PINNACLECARE

Medical Intelligence Report

Date: June 23, 2020

Topic: Update on COVID-19 Research

Potential COVID-19 Treatments

Dexamethasone

The results of a clinical trial investigating the effects of the steroid dexamethasone on severe symptoms from COVID-19 were announced in a press release and are expected to be published soon (Ledford, 2020 and Kupferschmidt, 2020). Dexamethasone is a readily available steroid that helps to reduce the inflammatory response associated with some illnesses. The trial was part of a larger trial called RECOVERY being performed in the United Kingdom to investigate the effects of a number of potential COVID-19 treatments. In the section testing dexamethasone, 2,100 participants received the drug at a low-to-moderate dose for 10 days, and the outcome was compared to 4,300 people who received standard care for coronavirus infection. The overall mortality rate for all patients given dexamethasone was reduced by 17% (Oxford University, 2020). When the researchers looked at the results of different groups within the trial, they found that **dexamethasone had the biggest effect on those who were the most sick**, which is a group that has not been helped in COVID-19 treatment trials thus far. There was a one third reduction in the number of deaths for the participants who were on ventilators and received dexamethasone. For participants who were receiving supplemental oxygen, there was a reduction in the number of deaths by one fifth. There was no effect on patients who did not require oxygen or ventilation. The results are somewhat surprising because in previous experiences with coronaviruses, the use of systemic steroids was found to have a negative effect on health rather than positive. In clinical trials with MERS, there was an increased amount of time before the virus was cleared from participant's systems due to the immune dampening effect of steroids. However, this result supports the current hypothesis that people who have progressed to severe COVID-19 symptoms are most affected by the extreme inflammatory response, or cytokine storm, rather than effects from replicating virus. Earlier in the progression of COVID-19, antiviral medications seem to be more useful at reducing the reproduction of viruses in the cells of the body.

Mavrilimumab

Another drug that reduces the inflammatory response associated with COVID-19 was published in the journal *Lancet Rheumatology* (De Luca et al., 2020). The treatment, called mavrilimumab, is an antibody-based treatment that reduces the inflammatory response controlled by a type of

white blood cells called macrophages. There were 39 participants in the study who had severe COVID-19 pneumonia, hypoxia, and systemic hyper-inflammation, and 13 received mavrilimumab while 26 received standard care at the same hospital. Participants were observed over 28 days, and none of the people who received mavrilimumab died while 27% of the control group died. By the end of the trial, all of the participants who received mavrilimumab had evidence of clinical improvement, and 65% of the participants who received standard care had evidence of clinical improvement. By day 28, one patient in the mavrilimumab group (corresponding to 8%) progressed to mechanical ventilation compared with nine patients in the control group (corresponding to 35%) who progressed to mechanical ventilation or died. After 14 days, ten of the eleven participants with a fever in the mavrilimumab group were no longer feverish (corresponding to 91%) while 61% of those with a fever in the control group no longer had a fever. Individuals in the control group did receive other experimental medications for the treatment of COVID-19, including hydroxychloroquine, azithromycin, and lopinavir–ritonavir. While these medications have not been found to have a beneficial effect when used for COVID-19, further study is needed for a comparison with a better matched control group.

Other similar drugs under investigation to reduce the effects of inflammation in COVID-19 include tocilizumab and anakinra, which have also shown promising results in preliminary trials (Favalli and Caporali, 2020). However, the amount of these types of medications that is currently manufactured may not be sufficient to treat the number of patients in need from the COVID-19 pandemic due to the relatively limited current use of the drugs for autoimmune and inflammatory diseases. They also are expensive and difficult to make compared to dexamethasone. Dexamethasone affects inflammation throughout the body while mavrilimumab, tocilizumab, and anakinra specifically target the inflammatory response resulting from cytokines. However, this specificity does not seem to be needed with COVID-19 based on the results described above.

FDA Withdraws the Emergency Use Authorization of Chloroquine

Based on several reports of non-effectiveness, the FDA revoked the Emergency Use Authorization of both chloroquine and hydroxychloroquine for the treatment of COVID-19 (Farzan et al., 2020 and Travis, 2020). In their announcement, the reason for the withdrawal was based on evidence that the drugs were unlikely to be effective. The national treatment guidelines have now been changed so that the use of chloroquine and hydroxychloroquine is not recommended for COVID-19 outside of a clinical trial.

Outpatient Monitoring

Not all people with COVID-19 require hospitalization, but the symptoms can quickly become more serious suggesting that monitoring by a health professional is warranted (Kricke et al., 2020). Providers at Feinberg School of Medicine at Northwestern University in Chicago, Illinois assessed the utility of a monitoring program to assess patients daily, provide advice, and facilitate additional care for those with concerning, worsening, or severe symptoms. The program included 93 nurses, 70 advanced practice professionals, 152 medical students, and 115 attending physicians to care for about 1000 patients per day using an electronic health

record registry. As of May 21, 6,853 individuals had been through the monitoring program, which allows for a reduction in the burden on primary care facilities.

In order to utilize resources and reduce the burden on active practitioners, medical students whose programs were suspended were supervised by primary care physicians, specialists, and other physicians who were quarantining after COVID-19 exposure, could not do face-to-face work based on personal risk, or were recently retired. People were included in the registry if they had a pending COVID-19 test, a positive or indeterminate COVID-19 test, or presumed presence of COVID-19 based on clinical criteria, and inpatients with COVID-19 were not enrolled. At 6 a.m. each day, enrolled patients with an electronic health record account received a questionnaire invitation to evaluate how the infection was affecting them based on the severity of ten symptoms, the amount of fever reducing medication (e.g. Tylenol) they had taken, and a temperature reading. If there was no response by 11 a.m., the enrollee had responded with concerning symptoms, or the participant did not have access to the electronic health record account, members of the group would make a follow-up call. Patients with severe symptoms, including shortness of breath, confusion, signs of hypoxia, or persistent chest pain or pressure, were referred to the emergency department, and if needed, an ambulance was called. On average, the symptoms of those being monitored remained mild, and around 20% a day reported concerning symptoms with around nine people each day going to the emergency department. About one third of those identified as eligible did not sign up for the service, and about 20% of those who did sign up did not respond to the questionnaire each day.

Antibody Therapies

Several articles were published describing the progress of research to develop an antibody treatment that could be used to treat COVID-19. This type of treatment utilizes antibodies produced by an animal or in cell culture that can neutralize SARS-CoV-2 infection of cells rather than stimulating a person's own immune system to produce antibodies. Scientists are pursuing two avenues to develop antibody treatments. One pathway uses antibodies from people who have recovered from COVID-19 to identify those that are most effective at neutralizing the virus. Other groups are utilizing knowledge about the life cycle of the virus along with three-dimensional structures of parts of the virus to determine where antibody binding would be the most effective.

The effectiveness of antibodies is expressed in a measurement called **antibody titer**. To determine this value, a sample of the antibody is exposed to the component it interacts with, also called an **antigen**. For COVID-19, the antigen is often the spike protein located on the surface of the virus. Laboratory testing measures the binding of the antibody to the antigen. The sample is then serially diluted and tested for binding to the antigen again. The titer is the amount of dilution where the binding of the antibody is no longer detected. Stronger antibodies are able to bind to antigens even at very low amounts, so a stronger antibody can be diluted more than a weak antibody. Titers are expressed as ratios of the dilution, e.g. 1:500 where the value signifies one unit of the original sample diluted into 500 units. The larger the ratio the stronger the antibody. For example, an antibody with a titer of 1:50 is weaker than an antibody with a titer of 1:1000.

Interaction Site of Neutralizing Antibodies

Scientists were able to isolate specific antibodies from recovered patients that bind to the spike protein on the surface of SARS-CoV-2 (Brouwer et al., 2020). In cell culture studies, the antibodies were shown to have a high level of inhibitory effect on the infection of cells by SARS-CoV-2. The researchers were able to determine where the antibodies were binding to the virus, which indicates areas where the virus is vulnerable to intervention and can be used to improve targeting of potential treatments. The information can be used for development of both antibody therapies and vaccine development.

The Characteristics of Neutralizing Antibodies Varies Between Individuals

In a study published in the journal *Nature*, plasma from 149 participants who had recovered from COVID-19 was evaluated to determine the antibody titer and the amount of antibody produced by each individual in response to SARS-CoV-2 (Robbiani et al., 2020). Testing was performed on antibodies that targeted the spike protein of SARS-CoV-2. The measured antibody titer varied greatly between individuals. It was found that 78% of the participants had produced antibodies that specifically targeted the receptor binding domain (RBD) of the spike protein, and 70% had produced antibodies to the spike protein in the three-dimensional form where three copies of the protein are stuck together, called the trimeric spike. The antibody titer of neutralizing antibodies was found to be low compared to the values measured for other viruses, and 33% of the participants' neutralizing antibodies had titers of 1:50 or lower, 79% had 1:1000 or below, and only 1% had 1:5000 or above (corresponding to only two participants). The amount of antibodies produced was correlated with the strength of neutralization as measured by the antibody titer, and those with stronger neutralization of the virus were produced at higher levels.

Antibodies from Recovered Patients can Stop SARS-CoV-2 Infection in Hamsters

The largest study investigated around 2,000 different antibodies harvested from the plasma of people who had recovered from COVID-19 (Rogers et al., 2020). The ability of plasma from recovered patients to neutralize SARS-CoV-2 was tested, and the plasma from eight participants was selected for expanded evaluation. The cells that produce the antibodies in the plasma were collected so that specific antibodies of interest could be produced in the laboratory. From this group, 2,045 antibodies were produced, and 92% were able to be tested for interaction with virus proteins. After testing, 43% interacted only with the trimeric spike protein while 5.9% bound to both the trimeric spike protein and RBD proteins, and 0.1% bound only to RBD. There were 33 antibodies that had desirable characteristics and were studied further. **The most potent neutralizing antibodies were found to bind to a specific section of the RBD, and antibodies that bind to the trimeric spike protein outside of the RBD were found to have poor neutralizing ability**. Two antibodies identified by the experiments were then tested in hamsters as a potential treatment for COVID-19. The hamsters were treated with five different amounts of the two antibodies and then infected with SARS-CoV-2. It was found that treatment with the antibodies led to reduced symptoms from SARS-CoV-2 infection, as measured by weight loss in the animal, and a reduced amount of virus in the lung tissue. The effect was dependent on the dose of antibody given, and higher doses had a more pronounced effect.

Use of Antibody Cocktails

One concern with the use of antibody therapies is that mutations of the virus over time may lead to a reduced effect of the treatment (Baum et al., 2020). In order to prevent this occurrence, researchers utilize a mixture of different antibodies with slightly different targets. One group investigated the efficacy of antibodies from previously infected mice and humans to work individually or as a group as the virus was grown for several generations in cell culture. The antibodies used were targeted against the spike protein of the virus, and when used individually, the virus mutated to avoid the neutralizing effect over several generations. **The researchers found that utilizing the antibodies as a group prevented mutations that allowed the virus to avoid the effects of the antibodies if the antibodies targeted different parts of the spike protein**. Those antibodies that interacted with the same regions did not protect from mutation.

Another group used a combination of antibodies produced by mice and human patients who had recovered from COVID-19, which is a strategy that has been employed previously for diseases including Ebola (Hansen et al., 2020). The antibodies produced were targeted against the spike protein of the virus, and several were identified that had strong neutralizing capabilities. A selection of neutralizing antibodies were further characterized to allow for identification of the area on the spike protein that interacts with the antibody. This knowledge allows researchers to include antibodies in a treatment that interact with different parts of the spike protein to improve efficacy and potentially avoid mutation by the virus. **Regeneron, the company involved in this study, is organizing a clinical trial to test the effectiveness of the antibodies identified in this study**, and it is described below.

Antibodies that Neutralize Multiple Types of Coronaviruses

Because of the relationship between different coronaviruses, there is also a potential that antibodies produced in response to infection by one of the viruses may provide protection against infection by the others. This effect could be important both for the development of a treatment for COVID-19 and for possible future outbreaks. Researchers investigated the characteristics of 200 antibodies isolated from the plasma of a person who had recovered from the previous outbreak of SARS (Wec et al., 2020).

The antibodies interacted with several areas on the spike protein of SARS-CoV-2. There was a class of antibody that bound to the spike protein, but did not elicit a neutralizing effect, which was attributed to antibodies reactivated from a past seasonal coronavirus infection. The researchers identified several different antibodies that were able to neutralize SARS-CoV-2, SARS-CoV, and a third related virus from bats. **There were eight antibodies from the SARS patient that neutralized SARS-CoV-2 infection in cell culture, and the antibodies interacted with the RBD, and, more specifically, the part of the spike protein that interacts with the ACE2 receptor on human cells.** The researchers also determined that binding of the antibodies to the ACE2 receptor region of the spike protein led to premature modification of the spike protein, rendering it unable to bind and infect cells. The researchers were able to produce the three-dimensional structure of how the antibodies bind to the spike protein using electron microscopy. Based on their results, the authors summarize that all of the

neutralizing antibodies interact with a single patch on the surface of the RBD. **The antibodies are able to potently neutralize different types of coronavirus, including SARS-CoV, SARS-CoV-2, and a third virus specific to bats**. This cross reactivity suggests that this surface is very similar among the SARS-like coronaviruses.

Clinical Trial of Antibody Therapy

Regeneron announced that it is beginning a series of clinical trials to test the effect of an antibody mixture for the treatment of COVID-19 (Dall, 2020). The trial is organized to include placebo-controlled trials of the antibody cocktail, called REGN-COV2, at multiple sites in four different populations: hospitalized COVID-19 patients, non-hospitalized patients with COVID-19 symptoms, uninfected people in high-risk groups such as healthcare workers, and uninfected people in close contact with infected patients. The preclinical results of testing are described by Hansen and colleagues and is described above. REGN-COV2 contains two antibodies that bind to the RBD of the virus. The antibodies were initially produced in mice in response to SARS-CoV-2 infections. The therapy is based on previous therapies the company has produced to treat Ebola.

Calculation of the Fatality Rate of COVID-19

Researchers and officials have been attempting to answer the question of the severity of COVID-19 compared to other diseases, but the calculation used to measure this characteristic, called the infection fatality rate, is determined by evaluating the number of infected people who die of the disease (Mallapaty, 2020). Therefore, accurate information on the number of infected individuals is required, and this statistic has been difficult to determine due to problems with testing and the large number of people with mild to no obvious symptoms who are hard to identify. Further complicating the calculation is the fact that people with COVID-19 can be ill for a very long time, and the time between infection and death can be as long as two months. **The most recent calculations suggest that between five and ten people will die for every 1,000 people infected with SARS-CoV-2, which is an infection fatality rate between 0.5% and 1%.** This value differs when applied to different groups of people, however, and some portions of the population, such as those with underlying, chronic conditions, have a higher chance of dying. For example, a study in Switzerland found that the infection fatality rate for the total population was 0.6%, but the rate for people aged 65 or older was 5.6%. Officials state that determining an accurate infection fatality rate helps to determine the correct level of response so that communities are not underprepared or forced to endure lock-down situations that are not needed.

Physiological Effects of COVID-19

Identifying Blood Serum Changes in Patients with Severe COVID-19

Researchers evaluated the characteristics of blood serum from people with COVID-19 to determine if there were components that correlated with the severity of disease (Shen et al, 2020). The researchers compared the protein and metabolic components of blood serum from

46 people who had had COVID-19 and 53 who had not. They also compared the possible differences between those with severe symptoms and those with milder symptoms. Based on the comparison they were able to identify changes in the blood serum that correlate with the development of more severe symptoms.

Specifically, they found that there was

- Dysregulation of macrophage cells (a part of the inflammatory response to illness)
- Changes in platelet degranulation (release of cellular components from platelet cells that increase the inflammatory response)
- Disruption in complement system pathways (part of the immune system that enhances the ability of antibodies and cells to clear microbes and damaged cells from an organism, by promoting inflammation, and attacks the pathogen's plasma membrane
- Massive disruption of metabolic pathways of lipids and amino acids in the liver.

Based on their assessment of the results, the authors suggest patients with COVID-19 should be monitored for changes in platelets during treatment. Additionally, measures to suppress the complement system may reduce the intensity of the inflammatory response that occurs in some people. There was also evidence that drugs that suppress the production of lipids (e.g. statins) may disrupt the formation of new virus, a process that requires high levels of cholesterol in cellular membranes to form correctly.

Gastrointestinal Symptoms and Fecal Transmission

While COVID-19 mainly effects the respiratory system, there is mounting evidence of an effect on other systems in the body. A recent analysis of the literature published in *JAMA* indicates that between 10% and 12% of people with COVID-19 experience gastrointestinal symptoms, including diarrhea, nausea, and vomiting (Parasa et al, 2020). The authors also report that the presence of gastrointestinal symptoms are correlated with a more severe disease course. In one study, individuals without gastrointestinal symptoms were more likely to recover and be discharged compared with those with gastrointestinal symptoms (60% versus 34%). There is also evidence of damage to the liver based on changes in the amount of liver proteins in the blood. When the liver is damaged, specific types of proteins, called enzymes, are released into the blood stream, and abnormal amounts of the enzymes are correlated with damage to the organ.

It has also been determined that between 30% and 50% of people with COVID-19 have been found to have viral shedding in their feces, which suggests that the virus is able to infect cells in the gastrointestinal system. There is also a possibility that the virus can be transmitted via feces to other people.

Genetic Analysis of Individuals with COVID-19

Researchers have been attempting to determine if there are genetic characteristics that may contribute to the wide variation in the effect of infection with SARS-CoV-2 (Ellinghause et al., 2020). To this end, a clinical trial was reported in the *New England Journal of Medicine* investigating the genetic differences between 1610 people with respiratory failure from COVID-19 in Spain and Italy and 2205 participants who had donated blood and did not have COVID-19.

One of the genetic regions (called a locus) identified is named 3p21.31 and contains six genes (SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1). The researchers found that people who received mechanical ventilation were more likely to have mutations in the genes located in this locus compared to individuals who required oxygen supplementation but not ventilation. SLC6A20 encodes for a protein called sodium-imino acid (proline) transporter 1 (also called SIT1) that has been found to interact with the ACE-2 receptor, the receptor on human cells that interacts with the virus during infection of the cell. Other genes in the locus, CCR9 and CXCR6, are involved in cellular signaling through cytokines (CC motif chemokine receptor 9 and the C-X-C motif chemokine receptor 6). The cytokine pathways regulate the location of a type of white blood cells (called memory CD8 T cells) within the lung during an immune response to pathogens in the airway. The contribution of this gene locus was also identified in another genetics-based investigation of individuals with COVID-19. Based on the information from the previous report and their own data, the authors conclude that the "**3p21.31 locus is involved in COVID-19 susceptibility with a possible enrichment in patients with severe disease**."

The second locus identified is 9q34.2, which includes the genes that determine a person's blood type. Based on their results, there was a higher risk for people who are in blood-group A compared to other blood groups and a protective effect for people in blood-group O compared with other blood groups. This association has also been reported by other research groups, but no functional basis for the association has been determined. This gene locus also contains a section of DNA that regulates the production of a protein that triggers strong immune responses (Zimmer, 2020).

Effect of ARBs and ACE Inhibitors on COVID-19

Angiotensin-receptor blockers (ARBs) and angiotensin-converting–enzyme (ACE) inhibitors are commonly used medications for the treatment of hypertension, heart failure, post-myocardial infarction states, and chronic kidney disease. The method of action of the medications is to increase the production of the ACE-2 receptor, which is the same receptor used by SARS-CoV-2 to bind a cell and infect it. There has been concern that increased production of the ACE-2 receptor may be one of the contributing factors of the increased susceptibility of those with hypertension and related chronic conditions to COVID-19. This question was previously addressed in an analysis by Mandeep and colleagues, but the report has since been retracted by the New England Journal of Medicine due to questions of fraudulent patient data being used for the analysis (Mehra et al., 2020).

Another group has presented information from the outbreak in Italy to investigate the potential correlation between ARBs and ACE inhibitor use and COVID-19 susceptibility (Mancia et al.,

2020). The publication includes information from 6,272 individuals in the Lombardy region of Italy who had severe acute respiratory syndrome (ARS) due to COVID-19. The outcomes of these individuals was compared to 30,759 individuals whose health records were available through the Regional Health Service. Based on this information, the use of ACE inhibitors and ARBs was more common among people with COVID-19 than among the control group. The use of other antihypertensive and non-related drugs was also higher in sick individuals. However, among the group with COVID-19, there was not an association between the use of ARBs or ACE inhibitors. Additionally, no association was observed for individuals with more serious symptoms and their use of the medications. Based on the data, the authors conclude that **there was no evidence that ACE inhibitors or ARBs affected the risk of COVID-19**.

Sex Differences of COVID-19

An increasing amount of evidence suggests that male sex hormones, called androgens, may be the basis for the sex difference in COVID-19 outcomes (Wadman, 2020). The connection was made based on the discovery that SARS-CoV-2 required a protein called TMPRSS2 in order to infect cells after binding to the ACE-2 receptor. TMPRSS2 is a type of protein called a protease that cuts other proteins. This protein has been shown to be mutated in some types of prostate cancers, and **production of TMPRSS2 is increased upon binding of androgens to nearby androgen receptors on prostate cancer cells**. If this occurs in cells in the respiratory tract, the presence of androgens may be leading to an increased amount of TMPRSS2 available for SARS-CoV-2 to utilize during infection.

When TMPRSS2 was linked to SARS-CoV-2 infectivity, members of the prostate cancer research community took notice and began to investigate if there is an effect on the risk for COVID-19 in people taking androgen suppression medication during prostate cancer treatment. In Italy, researchers evaluated the medical records of 42,000 men being treated for prostate cancer with androgen-deprivation therapy (ADT), a treatment that causes a dramatic decrease in the levels of testosterone. Evaluation of the outcome of men with prostate cancer showed that use of ADT led to statistically significant reduction in the risk of SARS-CoV-2 infection compared with patients who did not receive ADT (Monopoli et al, 2020). Another study that has not yet been published from the Icahn School of Medicine at Mount Sinai had similar results according to the lead investigator (Wadman, 2020).

A connection between male-pattern baldness and COVID-19 risk has also been observed. Male pattern baldness results from increased levels of dihydrotestosterone (DHT), another androgen, in the scalp, suggesting that people with the condition may have higher levels of androgen in other parts of the body as well that modify conditions for SARS-CoV-2 infection. This association with male pattern baldness was also observed in two studies in Spain and one study from China.

Based on the proposed connection with androgen production, there are multiple clinical trials underway to investigate the effect of ADT on individuals with COVID-19. One study is testing the effect of degarelix, an ADT, which nearly completely inhibits the production of testosterone and TMPRSS2 within three days of injection. The lowering of testosterone levels is temporary when given as a single dose. Another trial involves the use of an androgen receptor blocker called bicalutamide in men and women with COVID-19. The use of the ADT is being initiated

early in the progression of the COVID-19 because the resulting reduction in androgen production is expected to lead to a reduction in the amount of virus produced, which is more important in the early stages.

COVID-19 Risk and Children

A study of the COVID-19 infection rate of children was published in the journal *Nature Medicine* (Davies et al., 2020). Data from the outbreaks in China, Italy, Japan, Singapore, Canada, and Singapore were evaluated to calculate the susceptibility to infection in individuals under 20 years of age. **The rate was found to be about half that of adults over the age of 20, and clinical symptoms developed in only 21% of those between the age of 10 and 19**. For comparison, the proportion of individuals over the age of 70 who developed symptoms was 69%. Based on this information, the authors conclude that interventions based on reducing interaction between children will have a limited effect on stopping transmission due to both the low rate of infection for younger individuals and the reduced risk of infection from people who do not have symptoms. While this information may lead to changes in interventions directed at children, it may also suggest that regions with a higher proportion of older individuals may have an increased impact from the pandemic.

In an interview with the lead author, the Washington Post reports that he still has questions about the effectiveness of school closures because the researchers were not able to determine the extent to which children, with or without symptoms, can transmit the virus to others, such as teachers and other adult caregivers (Achenbach, 2020). He also pointed out that there was variation in the age-related infection rates in different countries. At this point, it was not possible to determine if these differences were real or just fluctuations in the collected data.

This lowered rate of infection in children is supported by information from the CDC, which indicates that children aged 17 and under, who make up 22% of the US population, account for fewer than 2% of confirmed COVID-19 infections in the United States. Additionally, only 5.7% required hospitalization for treatment, and only 0.001% of the children with COVID-19 had died (Cyranoski, 2020).

The basis of this lowered infection rate has not been elucidated, but scientists are investigating the contribution of the condition of the cells lining the surface of blood vessels in children compared to adults. The cells lining the blood vessels are called endothelial cells, and inflammation of these cells occurs with aging and has been linked with an increased risk from COVID-19.

However, some scientists are of the opinion that rather than a physical difference between adults and children, children are simply less likely to get infected because they have less exposure to sources of the virus due to the closure of schools and subsequent lock-downs (Malapaty, 2020). Scientists are also skeptical of a difference in transmission between adults and children because respiratory viruses have been found to be easily transmissible between both groups before, and adults and children with confirmed cases of COVID-19 have similar levels of viral RNA.

Transmission of SARS-CoV-2

Transmission of SARS-CoV-2 is surging in some states, but reductions in the transmission in highly populated areas have made nationwide infection data look favorable. Rather than the number of new cases, a more important measure for a community may be the utilization of the healthcare system in the area. A certain increase in the number of hospitalizations in a smaller community may lead to a severe strain on resources that would not affect larger communities, and these are the types of communities that have been reporting large increases in transmission (Collins and Findell, 2020). For example, as of June 11, Arizona reported that intensive care units in the state approached 80% capacity, and there were record numbers of hospitalizations in Texas from COVID-19.

Even statewide numbers may be hard to interpret as is the case in the state of Washington (Geranios, 2020). In Yakima County, which is a farming community 140 miles southeast of Seattle, hospitals are filled to capacity, and patients are being sent to other areas, including Seattle. As of June 21, Yakima County had at least 6,283 cases of coronavirus and 138 deaths. For comparison, King County, which includes Seattle and has nearly 10 times more people, had recorded around 9,211 cases and 600 deaths. Government officials have reported that the infection rate in Yakima County was 28 times higher than the rate in King County. The positive test rate is 26% compared to a state average of 6%, which suggests that many cases may be missed.

The *Washington Post* reported several interviews with infectious disease experts around the world where it was mentioned that it seems as if the United States has given up trying to contain the outbreak and is simply accepting rising numbers of cases and deaths (Noack, 2020). This was a prevailing sentiment even when many of the countries in the world have based their successful responses on research performed in the United States. For example, a member of the German parliament who was educated as an epidemiologist at Harvard told the newspaper that “A large portion of [Germany’s] measures that proved effective was based on studies by leading U.S. research institutes”, and thus even with an older population than the United States and a population one fourth the size, Germany has had only 9,000 confirmed COVID-19 related deaths compared almost 120,000 in the United States as of June 22.

Effectiveness of Limiting Interactions

A group in the United Kingdom used cell phone mobility data to monitor compliance with physical distancing measures and movement restrictions (Drake, 2020). They found that activity has begun to increase, not due to fatigue from restrictions, but rather due to the practicalities of daily living. The information used in the study was from mobility data released by Google for the period from February 16 to March 29 and was compared to similar data before the pandemic. Mobility could be tracked based on classification as residential areas; supermarkets, grocery shops, and pharmacies; workplaces; retail and recreational areas; transit stations (subway, bus, and train stations); and parks.

Mobility on March 29 showed an overall 63% reduction in movement compared to the values before the lockdown. There were larger reductions in some areas such as an 85% reduction for

retail and recreational locations and a 75% reduction at transit stations. As of May 2, the level of retail, recreational areas, and transit use had begun to increase. In general, non-residential and non-park movement increased by 5% since lockdown began, increasing by 2% to 3% per week. There was also increased mobility in certain regions of the country outside of large population areas.

China

A so-called second wave of COVID-19 local transmission has begun in China, and government officials are preparing to carry out mass testing to stop the outbreak (Fifield, 2020 and Normille, 2020). After a weekend with dozens of new cases, authorities reportedly mobilized around 100,000 community workers to test all the visitors to the Xinfadi market in the southwest area of Beijing. Based on information from Chinese officials, 77,000 people were tested on Sunday, June 15 and 200,000 were expected to be tested Monday, June 16. Restrictions have been enacted, such as requiring masks and cancelling gatherings, but a lockdown had not been ordered as of June 16. There was initially a rumor about contamination of salmon from the market involved, but links to the fish have not been substantiated. As of June 17, the source of the outbreak in Beijing had not been identified.

Asymptomatic/Pre-symptomatic Transmission

The question of whether asymptomatic carriers can transmit SARS-CoV-2 has not yet been conclusively answered, but there is a substantial amount of evidence in favor of transmission from non-symptomatic individuals. Some of the recent confusion stems from a difference in technical definitions of asymptomatic compared to the everyday usage of the word. In scientific research, someone who is asymptomatic does not have symptoms of the disease for the entire length of their infection. However, most people interpret someone who is asymptomatic as not having any symptoms at the moment, but who may later develop symptoms. This scenario is referred to as pre-symptomatic in disease research. Based on these more strict definitions, asymptomatic transmission of SARS-CoV-2 is considered rare and not a major contributor to community spread of the virus. However, pre-symptomatic transmission has been shown to have a substantial role in the evolution of the pandemic.

Researchers at the CDC recently published a report describing the transmission of SARS-CoV-2 in communities in Japan (Furuse et al., 2020). Based on the information collected from 3,184 confirmed cases, the researchers identified 61 clusters of transmission between January 15 and April 4. They were also able to identify the initial case for 22 of the clusters, and in clusters that did not occur in healthcare facilities, half of the primary cases were between 20 and 39 years of age with transmission of the virus while they were not experiencing symptoms.

There have also been documented cases of pre-symptomatic transmission at skilled nursing facilities in the United States (Arons et al., 2020). Because officials were able to test almost everyone at the facility once outbreaks at nursing homes started, it was easier to identify people with COVID-19 who were not experiencing symptoms. Within 23 days of the first positive test at one nursing home, 64% of the residents had tested positive for SARS-CoV-2, and 56% were found to not be exhibiting symptoms. Eventually, 88% of those without symptoms developed

symptoms with a median onset of four days from the positive test. Researchers were able to recover infectious virus from 70% of the residents not showing symptoms. This scenario has contributed to a very high rate of deaths in nursing homes in the United States. As of June 2, **deaths in nursing homes accounted for 40% of the deaths nationwide** representing 40,600 residents with only 80% of the facilities having reported current figures (Soucheray, 2020). As of June 17, the reported number of deaths had surpassed 50,000 with over 250,000 cases associated with the facilities (Kamp and Mathews, 2020).

A study of individuals staying at a quarantine facility in Ho Chi Minh City, Vietnam allowed researchers to collect clinical data, travel and contact history, saliva at enrollment, and daily nasopharyngeal throat swabs for RT-PCR testing (Chau et al., 2020). Based on the information collected on the individuals who tested positive for COVID-19, 43% never had symptoms, and 57% were symptomatic. The authors of the report concluded that "**asymptomatic SARS-CoV-2 infection is common and can be detected by analysis of saliva or nasal swabs**."

There was also evidence of asymptomatic transmission aboard the Diamond Princess cruise ship (Sakuri et al., 2020 and Hung et al., 2020). Overall, 712 people were infected out of 3,711 passengers and crew on the ship, and 58% of these infected individuals were asymptomatic at the time of testing. A group of 96 passengers who were asymptomatic at the time of a positive test were transferred to a hospital in Japan where 11% later developed symptoms within a median of 4 days. There was a higher risk of being pre-symptomatic with increasing age. In total, of the sick passengers and their companions who were transferred off the ship in Japan, 90 had asymptomatic SARS-CoV-2 infections, which was defined as those who were asymptomatic at the time of the positive PCR test and remained so until the resolution of infection.

References

Achenbach J, Meckle L. Children are only half as likely to get infected with the coronavirus, study finds. *The Washington Post*. Published June 16, 2020. Accessed June 18, 2020 at https://www.washingtonpost.com/health/children-are-only-half-as-likely-to-get-infected-by-the-coronavirus-research-shows/2020/06/16/be86aff4-afb6-11ea-856d-5054296735e5_story.html

Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. *N Engl J Med*. 2020;382(22):2081-2090. doi:10.1056/NEJMoa2008457

Baum A, Fulton BO, Wloga E, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies [published online ahead of print, 2020 Jun 15]. *Science*. 2020;eabd0831. doi:10.1126/science.abd0831

Brouwer PJM, Caniels TG, van der Straten K, et al. Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability [published online ahead of print, 2020 Jun 15]. *Science*. 2020;eabc5902. doi:10.1126/science.abc5902

Collins E, Findell E. Covid-19 Hospitalizations Surge in Some States. *The Wall Street Journal*. Published June 11, 2020. Accessed June 12, 2020 at https://www.wsj.com/articles/covid-19-hospitalizations-surge-in-some-states-11591912459

Chau NVV, Thanh Lam V, Thanh Dung N, et al. The natural history and transmission potential of asymptomatic SARS-CoV-2 infection [published online ahead of print, 2020 Jun 4]. *Clin Infect Dis*. 2020;ciaa711. doi:10.1093/cid/ciaa711

Dall C. Regeneron to begin trials for COVID-19 antibody cocktail. *CIDRAP News*. Published June 11, 2020. Accessed on June 12, 2020 at https://www.cidrap.umn.edu/news-perspective/2020/06/regeneron-begin-trials-covid-19-antibody-cocktail

De Luca G et al., GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. *Lancet Rheumatology*. Published June 16, 2020. Accessed June 18, 2020 at https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30170-3/fulltext

Drake TM. The effects of physical distancing on population mobility during the COVID-19 pandemic in the UK. *The Lancet Digital Health*. Published June 12, 2020. Accessed on June 15, 2020 at https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30134-5/fulltext

Ellinghaus D, Degenhardt F, Bujanda L, et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure [published online ahead of print, 2020 Jun 17]. *N Engl J Med*. 2020;10.1056/NEJMoa2020283. doi:10.1056/NEJMoa2020283

Farzan AN, Shepherd K, Hassan J, Noack R, Beachum L, O'Grady S, Shammas B, Shaban H, Mettler, K. Live updates: FDA pulls emergency authorization for hydroxychloroquine as covid-19 treatment. *The Washington Post*. Published June 15, 2020. Accessed on June 15, 2020 at https://www.washingtonpost.com/nation/2020/06/15/coronavirus-live-updates-us/

Favalli EG, Caporali R. GM-CSF in the treatment of COVID-19: a new conductor in the pathogenesis of cytokine storm? *Lancet Rheumatology*. Published June 16, 2020. Accessed on June 18, 2020 at https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30185-5/fulltext

Fifield A. Beijing carries out mass testing as coronavirus spreads in the Chinese capital. *The Washington Post*. Published June 15, 2020. Accessed on June 15, 2020 at https://www.washingtonpost.com/world/asia_pacific/beijing-carries-out-mass-testing-as-coronavirus-spreads-in-the-chinese-capital/2020/06/15/

Furuse Y, Sando E, Tsuchiya N, Miyahara R, Yasuda I, Ko YK, et al. Clusters of coronavirus disease in communities, Japan, January–April 2020. *Emerg Infect Dis*. 2020 Sep. Accessed on June 18, 2020 at https://doi.org/10.3201/eid2609.202272

Geranios NK. Virus is taking big toll on farm county in Washington state. *The Washington Post*. Published June 22, 2020. Accessed on June 22, 2020 at https://www.washingtonpost.com/business/virus-is-taking-big-toll-on-farm-county-in-washington-state/2020/06/22/21a77a0a-b4b7-11ea-9a1d-d3db1cbe07ce_story.html

Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail [published online ahead of print, 2020 Jun 15]. *Science*. 2020;eabd0827. doi:10.1126/science.abd0827

Hung IF, Cheng VC, Li X, et al. SARS-CoV-2 shedding and seroconversion among passengers quarantined after disembarking a cruise ship: a case series [published online ahead of print, 2020 Jun 12]. *Lancet Infect Dis*. 2020;S1473-3099(20)30364-9. doi:10.1016/S1473-3099(20)30364-9

Kamp J, Mathews AW. As U.S. Nursing-Home Deaths Reach 50,000, States Ease Lockdowns. *The Wall Street Journal*. Published June 16, 2020. Accessed June 18, 2020 at https://www.wsj.com/articles/coronavirus-deaths-in-u-s-nursing-long-term-care-facilities-top-50-000-11592306919

Kricke G. et al. Rapid Implementation of an Outpatient Covid-19 Monitoring Program. *NEJM Catalyst*. Published June 16, 2020. Accessed on June 18, 2020 at https://catalyst.nejm.org/doi/pdf/10.1056/CAT.20.0214

Kupferschmidt K. A cheap steroid is the first drug shown to reduce death in COVID-19 patients. *Science*. Published June 16, 2020. Accessed on June 18, 2020 at https://www.sciencemag.org/news/2020/06/cheap-steroid-first-drug-shown-reduce-death-covid-19-patients

Ledford H. Coronavirus breakthrough: dexamethasone is first drug shown to save lives. *Nature*. Published June 16, 2020. Accessed on June 18, 2020 at https://www.nature.com/articles/d41586-020-01824-5

Mallapaty S. How do children spread the coronavirus? The science still isn't clear. *Nature*. Published May 7, 2020. Accessed on June 12, 2020 at https://www.nature.com/articles/d41586-020-01354-0

Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. *N Engl J Med*. 2020;382(25):2431-2440. doi:10.1056/NEJMoa2006923

Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621 [published online ahead of print, 2020 Jun 4] [retraction of: N Engl J Med. 2020 May 1;:]. *N Engl J Med*. 2020;10.1056/NEJMc2021225. doi:10.1056/NEJMc2021225

Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532) [published online ahead of print, 2020 May 6]. *Ann Oncol*. 2020;S0923-7534(20)39797-0. doi:10.1016/j.annonc.2020.04.479

Normille D. Source of Beijing's big new COVID-19 outbreak is still a mystery. *Science*. Published on June 17, 2020. Accessed June 18, 2020 at

https://www.sciencemag.org/news/2020/06/source-beijing-s-big-new-covid-19-outbreak-still-mystery

Noak R. In countries keeping the coronavirus at bay, experts watch U.S. case numbers with alarm. *The Washington Post*. Published June 22, 2020. Accessed on June 22, 2020 at https://www.washingtonpost.com/world/2020/06/19/countries-keeping-coronavirus-bay-experts-watch-us-case-numbers-with-alarm/

Oxford University. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. *Oxford University News*. Published on June 16, 2020. Accessed on June 22, 2020 at https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_final.pdf

Parasa S, Desai M, Thoguluva Chandrasekar V, et al. Prevalence of Gastrointestinal Symptoms and Fecal Viral Shedding in Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2020;3(6):e2011335. Published 2020 Jun 1. doi:10.1001/jamanetworkopen.2020.11335

Robbiani DF, Gaebler C, Muecksch F, et al. Convergent antibody responses to SARS-CoV-2 in convalescent individuals [published online ahead of print, 2020 Jun 18]. *Nature*. 2020;10.1038/s41586-020-2456-9. doi:10.1038/s41586-020-2456-9

Rogers TF, Zhao F, Huang D, et al. Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model [published online ahead of print, 2020 Jun 15]. *Science*. 2020;eabc7520. doi:10.1126/science.abc7520

Sakurai A, Sasaki T, Kato S, et al. Natural History of Asymptomatic SARS-CoV-2 Infection [published online ahead of print, 2020 Jun 12]. *N Engl J Med.* 2020;NEJMc2013020. doi:10.1056/NEJMc2013020

Shen B, Yi X, Sun Y, et al. Proteomic and Metabolomic Characterization of COVID-19 Patient Sera [published online ahead of print, 2020 May 28]. *Cell*. 2020;S0092-8674(20)30627-9. doi:10.1016/j.cell.2020.05.032

Soucheray S. Nursing homes site of 40% of US COVID-19 deaths. *CIDRAP News*. Published on June 2, 2020. Accessed on June 15, 2020 at https://www.cidrap.umn.edu/news-perspective/2020/06/nursing-homes-site-40-us-covid-19-deaths

Travis J. FDA just gave a thumbs down to Trump's favorite COVID-19 drugs. *Science*. Published June 15, 2020 Accessed on June 15, 2020 at https://www.sciencemag.org/news/2020/06/fda-just-gave-thumbs-down-trump-s-favorite-covid-19-drugs

Wadman M. Why coronavirus hits men harder: sex hormones offer clues. *Science*. Published June 3, 2020. Accessed on June 15, 2020 at https://www.sciencemag.org/news/2020/06/why-coronavirus-hits-men-harder-sex-hormones-offer-clues

Wec AZ, Wrapp D, Herbert AS, et al. Broad neutralization of SARS-related viruses by human monoclonal antibodies [published online ahead of print, 2020 Jun 15]. *Science*. 2020;eabc7424. doi:10.1126/science.abc7424

Zimmer C. Genes May Leave Some People More Vulnerable to Severe Covid-19. *The New York Times.* Published June 3, 2020. Accessed on June 8, 2020 at https://www.nytimes.com/2020/06/03/health/coronavirus-blood-type-genetics.html