing has not led to increased numbers of new cases, but rather an increase in transmission is occurring.

The number of people seeking treatment for COVID-19 has also been increasing. The National Syndromic Surveillance Program, which monitors emergency department visits for COVID-19 symptoms or influenza-like symptoms, has reported that as of the week ending on June 20, 2020 (the most recent data published), there have been an increasing percentage of emergency room visits for the first time since April, which coincides with the peak of the outbreak in New York and surrounding areas. The information provided is categorized based on regions of the country designated by the Department of Health and Human Services, and three regions saw an increase, South East, South Central, and South West/Coast. The Mountain region also saw a slight increase in the number of visits for COVID-19 symptoms, but not influenza symptoms, and the Mid-Atlantic and Central regions saw a slight increase in reported visits to the emergency room for influenza-like symptoms, but not COVID-19 symptoms. There is a large amount of overlap in the symptoms for both, and the influenza-like illness reporting system is being used to track trends of COVID-19 illness as well.

Reports on July 5, show that South Carolina, Texas, Arizona, Nevada, and California reported record numbers of current COVID-19 hospitalizations (Hawkins et al., 2020). The mayor of Austin, Texas stated in an interview that there will not be enough medical personnel to keep up with the spike in cases if the rate of increase continued unabated, and he stated that the city is within two weeks of the hospitals being overrun. The mayor of Houston also reported a similar timeline for the Houston area, and he mentioned that the demand for testing has exceeded the area's supply with the testing positivity rate rising from 10% to 25%.

There have also been claims that even though the number of cases in the United States is rising, the mortality from COVID-19 is not (Phillips, 2020). This viewpoint disregards the lag observed between an increase in confirmed infections and deaths as mentioned above.

Arizona

There has been a large amount of discussion about the manner in which state officials and the governor of Arizona handled the reopening of the state and the contribution to the current increase in new cases in the state. Many of the decisions made did not conform to the official recommendations released by the White House such as waiting to reduce social distancing

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measures until there was a 14-day decline in the number of new cases (Duda et al., 2020). The governor accelerated the planned reopening as the President visited, and remarked at a news conference during the announcement of reopening that a chart displaying an increasing number of new cases “doesn’t really tell you much.” There was also controversy over the ending of the partnership between the state and the university modeling team that depicted a rising caseload in Arizona. Soon after, top health officials acknowledged having changed the testing count to include viral tests confirming an infection and serology tests determining the presence of coronavirus antibodies, which would have artificially lowered the positivity rate announced at the announcement of Arizona’s reopening. The governor has also prevented local officials from setting local rules for the use of masks and social distancing against the recommendations and gone against the recommendation of the CDC to use a mask when social distancing is not possible.

World Health Organization

A group of 239 researchers and other experts have submitted a letter to the journal *Clinical Infectious Diseases* in criticism of the World Health Organization’s (WHO) lack of response to the possibility of airborne spread of SARS-CoV-2 (McAuley and Rauhala, 2020). The letter is to raise awareness about the growing evidence of indoor spread through aerosols with smaller amounts of virus needed to cause infection. The authors of the letter do not suggest that the mode of transmission of the virus has changed, rather that airborne transmission has been occurring since the beginning of the outbreak. However, they feel that even though it has been difficult to unequivocally identify airborne particles, the amount of other types of evidence is sufficient to warrant a change in measures to control the pandemic.

Other experts around the world have criticized the WHO for its lack of a consistent message regarding asymptomatic transmission and the use of masks by the general public. The WHO was the last major group to recommend the use of cloth masks for the general public when social distancing was not possible. Lawrence Gostin, a professor of global health law at Georgetown University who provides technical assistance to the organization, spoke with the Washington Post and said that “the public, and even scientists, will lose full confidence in WHO without clearer technical guidance”.

Adding to the skepticism is the way in which the WHO withheld criticism of case numbers and transmission reported by China. China has been known to report false information in order to present a more positive view of the government of the country, and WHO officials defended the reported statistics from China and praised the Chinese President for his leadership in the early days of the pandemic. Some felt that the director-general of the WHO was simply being diplomatic because the WHO is not able to compel China to provide accurate data or to collect their own information. However, experts were and are concerned that the attention over the response to China undermined the other aspects of coordinating a response to pandemic.

Former United States Government Officials Call for a Science-Based Pandemic Response

On July 6, 57 previous officials from the Trump, Obama, and George W. Bush administrations released a statement calling for a science-based approach to the coronavirus pandemic

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(Abutaleb, 2020). The group would like to use the results from research studies and collected data to help make decisions on the production and allocation for personal protective equipment and ventilators. They also promote the release of data on new cases, deaths, and hospitalizations that would be easy for outside experts to use and analyze. There are also recommendations to support inspectors general throughout the government so that they can protect the public trust without retaliation, to ensure that data collection methods within federal agencies is transparent and easily accessible, and that federal employees be allowed to speak on their fields of scientific expertise without interference from political officials.

Viral Shedding and Immune Response in Asymptomatic Individuals

A study in China followed 37 asymptomatic individuals who were diagnosed with COVID-19 based on PCR-based testing who remained without symptoms for the entire length of their illness (Long et al., 2020). The characteristics and outcomes were compared to a similar group of 37 individuals diagnosed with COVID-19 who exhibited mild symptoms during their illness. The researchers found that there was extended viral shedding for those without symptoms, up to 19 days, compared to 14 days for those with mild symptoms. The information was collected with PCR-based tests, which can detect viral RNA, but not determine if there is infectious virus present.

However, the most compelling discovery was the differing level of immune response between the two groups. **Those without symptoms had a lower level of virus-specific antibodies compared to the symptomatic group. The levels of neutralizing antibodies specific for SARS-CoV-2 also decreased more quickly for those who did not have symptoms during their illness.** During the time period right after illness, symptomatic individuals had a 96.8% reduction in the amount of IgG antibodies (the type of antibodies that persist after illness) and a 62.2% reduction in neutralizing antibodies. Those who had a milder case of COVID-19 without symptoms had larger reductions in antibody levels, and the researchers reported a 93.3% reduction in IgG and an 81.1% reduction in neutralizing antibodies.

Importantly, eight weeks after testing negative for the virus 40% of individuals who were asymptomatic during their illness became seronegative where antibodies targeted against SARS-CoV-2 could no longer be detected.

Fewer individuals who had symptoms during the infection became seronegative, only 12.9%, but in both cases this result suggests that **a number of people who have had COVID-19 may not retain immunity after infection.**

Based on their study, the researchers conclude that a high proportion of individuals who recovered from SARS-CoV-2 infection have a decrease in the amount of IgG levels and neutralizing antibodies **within 2 to 3 months after infection.** This result has also been observed in a smaller study of eight individuals where four of the participants had a decrease in the amount of neutralizing antibodies around six to eight weeks from the onset of illness.

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Percentage of Spanish Population who have been Exposed to SARS-CoV-2

After a large outbreak early in the worldwide pandemic, health officials in Spain released the results from a nationwide antibody study to determine how much of the population had been exposed to SARS-CoV-2 (Pollán et al., 2020 and Reuters, 2020). The study involved the testing of 70,000 people three times during April, May, and June. The prevalence of antibodies indicates that 5% of the Spanish population was exposed to the virus, and the number of people exposed has not changed by a large amount since May. There were higher levels of prevalence in urban areas, such as Madrid, where the rate ranged from 10% to 13%. **Even with the large and sudden outbreak that overwhelmed the healthcare system in the country, the results of the study suggest that around 95% of the population of Spain is still vulnerable to infection by SARS-CoV-2.**

Another sobering outcome of the study was that **14% of participants who tested positive for antibodies in the first stage subsequently tested negative in the last stage, which suggests a waning immunity with the disappearance of the antibodies targeted to the virus.** The reduction in antibodies occurred most often in those who did not develop symptoms, which is similar to the results reported by Long and colleagues in the Chinese study mentioned above. Recent resurgences have occurred in the Catalonia and Galacia regions of Spain, leading government officials to re-implement lockdowns in the regions.

Worldwide Implications of Antibody Testing

Based on the results in Spain, as well as other countries, most of the world's population appears to have remained unexposed to SARS-CoV-2, even in areas with widespread virus circulation (Eckerle and Meyer, 2020). There have been proposals to achieve herd immunity of the community through natural infection, but the available evidence indicates that virus circulation would most likely accelerate to a point where transmission was uncontrolled, leading to unsustainable use of healthcare resources. Additionally, the people most likely to be affected are those described above who are unable to work from home and who live in more vulnerable environments. This highly unethical proposal would also put the 1.7 billion people worldwide with at least one underlying health condition associated with more severe outcomes from COVID-19 in danger (Wu, 2020).

Remdesivir

The company who manufactures remdesivir is beginning trials of a formulation of remdesivir that can be administered using a nebulizer (Wu, 2020). This would be an improvement because currently, the medication is only available by intravenous administration, which means it is limited to use in a hospital setting. Remdesivir seems to be most effective early in the infection from SARS-CoV-2 and before life-threatening symptoms have developed. Researchers would like to use the medication for individuals at multiple early stages of COVID-19 and possibly before there is a need for hospitalization. The company reported that they expect to begin Phase 1 trials of the inhaled form of remdesivir in COVID-19 patients by August (O'Day, 2020).

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Anti-inflammatory Treatments

Additional anti-inflammatory treatments are being identified that help reduce the severity of symptoms for hospitalized individuals with COVID-19. The effect of two additional medications, colchicine and tocilizumab, were published, and both were found to improve the outcome of individuals who were hospitalized with severe COVID-19 (Guaraldi et al., 2020 and Deftereos et al., 2020). The identification of additional medications allows for expanded treatment options, especially in the event of shortages of one particular drug.

Colchicine is an anti-inflammatory medication used most often for the treatment of gout. In the study, 105 individuals hospitalized with COVID-19 from 16 hospitals in Greece between April 3 and April 27 received either standard medical treatment or colchicine with standard medical treatment (Deftereos et al., 2020 and CIDRAP, 2020). After treatment, more individuals taking colchicine had a reduction in the level of inflammatory markers in the blood than those receiving standard care. There was also an increase in the event-free survival time for individuals taking colchicine from 18.6 days in those receiving standard care and 20.7 days in those receiving colchicine. Based on the information collected during the study, the authors conclude that there was a statistically significant improvement for participants who received colchicine in the time to clinical deterioration.

Tocilizumab is an antibody medication that targets interleukin-6 (IL-6), which is one of the cytokines that is involved in the over-activation of the immune response with severe cases of COVID-19 (Guaraldi et al., 2020). The medication is normally used for treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, and life-threatening cases of cytokine release syndrome. This study investigated the effects of tocilizumab on individuals with severe COVID-19 pneumonia who were admitted hospitals in Bologna and Reggio Emilia, Italy, between February 21 and March 24 or at a hospital in Modena, Italy, between February 21 and April 30. The study included 544 individuals, and 179 were treated with tocilizumab and the remaining individuals received standard care. The choice of study groups was not randomized, which could affect the outcomes as the people chosen to be treated with tocilizumab was based on physician assessment and is subject to biases associated with that process. Tocilizumab can be administered intravenously or by subcutaneous injection, and both methods were used in this study. The intravenous dosage is higher, and injections were used in cases where the intravenous form was not available. It was observed that 16% of the people in the group receiving standard care required mechanical ventilation while 18% of 88 individuals treated intravenously with tocilizumab and 19% of 91 individuals given tocilizumab injections required mechanical ventilation. In the group receiving standard care, 20% died compared to 7% of the group being treated with tocilizumab (7% intravenous administration and 8% subcutaneous administration). The authors reported that use of tocilizumab was associated with a reduced risk of invasive mechanical ventilation or death, and both forms of the medications were effective for treatment of severe COVID-19.

As has been mentioned previously, researchers have observed that illness associated with SARS-CoV-2 infections seems to have two phases (Rabin, 2020). In the first phase, viral replication causes mild symptoms, and the severity of infection can be reduced by reducing the replication of the virus. In the second phase, symptoms and damage to the body are due to dysregulation of the immune system, which can be countered by use of anti-inflammatory medications. Anti-inflammatory medications also reduce the immune response, which is less of

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a concern later in COVID-19 because viral replication is less important. However, use of anti-inflammatory medications can disrupt the initial immune response to the infection and lead to worse outcomes when taken early for COVID-19.

With this in mind, researchers and providers are concerned about inappropriate use of anti-inflammatory medications for COVID-19. In the paper by Ledford and colleagues at Oxford University mentioned in the last PCI Update, dexamethasone was beneficial for those who had been sick for more than a week and reduced deaths by one-third among patients on mechanical ventilators and by one-fifth among patients receiving supplemental oxygen. However, those not receiving respiratory support died at a slightly higher rate than those not given the drug (Rabin, 2020). **Based on this evidence, experts have agreed that dexamethasone cannot be used to treat mild illness, or as a preventive measure.** Therefore, use of dexamethasone is not recommended for treatment of COVID-19 in anyone who is not being treated in a hospital. There have also been shortages developing for the medication, and hospital orders for dexamethasone increased by 186% from normal levels on the day that the Ledford study was released, and between June 16 and June 19 hospital orders increased by 610%.

Symptom Updates

The range and extent of symptoms and long-term consequences associated with COVID-19 are astonishingly broad and have been found to affect an increasing number of bodily systems.

COVID-19 Associated with New Cases of Diabetes

There is emerging evidence that SARS-CoV-2 infection may lead to development of new cases of diabetes (Rubino et al., 2020 and Mallapaty, 2020b). Researchers had previously noted the association between people with diabetes and severe cases of COVID-19, but the new information suggests that SARS-CoV-2 may also cause diabetes to develop and aggravate existing cases. COVID-19 has been found to lead to conditions such as diabetic ketoacidosis, where blood sugar levels are very high and the amount of toxic substances called ketones increases. Cases of hyperosmolarity, where the blood contains extremely high blood sugar levels which require treatment with very high levels of injected insulin, have also been associated with COVID-19. These types of complications have also been observed previously in other infections from other viruses.

However, there is additional concern about new cases of diabetes that have been observed in people who have recovered from COVID-19. The journal *Nature* describes the case of an 18-year-old who had tested positive for the virus in the middle of April after his parents became ill, but he had no observable symptoms. Early in May, the young man began to show symptoms of type-1 diabetes, mainly fatigue and extreme thirst, and he was subsequently diagnosed with the condition. When researchers examined his blood, they were surprised to find that the typical type of white blood cell responsible for damaging the insulin-producing cells in the pancreas was not present. Instead, the researchers suspect that the virus was responsible for the damage to the insulin-producing cells. This effect was also observed during the SARS outbreak. In one study of individuals with SARS, 20 of the 39 participants were reported to have type-1 diabetes while they were hospitalized, but after three years only two of the participants

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remained diabetic (Yang et al., 2010). Insulin-producing cells in the pancreas have been found to produce high amounts of the ACE2 receptor, which SARS-CoV-2 uses to infect cells, the receptor is thought to be the means by which the virus damages pancreatic cells. There is also evidence of an immune response to SARS-CoV-2 that might lead to death of the insulin-producing cells (Mallapaty, 2020b).

In order to better establish whether there is a link between developing diabetes and COVID-19, researchers have set up a database to log cases of patients with Covid-19–related diabetes.

Neurological Complications Associated with COVID-19

There is also increasing evidence of significant neurological complications associated with SARS-CoV-2 infection. A recent analysis of databases established at the beginning of April in the United Kingdom showed that cerebrovascular events are occurring in relation to COVID-19 (Varatharaj et al., 2020).

As of April 26, complete clinical datasets were available for 125 participants, which indicated that 62% had a cerebrovascular event at the time of evaluation for hospital admittance. The breakdown of cerebrovascular events showed that 74% had an ischemic stroke, 12% had an intracerebral hemorrhage, and 1% were found to have central nervous system vasculitis.

The researchers also reported that 31% were found to have an altered mental status at the time of admission, with 23% of participants found to have unspecified physical changes that altered mental state (encephalopathy) and 18% of participants with encephalitis (inflammation of the brain). Of those with an altered mental status, 59% participants fulfilled the clinical case definitions for psychiatric diagnoses.

Changes in mental status occurred about equally in those below and those above the age of 60 years while cerebrovascular events were more common in those over the age of 60 (82% of participants).

Altered mental status in hospitalized patients is not uncommon. However, those affected are typically older individuals. The authors report that there were a disproportionate number of neuropsychiatric symptoms in younger patients while most of the cerebrovascular complications were observed in older patients. Because of the manner in which the database was constructed, the cases included likely represent the most severe cases in the United Kingdom, and the correlation within all cases may not be the same, but the results confirm the growing number of reports of severe neurological complications associated with COVID-19 that is in addition to the respiratory symptoms that are the main cause of death (Joseph, 2020).

SARS-CoV-2 Infections in Animals

As of yet, there has been little evidence of transfer of SARS-CoV-2 to animals from humans and then back again to humans (Santini et al., 2020). There have been reports of infections of dogs, cats, and tigers, but the cycle did not lead back to human infections. Infection with SARS-CoV-2 has been documented to be possible in a variety of mammals, including monkeys, ferrets, cats,

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and hamsters during laboratory-based research efforts to study the virus and develop potential treatments. There is also analysis of the genome of different species that suggests that rabbits, sheep, goats, pigs, cattle, and horses may be susceptible to SARS-CoV-2 based on the sequence of their ACE2 receptors, and bats are known to be susceptible to multiple coronaviruses. There have been conflicting results on the infectivity of mice, rats, and squirrels with SARS-CoV-2.

Researchers from both Spain and the Netherlands have recently reported that there may have been spread from humans to minks and back to humans on farms that raise the animals. Researchers are worried that these occurrences may indicate the possibility of the establishment of reservoirs of the virus that would allow for repeated reemergence of outbreaks, which did not occur in previous coronavirus pandemics such as SARS.

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