PINNACLECARE

Medical Intelligence Report

Date: December 9, 2020

Topic: Update on COVID-19 Research

Timeline and Spectrum of COVID-19

As more information becomes available, researchers are better able to define the period of illness associated with SARS-CoV-2 infection (Datta et al., 2020).

Currently, there are three periods of illness associated with SARS-CoV-2 infection:

- Acute COVID-19 disease that infects the respiratory tract
- A hyper-inflammatory response after the end of the infection
- Late inflammatory-based and virus-based symptoms that persist for months after resolution of infection

The initial illness period, or acute COVID-19 disease, following infection with SARS-CoV-2 is currently the best characterized of the three periods. During this initial period, many people experience symptoms such as cough, fever, and difficulty breathing (or dyspnea) that are caused by viral replication and the initial host immune response. There is also a high rate of asymptomatic individuals who have SARS-CoV-2 infections, ranging from 3% to 67% in different studies.

However, progression to the other periods of COVID-19 illness is not always preceded by the presence of symptoms during the initial infection, and those without symptoms during the acute stage of COVID-19 can have later problems.

The acute phase of COVID-19 lasts between a few days and weeks, and is identified by positive tests of either PCR-based testing or antigen tests. The majority of individuals test positive for antibodies (IgM and IgG) against SARS-CoV-2 within two weeks of initial symptom onset.

The second phase of illness is defined by a multisystem inflammatory syndrome (MIS) that can occur in both children and adults after the end of the acute phase. The inflammatory response in this stage differs from those that occur during the initial infection in that they occur in organ systems not directly infected by the virus. The cause of the syndrome is thought to be a dysregulated host immune response after clearance of the virus from the body. The most prominent symptoms are in the cardiovascular and gastrointestinal systems, but there are also

changes in the skin and mucous membranes. Laboratory tests have been found to be similar to the responses observed in the hyper-inflammatory condition called Kawasaki disease, including high levels of inflammatory molecules, evidence of dysregulation of blood clotting mechanisms, and elevated levels of molecules associated with cardiac damage. The incidence of MIS in children (MIS-C) seems to be higher, but there is more difficulty in diagnosing the syndrome in adults (MIS-A) because adults often have more severe symptoms during the acute phase making it more difficult to differentiate a distinct progression between the two phases.

The emergence of late symptoms after viral infections has been observed in numerous different types of viruses, including Lyme disease, syphilis, and Ebola. The cause of these late symptoms are proposed to be a combination of organ involvement during the acute infection period, manifestations of a long-term hyper-inflammatory state, physical debilitation or psychological symptoms following a long or difficult disease course, or ongoing viral activity from a viral reservoir within the body. Because infections from SARS-CoV-2 are still a recent occurrence, research on this phase of the disease is the least understood. Most of the research reports include only single individuals, and large studies are not yet available. However there are some associations that have been identified. First, symptoms from the third phase of COVID-19 are not limited to people who required hospitalization for treatment of the acute infection. The types of symptoms that have been reported thus far include cardiovascular, pulmonary, neurological, and psychological manifestations. The third stage seems to begin about four weeks after the initial infection and can continue for an unknown length of time.

Defining the phases of infection can aid public health officials in determining the extent of adverse, long-term outcomes and mortality from SARS-CoV-2 infection and may have important implications for public health surveillance, clinical research, future treatments, and health services planning.

Potential COVID-19 Vaccines

AstraZeneca and Oxford University Vaccine

AstraZeneca announced the interim results of the Phase 3 clinical trial of their vaccine candidate for COVID-19 in a press release. The results show that the there was an overall average efficiency of 70% (AstraZeneca, 2020). Due to a procedural error, one group of patients received a half dose at the first injection and a full dose for the second injection, and the efficacy of this group was found to be 90%. Results from the group that received two full doses showed that the vaccine had an efficacy of 62%. The safety profile of the vaccine was good, no serious adverse events related to the vaccine were reported, and the vaccine was well tolerated in both dosing regimens.

The results suggest that, while the vaccine reached the efficiency threshold previously set for a successful COVID-19 vaccine, it seems to be less effective than the two other vaccines that have reported results from Phase 3 trials.

The differences in efficacy between the two groups with different dosing are somewhat puzzling as typically increased doses or medication and vaccines lead to a stronger response.

The reduced efficacy may lead to issues with approval of the vaccine for use in the United States because of the availability of more efficacious alternatives and the differences in treatment groups due to the dosing error, and it would cause difficult decisions on who would be immunized with the less effective vaccine (Branswell and Fererstein, 2020). It is possible that the lower dose allows for a more robust immune response when the second dose is administered, but it has also been determined that the group receiving the lower dose were all participants who were under the age of 55 years, which is a group that would be expected to have a more robust response to a vaccine than older individuals, suggesting that the vaccine may be more effective in younger individuals (Lauerman and LaVito, 2020).

Experts, who were not part of the study, felt positive about the vaccine even with the potentially lower efficacy data because none of the participants who received the vaccine had severe symptoms of COVID-19 (Branswell and Fererstein, 2020 and Callaway, 2020). There were also fewer asymptomatic cases associated with the AstraZeneca vaccine, which along with previous research, suggests that the vaccine may reduce transmission.

Importantly, the vaccine can be stored for up to six months at normal refrigerator temperatures, making it easier to distribute than the vaccines developed by Pfizer, which requires ultra-cold storage, or Moderna, which requires storage at freezer temperatures.

Results from the Phase 2 clinical trial of the vaccine were published in *The Lancet*. The study included information on 560 participants between May 30 and August 8 and examined the response to either inoculation with the COVID-19 based vaccine or with a placebo vaccine that protects against meningococcal bacterial infections (Ramasamy et al., 2020). The results were analyzed both as the whole group and based on age.

Side effects were more common in the group receiving the COVID-19 vaccine and included infection-site pain, feeling feverish, muscle ache, and headache. These side effects were less common in participants over the age of 55. In total, 13 serious adverse events were reported, but further investigation showed that they were not related to the vaccine.

There were similar levels of IgG antibodies produced against the SARS-CoV-2 spike protein across the different age groups in the study, and by 14 days after the second dose, greater than 99% had a neutralizing antibody response. The T-cell response was found to peak 14 days after the initial dose.

Based on the results from this clinical trial, the researchers concluded that the AstraZeneca vaccine was better tolerated by older adults and had similar levels of immune response based on the measurement of antibodies and T-cell response.

The CEO of AstraZeneca stated that it is likely that another clinical trial will be needed to address the inconsistencies in the Phase 3 trial (Lauerman and LaVito, 2020).

Moderna Vaccine

The final analysis of the Phase 3 study of the vaccine developed by Moderna was published in a press release (Moderna, 2020 and Herper and Garde, 2020). The analysis was performed when there were 196 confirmed, symptomatic cases of COVID-19 reported, and the results confirm the results reported after the interim analysis with a vaccine efficacy of 94.1%. No new safety concerns were observed. Additionally, as agreed upon by the FDA and other experts, the company was able to apply for an Emergency Use Authorization (EUA) because two months had accrued since the last participant had received the second dose of the vaccine. This time period is thought to allow for any serious adverse events to emerge from exposure to the vaccine.

There were a total of 196 cases of COVID-19 reported, and 185 were from participants who received the placebo while 11 occurred in participants receiving the vaccine. There were 30 cases who had severe symptoms, and all of the participants with severe symptoms were in the placebo group. There was one COVID-19 related death that occurred with a participant in the placebo group.

The researchers found that efficacy was consistent across age, race or ethnicity, and gender.

The company also announced that they will begin testing the vaccine in children aged 12 to 17 (Grady, 2020). Based on information from ClinicalTrials.gov, the study plans to enroll 3,000 children for a placebo controlled investigation of the effects of the vaccine. Pfizer and AstraZeneca have already included children starting at age 12 in their studies.

Pfizer Vaccine

The officials who regulate new drug products in the United Kingdom have granted emergency approval to the Pfizer vaccine (Booth and Adam, 2020). In the announcement, officials stated that distribution of the first doses is expected to begin in the second week of December. The government has decided to prioritize those who have the highest risk of dying, and residents and staff at nursing homes are expected to be the first to be inoculated. The next groups to receive a vaccine are individuals over the age of 80 and front-line medical workers. The order for the next groups is reported to be people over 75, people over 70, and individuals who are extremely vulnerable based on their clinical condition.

Sinovac Vaccine

Results from the Phase 1/2 trial of the Sinovac vaccine candidate, called CoronaVac, were published in *The Lancet* (Zhang et al., 2020). CoronaVac is an inactivated vaccine rather than an mRNA vaccine as with the three candidates that have recently reported Phase 3 results. The clinical trial included 144 participants in the Phase 1 section of the trial and 600 participants in the Phase 2 section of the trial. The vaccine is administered in two doses separated by either 14 days or 28 days, and the effect of different doses was also investigated.

Table 1. Results of the Phase 1 section

Dose	Percentage of Participants with Neutralizing Antibodies	Percentage of Participants with Adverse Reactions
3 µg group, 14 day schedule	46%	29%
6 µg group, 14 day schedule	50%	38%
Placebo, 14 day schedule	0%	8%
3 µg group, 28 day schedule	83%	13%
6 µg group, 28 day schedule	79%	17%
Placebo, 28 day schedule	4%	13%

The same doses and schedules were evaluated in the Phase 2 section of the clinical trial.

Table 2. Results from the Phase 2 section.

Dose	Percentage of Participants with Neutralizing Antibodies	Percentage of Participants with Adverse Reactions
3 µg group, 14 day schedule	92%	33%
6 µg group, 14 day schedule	98%	35%
Placebo, 14 day schedule	3%	22%
3 µg group, 28 day schedule	97%	19%
6 µg group, 28 day schedule	100%	19%
Placebo, 28 day schedule	0%	18%

Based on the results, the researchers recommended proceeding to Phase 3 trials with the 3 µg dose of CoronaVac.

Strain Monitoring for Vaccines

The Coalition for Epidemic Preparedness Innovations (CEPI) has announced a collaboration to monitor the emergence on new strains of SARS-CoV-2 that might contain genetic differences that affect the efficacy of vaccines (Galford, 2020). The initiative will strengthen the global tracking and testing of SARS-CoV-2 genetic sequences to determine if circulating strains will impact COVID-19 vaccine development. The data collected will be analyzed by a group started during the previous bird flu epidemic called Global Initiative on Sharing All Influenza Data, or GISAID. Specifically, GISAID will report on how many of the components of the spike protein change over time and track the diversity of the spike protein in strains around the world. This information will allow researchers to make sure that vaccine candidates can be tested against existing strains. Another group in the collaboration, the National Institute for Biological Standards and Control (or NIBSC) from the United Kingdom will test currently identified neutralizing antibodies to determine if they react to the spike proteins of different strains.

Treatments for COVID-19

Casirivimab and Imdevimab

The FDA announced an EUA for the antibody cocktail from Regeneron, called REGEN-COV2, that contains casirivimab and imdevimab (Regeneron Drug Facts, 2020). The indications for use are that the two must be administered together to treat mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results from viral testing, and who are at high risk for progressing to severe COVID-19 and hospitalization. The use of the antibodies is not authorized for people who already require treatment in a hospital for COVID-19 or those who require oxygen therapy for COVID-19. There is evidence of poorer outcomes in individuals who already required supplemental oxygen and then received casirivimab and imdevimab.

It was reported in the press release that "The clinical evidence from Regeneron's outpatient trial suggests that monoclonal antibodies such as casirivimab and imdevimab have the greatest benefit when given early after diagnosis and in patients who have not yet mounted their own immune response or who have high viral load."

The antibody cocktail was designed to mimic a well-functioning immune system by supplying strong neutralizing antibodies that may be lacking in a natural response for some individuals. During the testing of the treatment, no strains of SARS-CoV-2 were found that were resistant to the cocktail.

In the clinical trial, 799 participants who were not hospitalized were treated with REGEN-COV2. Within seven days of treatment, there was a statistically significant reduction in the level of virus measured (FDA Antibodies, 2020). There was also a reduction in COVID-19-related hospitalization or emergency room visits (3% of participants) compared to a placebo (9% of participants).

The definition provided by Regeneron of "high-risk" individuals includes people with

- A body mass index greater than 35
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease, immunocompromised, currently receiving immunosuppressive treatment
- Older than 65 years of age
- Older than 55 years of age and have cardiovascular disease, hypertension, chronic obstructive pulmonary disease, or other chronic respiratory disease
- 12 to 17 years of age and have a BMI in the 85th percentile or higher for their age and gender, sickle cell disease, congenital or acquired heart disease, neurodevelopmental disorders (e.g. cerebral palsy), a medical-related technological dependence (e.g. tracheostomy, gastrostomy), asthma, or reactive airway or other chronic respiratory disease that requires daily medication for control.

The company announced that they would be able to initially provide 300,000 doses of the combination treatment with no out-of-pocket costs due to a United States government allocation program. The timeline for production is expected to provide doses for approximately 80,000 individuals by the end of November, approximately 200,000 doses by the first week of January, and approximately 300,000 doses in total by the end of January 2021 (Regeneron, 2020).

Distribution of the antibody is being coordinated by the United States government through the national distributor Amerisource Bergen.

Doses will be allocated each week based on the number of COVID-19 cases in each state.

Baricitinib

The FDA issued an EUA for the use of baricitinib in combination with remdesivir. Baricitinib works by interfering with cellular signaling molecules that control inflammation, and it has been previously approved for use in people with rheumatoid arthritis.

The indications for use of baricitinib include the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients two years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (FDA, 2020). The medication is not authorized for use by itself for COVID-19. In the clinical trial of the medication, it was found that use in combination with remdesivir led to a reduction in the time to recovery (seven days) compared to those receiving remdesivir and a placebo (eight days). Additionally, the odds of a participant dying or being put on a ventilator was lower for those taking baricitinib plus remdesivir compared to the placebo plus remdesivir. Finally, the trial showed that there was a larger change in clinical improvement after 15 days of treatment in people taking the combination therapy compared to remdesivir plus placebo.

Bamlanivimab

The COVID-19 Treatment Guidelines Panel at the National Institutes of Health released a statement on the use of bamlanivimab, an antibody cocktail developed by Eli Lilly that was previously known as LY-CoV555 (NIH, 2020). The medication was approved for use in the United States under an EUA from the FDA for the treatment of non-hospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization.

After reviewing the information available, the panel released a statement on the use of bamlanivimab, including the opinion that

- There are insufficient data to recommend either for or against the use of bamlanivimab for the treatment of outpatients with mild to moderate COVID-19.
- Bamlanivimab should not be considered the standard of care for the treatment of patients with COVID-19.
- The small number of participants in the study used for granting EUA and the low number of people who needed treatment in the hospital or emergency department make it difficult to draw definitive conclusions about the clinical benefit of bamlanivimab.
- Healthcare providers are encouraged to discuss participation in bamlanivimab clinical trials with their patients.

Remdesivir

The World Health Organization has reviewed the clinical trials on remdesivir and advised against the use of the treatment for hospitalized individuals due to a lack of evidence that use of the medication improves survival or avoids the need for mechanical ventilation (Marchione, 2020 and Rochwerg et al., 2020). In the statement, the WHO stressed that the high cost and lack of a “meaningful effect” on mortality make it a poor choice for treatment. There are two placebo controlled trials available for review, one from the United States that showed a reduction in recovery time for hospitalized patients by an average of five days, or from 15 days to 10. The other trial, called the WHO SOLIDARITY trial, was sponsored by the WHO and showed no benefit from treatment with remdesivir for COVID-19.

The SOLIDARITY trial is an ongoing trial that was designed to analyze a treatment using interim results while additional participants are added or other treatments are added for investigation (WHO Solidarity Trial Consortium, 2020). In the middle of October, 11,266 participants were added to the analysis with 2570 taking remdesivir, 954 taking hydroxychloroquine, and 1411 taking lopinavir-ritonavir, and 6331 receiving usual care, which is used as the placebo comparator. The addition of the participants to the analysis led to release of this most recent guideline for treatments. Currently use of hydroxychloroquine or lopinavir-ritonavir are not recommended for treatment of COVID-19 by any of the major governmental or professional guidelines. However, the guidelines for remdesivir vary.

Tocilizumab

Researchers at Imperial College Healthcare NHS Trust in the United Kingdom reported partial results from a study on the use of the anti-inflammatory drug tocilizumab in a press release (Imperial College, 2020). The trial, called REMAP-CAP, involves over 2,000 hospitalized patients with either moderate or severe (requiring care in the intensive care unit) COVID-19 who are treated with multiple combinations of treatments, enabling researchers to evaluate different

treatments for Covid-19, including antivirals, drugs which control the immune response, and therapies that control or support other vital aspects of the body's response to the virus.

One of the medications being investigated is tocilizumab, and interim analysis of 303 participants showed that critically ill individuals treated with tocilizumab were more likely to improve when compared to individuals who did not receive the treatment.

The researchers felt that the positive results were important to release before peer-review, but a full analysis of the full trial will be published as soon as possible.

Convalescent Plasma

Another study on the use of convalescent plasma to treat COVID-19 was completed and was published in the *New England Journal of Medicine* (Simonovich et al., 2020).

The study included 333 participants with 228 receiving convalescent plasma and 105 receiving a placebo. Convalescent plasma was from either a single donor or from a pool of two to five donors, and the amount of IgG antibody was measured in each convalescent plasma pool before transfusion. The median time from onset of symptoms to enrollment was eight days with a range from five to ten. Before infusion of the plasma, the level of antibody produced by the patients themselves was also measured, and all had low levels with 46% of the participants having no detectable antibodies present.

At day 30 after the onset of symptoms, assessment of the participants showed that there was no statistically significant difference between the convalescent plasma group and the placebo group in clinical outcomes.

The overall mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group. There were also no differences in the outcome in those treated with convalescent plasma and those receiving a placebo when the overall group was analyzed in smaller groups, such as by age or by the amount of total or neutralizing antibodies in the convalescent plasma.

The authors report that there was no clinical benefit in the use of convalescent plasma compared to a placebo even with the use of plasma with high levels of antibodies (titer) and with adjustments in the volume administered based on the participant's weight. These factors were associated with possible discrepancies in previous studies. The results in this study agree with the results of the previously mentioned (PinnacleCare COVID-19 Update on October 12, 2020) randomized and controlled PLACID trial that reported no difference in severe disease or death at day 30 after the start of treatment.

SARS-CoV-2 Infectiousness

Researchers have published a review of the available literature investigating the duration of viral shedding and timeline for peak production of the SARS-CoV-2, SARS-CoV-1, and MERS-CoV (Cevik et al., 2020). The researchers evaluated all available published and pre-release studies

available, and included 79 studies on SARS-CoV-2, eight studies on SARS-CoV-1, and 11 studies on MERS-CoV. The researchers performed a statistical analysis, called a meta-analysis, to evaluate the trends across the studies. They reported on both viral RNA shedding and presence of infectious virus. PCR tests for SARS-CoV-2 detect the presence of RNA from the virus, but the RNA may or may not be part of infectious virus particles. RNA from the virus is released after the active infection is over when virus fragments are cleared from the system and previously infected cells are removed from the body. A separate test is required to identify whether infectious virus is still present.

Overall, the mean duration of viral RNA shedding for SARS-CoV-2 was 17 days in the upper respiratory tract, 14.6 days in the lower respiratory tract, 17.2 days in stool, and 16.6 days in blood serum samples. The longest duration reported for viral RNA shedding was 83 days from the upper respiratory tract, 59 days in the lower respiratory tract, 126 days in stool, and 60 days in blood serum. Increases in the duration of viral RNA shedding were associated with increased age.

There were no studies that detected live virus more than nine days from the onset of symptoms even though the amount of viral RNA remained high for longer time periods.

The amount of viral RNA detected peaked in the first seven days in individuals with SARS-CoV-2 while the peak of viral RNA detection from SARS-CoV-1 was between 10 and 14 days and the peak for MERS-CoV was between 7 and 10 days.

RNA Shedding Versus Infectious Virus

A study of 176 individuals who had recovered from COVID-19 and were evaluated afterward as outpatients was published in *JAMA Internal Medicine* (Liotti et al., 2020). All of the individuals had been deemed recovered from the acute infection based on the criteria at the time, which included no fever for three consecutive days, improvement in other symptoms, and two negative RT-PCR results for SARS-CoV-2 RNA taken 24 hours apart. It was found that 18% of the individuals later tested positive again after clinical recovery and negative test results. However, further investigation showed that only one of the individuals had replicating virus and developed symptoms, and the remaining individuals had no evidence of infectious virus and remained asymptomatic.

The authors conclude that, as reported previously, individuals who have recovered from COVID-19 may test positive based on the presence of viral RNA, but only a minority have an active infection that produces infectious virus.

CDC Recommendations for Length of Isolation

Based on emerging evidence, the CDC announced a change in the length of quarantine times (CDC, 2020). **Isolation** is the term used for individuals who are known to have COVID-19, and **quarantine** is the term used for people who have had a known exposure to someone with the

virus, but do not yet know if they contracted COVID-19. Previous recommendations suggested a quarantine period of 14 days after known exposure.

The new recommendations state:

- Quarantine can end after **day 10 without testing** and if no symptoms have been reported during daily monitoring.
- When diagnostic testing is available, quarantine can end after **day 7 if with a negative test** within 48 hours of the end of the 7-day period and if no symptoms were reported during daily monitoring.

Though it is no longer recommended that quarantine last for 14 days, additional steps to prevent possible transmission should be followed, including continued symptom monitoring and wearing a mask when around other people or in public spaces through the full 14 days.

The changes were made to better balance the burden of remaining in quarantine with the calculated risk of transmission for different quarantine scenarios. Based on the available data, researchers at the CDC estimated that the post-quarantine transmission risk at ten days without testing is estimated to be about 1% with a worst-case-scenario of about 10%. The calculated post-quarantine transmission risk at seven days is estimated to be about 5% with a worst-case-scenario of about 12%.

They also state that being tested at the start of quarantine has little added value in reducing the risk of transmission.

Testing at the start of quarantine is not necessary because the negative test required for exiting quarantine must be performed within 48 hours of the end of the 7-day period. Tests taken at the beginning of the quarantine period are more likely to be falsely negative due to a low amount of virus in nasal samples early in the infection. In areas where community transmission is high, there may not be sufficient tests available, and the CDC states that “Testing for the purpose of earlier discontinuation of quarantine should be considered only if it will have no impact on community diagnostic testing” of symptomatic individuals.

Officials also mentioned that “Persons can continue to be quarantined for 14 days without testing per existing recommendations. **This option maximally reduces risk of post-quarantine transmission risk** and is the strategy with the greatest collective experience at present.”

Reinfection and Immunity from SARS-CoV-2

The information about reinfection with SARS-CoV-2 and the length of possible immunity after infection has been difficult to pin down because of the conflicting results from different studies. Some studies suggest that antibodies are produced and T cells are activated in a way that would lead to long-term protection, but other studies have identified cases of people being re-

infected within a few weeks or months and have shown a steep decline in antibody levels a few weeks after recovery.

Confirming **reinfection** can be difficult due to the lingering effects of COVID-19, but in several cases it was possible to genetically sequence the virus from both potential infections and substantiate that they were different strains and therefore separate infections (de Vrieze, 2020). So far there have been 24 genetically confirmed cases of reinfection, which is an underestimate of that actual number that have occurred. The suspected number of cases of re-infection not confirmed by genetic sequencing that have been reported include 50 in the Netherlands, 150 in Sweden, 285 in Mexico, and 243 in Qatar. South Korea also reported 111 confirmed cases of reinfection (Si-soo, 2020).

There is also evidence of **persistent infections** where the initial infection is not completely cleared from the body and becomes active a second time (de Vrienze, 2020). In one case, the resurgence of a previous infection was confirmed by sequencing of the viral genome. The individual, a surgeon working with COVID-19 patients, had COVID-19 in April and the virus was reactivated in June. The second bout of illness is often milder or asymptomatic due to some level of immune response, but some cases have been more severe. The surgeon's first round of illness was mild and included a period between where she tested negative. The second activation of the illness resulted in infection of the lungs and debilitating fatigue.

> **In both reinfection and resurgence of the initial infection, it is proposed that the immune system did not provide an adequate response to protect from subsequent illness.**

However, there is also evidence of many people having a robust and stable immune response to COVID-19. A preprint from *bioRxiv* details the duration of the immune response in 185 cases of COVID-19 (Dan et al., 2020). There were 41 cases included in the study that were six months or longer from the initial SARS-CoV-2 infection. There was also a range in the severity of symptoms from asymptomatic to severe, and participants were recruited from different areas in the United States. Of the participants, 92% had not been hospitalized for treatment of COVID-19, and 97% reported having some symptoms during their illness. The participants were aged 19 to 81 years old. Most of the blood samples were provided at a single time point, but 38 provided two to four samples over a period of several months.

The researchers found that long-term antibodies (IgG) to spike protein were present at stable levels for more than six months, and the memory B cells that produce IgG antibodies specific to the spike protein were more abundant at six months than one month after infection. The amount of antibodies produced varied greatly between participants as was observed in previous studies.

> **The percentage of subjects with detectable levels of spike IgG antibodies at one month after the onset of symptoms was 98%, and 90% at six to eight months.**

The average half-life, or time it takes for the level to decline by one half, for spike IgG antibodies was 100 days, and the average half-life for nucleocapsid IgG, a non-neutralizing antibody, was 67 days.

The amount of killer and helper T cells that were specific for the SARS-CoV-2 spike protein declined over time with a half-life of between 3 and 5 months. The T cells most commonly detected were those that react to spike protein, membrane protein, nucleocapsid, and another protein called ORF3a, which aligns with previously reported studies.

The researchers stress that, while sterilizing immunity, where the immune system completely prevents infection, requires a large amount of neutralizing antibodies, successful protection against clinical disease or death can be accomplished by several other immune memory scenarios.

For example, the immune system can prevent a second case of hepatitis B without measurable amounts of circulating antibodies. The hepatitis B virus has a slow course of disease, similar to COVID-19, so that maintaining high levels of antibodies is not required. Maintenance of high levels of antibodies would be necessary for control of a virus that leads to early symptoms after infection, but the immune system can take the several days necessary to reactive B cells and T cells in response to viruses with a slower course of action.

Activation of the memory immune cells would allow for the re-infecting virus to be confined within the upper respiratory tract, leading to milder symptoms similar to a cold rather than life-threatening symptoms from infection in the lower respiratory tract. Additionally, the activities of the immune cells would presumably reduce the amount of virus produced, which would reduce the severity of the upper respiratory symptoms.

The duration of the half-life of T cells that react to SARS-CoV-2 proteins was found to be similar to that of the response observed after immunization for yellow fever, suggesting that the response could be long-lived. Studies of T cells produced during SARS-CoV-1 infections have shown that they persist for up to 17 years after the initial infection.

Based on previous studies, it has been found that between 91% and 99% of individuals produce a measurable amount of antibodies after infection and resolution of COVID-19.

Also, studies in primates show that even low levels of circulating neutralizing antibodies were associated with a substantial degree of protection against COVID-19.

The authors state that “While immune memory is the source of long-term protective immunity, direct conclusions about protective immunity cannot be made on the basis of quantifying SARS-CoV-2 circulating antibodies, memory B cells, CD8+ T cells, and CD4+ T cells, because mechanisms of protective immunity against SARS-CoV-2 or COVID-19 are not defined in humans.”

However, they also stress that there was a measurable immune system memory response in three components of the system in 90% of individuals for over six months, meaning that durable immunity against COVID-19 disease is a possibility in most individuals.

Mask Mandates

There have been numerous studies that have shown that wearing a mask in public spaces reduces the spread of SARS-CoV-2, and the CDC released a report describing the reduction in COVID-19 incidence in counties that adopted mask mandates (Van Dyke et al., 2020). On July 3, the governor of Kansas issued an executive order that required wearing masks in public spaces, but individual county authorities were allowed to opt out of the requirement. In total, 24 counties complied with the order, and 84 opted out.

Before the mandate was put in place, from June 1 to June 7, the seven day average of COVID-19 incidence was similar in counties that eventually did and did not adopt a mask mandate and ranged from three to four cases per 100,000 people. The COVID-19 incidence in the state increased between June and July, and by the time the mask mandate was put in place, there had been a 50% to 467% increase in the number of cases, depending on the county.

After the mandate was put in place, the researchers found that the number of new cases decreased in counties with a mask mandate, but increased in counties without a mandate.

During the time frame of the study, from July 3 to August 23, the number of new cases per 100,000 people decreased by 6% in the 24 counties that implemented mask mandates, and the number of new cases per 100,000 people increased by 100% in the 81 counties that opted out of the mask mandate. This change was observed even though the counties that adopted the mask mandate had a higher incidence of COVID-19 cases at the start of the mandate (17 cases per 100,000 people versus six cases per 100,000 people).

After the governor's executive order, COVID-19 incidence decreased each day in counties with a mandate and increased each day in counties without a mandate.

It is somewhat difficult to determine the exact contribution of mask mandates to the decrease in COVID-19 incidence because additional procedures were also in place. The researchers stress that the only other state mandates issued were focused on mitigation strategies for schools as they reopened. The contribution of the mask mandates is supported by the fact that there was a similar decrease in COVID-19 incidence after July 3 in counties with mask mandates even though the implementation of other mitigation strategies varied.

Based on the results, the authors conclude that implementing multiple mitigation strategies together is the recommended approach, but strategies related to mask use mandates appear to be an important contribution that, when implemented, can reduce transmission.

Proportion of the United States Previously Infected with SARS-CoV-2

In order to determine the prevalence of SARS-CoV-2, testing for antibodies in communities allows for identification of those who were not tested or who were asymptomatic and unaware of their infection (Bajema et al., 2020). Early tests for antibodies varied widely in the accuracy, but

the tests used in this study had both high sensitivity and specificity and provide a good estimate of the prevalence in the population of antibodies from SARS-CoV-2 infection.

The samples for testing in this study were obtained from excess blood samples submitted to two commercial laboratories for routine screenings (e.g., cholesterol, thyroid) or clinical management during hospitalization for conditions other than COVID-19. The samples were collected in all 50 states, Washington D.C., and Puerto Rico, and of the 3,141 counties in the United States, there were clinical specimens representing 79.5%. Around 14.8% of the sample were from people who did not reside in a metropolitan area, which matches the distribution of residents within United States. The frequency of testing was about every two weeks from July to September. During this time period, 177,919 samples were tested. Within the group of people providing samples, 58.3% were women, 15% were under 17 years of age, and 26.7% were 65 years or older.

The time of study was divided into four, two-week periods to evaluate the data, and period 1 corresponded to July 27 to August 13, period 2 was from August 10 to 27, period 3 was from August 24 to September 10, and period 4 was September 7 to 24.

Over the full time period in all areas of the United States, fewer than 10% of specimens had detectable SARS-CoV-2 antibodies, suggesting that there are still a large number of vulnerable people susceptible to SARS-CoV-2 infection.

As might be expected, the prevalence varied by jurisdiction and the time period as different areas of the country experienced different levels of transmission. There was no consistent, overall difference in the proportion of men and women with antibodies when examined as a whole. When looking at certain states, there were some areas that had higher proportions of men or women. For example, Iowa, Louisiana, and Mississippi had a higher seroprevalence for women while the seroprevalence was higher for men in Maryland and Pennsylvania. There was a higher number of individuals aged 18 to 49 years with antibodies compared to people aged 65 or older. The proportion of people infected who lived in rural or metropolitan areas was also not consistent around the country. In Iowa, Pennsylvania, and, Tennessee seroprevalence was higher in metropolitan areas, but in Alabama and Mississippi, seroprevalence was higher in nonmetropolitan counties.

Based on the results, the authors conclude that

- As of September, most people in the United States did not have evidence of previous SARS-CoV-2 infection, which agrees with previous reports.
- The overall prevalence of SARS-CoV-2 is the highest in the Northeast most likely due to the early outbreak in the New York City area.
- Not all areas with high levels of seroprevalence were located in urban or metropolitan areas.
- Seroprevalence was lower in older adults compared with younger adults across nearly all jurisdictions.
- The changes in overall seroprevalence over four collection periods that spanned 2 months were modest.

References

AstraZeneca. AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19. Published November 23, 2020. Accessed November 30, 2020 at https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222hlr.html

Bajema KL, Wiegand RE, Cuffe K, Patel SV, Iachan R, Lim T, Lee A, Moyse D, Havers FP, Harding L, Fry AM, Hall AJ, Martin K, Biel M, Deng Y, Meyer WA 3rd, Mathur M, Kyle T, Gundlapalli AV, Thornburg NJ, Petersen LR, Edens C. Estimated SARS-CoV-2 Seroprevalence in the US as of September 2020. *JAMA Intern Med*. 2020 Nov 24. doi: 10.1001/jamainternmed.2020.7976. Epub ahead of print. PMID: 33231628.
Booth W, Adam K. Britain first country to grant Pfizer coronavirus vaccine emergency authorization. The Washington Post. Published December 2, 2020. Accessed on December 2, 2020 at https://www.washingtonpost.com/world/europe/britain-pfizer-coronavirus-vaccine/2020/12/02/90f7276e-3470-11eb-9699-00d311f13d2d_story.html

Branswell H, Fererstein A. AstraZeneca Covid-19 vaccine is 70% effective on average, early data show. *STAT News*. Published November 23, 2020. Accessed on November 30, 2020 at https://www.statnews.com/2020/11/23/astrazeneca-covid-19-vaccine-is-70-effective-on-average-early-data-show/

Callaway E. Why Oxford's positive COVID vaccine results are puzzling scientists. *Nature*. 2020 Dec;588(7836):16-18. doi: 10.1038/d41586-020-03326-w. PMID: 33230278.

CDC. Options to Reduce Quarantine for Contacts of Persons with SARS-CoV-2 Infection Using Symptom Monitoring and Diagnostic Testing. Updated December 2, 2020. Accessed on December 3, 2020 at https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-options-to-reduce-quarantine.html

Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *The Lancet Microbe*. Published November 19, 2020. Accessed on November 30, 2020 at https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30172-5/fulltext

Dan JM et al., Immunological memory to SARS-CoV-2 assessed for greater than six months after infection. *bioRxiv*. Published on November 16, 2020. Accessed on November 30, 2020 at https://www.biorxiv.org/content/10.1101/2020.11.15.383323v1

Datta SD, Talwar A, Lee JT. A Proposed Framework and Timeline of the Spectrum of Disease Due to SARS-CoV-2 Infection: Illness Beyond Acute Infection and Public Health Implications. *JAMA*. 2020 Nov 18. doi: 10.1001/jama.2020.22717. Epub ahead of print. PMID: 33206133.

De Vrieze. More people are getting COVID-19 twice, suggesting immunity wanes quickly in some. *Science*. Published November 18, 2020. Accessed on November 30, 2020 at https://www.sciencemag.org/news/2020/11/more-people-are-getting-covid-19-twice-suggesting-immunity-wanes-quickly-some

FDA Antibodies. Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19. Published November 21, 2020. Accessed on November 30, 2020 at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19

FDA. Coronavirus (COVID-19) Update: FDA Authorizes Drug Combination for Treatment of COVID-19. Published November 19, 2020. Accessed on November 30, 2020 at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-combination-treatment-covid-19

Galford C. CEPI builds collaborative task force to monitor new COVID-19 viral strains and their effects on vaccines. *Homeland Preparedness News*. Published November 20, 2020. Accessed on November 30, 2020 at https://homelandprepnews.com/stories/57817-cepi-builds-collaborative-task-force-to-monitor-new-covid-19-viral-strains-and-their-effects-on-vaccines/

Grady D. Moderna Plans to Begin Testing Its Coronavirus Vaccine in Children. *The New York Times*. Published December 2, 2020. Accessed on December 3, 2020 at https://www.nytimes.com/2020/12/02/health/Covid-Moderna-vaccine-children.html

Herper M, Garde D. Moderna to submit Covid-19 vaccine to FDA as full results show 94% efficacy. *STAT News*. Published November 30, 2020. Accessed on December 2, 2020 at https://www.statnews.com/2020/11/30/moderna-covid-19-vaccine-full-results/

Imperial College. Initial data shows arthritis drug is effective in treating sickest Covid-19 patients. Published November 19, 2020. Accessed on November 30, 2020 at https://www.imperial.nhs.uk/about-us/news/initial-data-shows-arthritis-drug-is-effective-in-treating-sickest-covid-19-patients

Lauerman J, LaVito A. Astra Vaccine's 90% Efficacy in Covid Came in Younger Group. *Bloomberg News*. Published November 24, 2020. Accessed December 2, 2020 at https://www.bloomberg.com/news/articles/2020-11-24/astra-vaccine-s-90-efficacy-in-covid-came-in-younger-population

Liotti FM, Menchinelli G, Marchetti S, Posteraro B, Landi F, Sanguinetti M, Cattani P. Assessment of SARS-CoV-2 RNA Test Results Among Patients Who Recovered From COVID-19 With Prior Negative Results. *JAMA Intern Med*. 2020 Nov 12:e207570. doi: 10.1001/jamainternmed.2020.7570. Epub ahead of print. PMID: 33180119; PMCID: PMC7662488.

Marchione M. Health experts clash over use of certain drugs for COVID-19. *The Associated Press*. Published November 20, 2020. Accessed on November 30, 2020 at https://apnews.com/article/health-experts-clash-drugs-for-covid-19-eda78c1994d6812cc72c13a1bd42828d

Moderna. Moderna Announces Primary Efficacy Analysis in Phase 3 COVE Study for Its COVID-19 Vaccine Candidate and Filing Today with U.S. FDA for Emergency Use Authorization. Published November 30, 2020. Accessed on November 30, 2020 at

https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-primary-efficacy-analysis-phase-3-cove-study

NIH. The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Bamlanivimab for the Treatment of COVID-19. Published November 18, 2020. Accessed on November 30, 2020 at https://www.covid19treatmentguidelines.nih.gov/statement-on-bamlanivimab-eua/

Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, Voysey M, Aley PK, Angus B, Babbage G, Belij-Rammerstorfer S, Berry L, Bibi S, Bittaye M, Cathie K, Chappell H, Charlton S, Cicconi P, Clutterbuck EA, Colin-Jones R, Dold C, Emary KRW, Fedosyuk S, Fuskova M, Gbesemete D, Green C, Hallis B, Hou MM, Jenkin D, Joe CCD, Kelly EJ, Kerridge S, Lawrie AM, Lelliott A, Lwin MN, Makinson R, Marchevsky NG, Mujadidi Y, Munro APS, Pacurar M, Plested E, Rand J, Rawlinson T, Rhead S, Robinson H, Ritchie AJ, Ross-Russell AL, Saich S, Singh N, Smith CC, Snape MD, Song R, Tarrant R, Themistocleous Y, Thomas KM, Villafana TL, Warren SC, Watson MEE, Douglas AD, Hill AVS, Lambe T, Gilbert SC, Faust SN, Pollard AJ; Oxford COVID Vaccine Trial Group. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet*. 2020 Nov 18:S0140-6736(20)32466-1. doi: 10.1016/S0140-6736(20)32466-1. Epub ahead of print. PMID: 33220855; PMCID: PMC7674972.

Regeneron Drug Facts. Casirivimab and Imdevimab. Published November, 2020. Accessed on November 30, 2020 at https://www.regeneron.com/casirivimab-imdevimab

Regeneron. Regeneron's Casirivimab And Imdevimab Antibody Cocktail for Covid-19 Is First Combination Therapy To Receive FDA Emergency Use Authorization. Published November 21, 2020. Accessed on November 30, 2020 at https://investor.regeneron.com/news-releases/news-release-details/regenerons-regen-cov2-first-antibody-cocktail-covid-19-receive

Rochwerg B et al. Update to living WHO guideline on drugs for covid-19. *BMJ*. 2020 Nov 19;371:m4475. doi: 10.1136/bmj.m4475. PMID: 33214213.

Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, Savoy N, Giunta DH, Pérez LG, Sánchez MDL, Gamarnik AV, Ojeda DS, Santoro DM, Camino PJ, Antelo S, Rainero K, Vidiella GP, Miyazaki EA, Cornistein W, Trabadelo OA, Ross FM, Spotti M, Funtowicz G, Scordo WE, Losso MH, Ferniot I, Pardo PE, Rodriguez E, Rucci P, Pasquali J, Fuentes NA, Esperatti M, Speroni GA, Nannini EC, Matteaccio A, Michelangelo HG, Follmann D, Lane HC, Belloso WH; PlasmAr Study Group. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. *N Engl J Med.* 2020 Nov 24. doi: 10.1056/NEJMoa2031304. Epub ahead of print. PMID: 33232588.

Si-soo P. South Korea confirms 111 cases of coronavirus reinfection. *Korea Times*. Published April 12, 2020. Accessed November 30, 2020 at https://www.koreatimes.co.kr/www/nation/2020/04/119_287752.html

Van Dyke ME, Rogers TM, Pevzner E, et al. Trends in County-Level COVID-19 Incidence

in Counties With and Without a Mask Mandate — Kansas, June 1–August 23, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1777-1781.

WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernández García C, Kieny MP, Malekzadeh R, Murthy S, Reddy KS, Roses Periago M, Abi Hanna P, Ader F, Al-Bader AM, Alhasawi A, Allum E, Alotaibi A, Alvarez-Moreno CA, Appadoo S, Asiri A, Aukrust P, Barratt-Due A, Bellani S, Branca M, Cappel-Porter HBC, Cerrato N, Chow TS, Como N, Eustace J, García PJ, Godbole S, Gotuzzo E, Griskevicius L, Hamra R, Hassan M, Hassany M, Hutton D, Irmansyah I, Jancoriene L, Kirwan J, Kumar S, Lennon P, Lopardo G, Lydon P, Magrini N, Maguire T, Manevska S, Manuel O, McGinty S, Medina MT, Mesa Rubio ML, Miranda-Montoya MC, Nel J, Nunes EP, Perola M, Portolés A, Rasmin MR, Raza A, Rees H, Reges PPS, Rogers CA, Salami K, Salvadori MI, Sinani N, Sterne JAC, Stevanovikj M, Tacconelli E, Tikkinen KAO, Trelle S, Zaid H, Røttingen JA, Swaminathan S. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2020 Dec 2. doi: 10.1056/NEJMoa2023184. Epub ahead of print. PMID: 33264556.

Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, Han W, Chen Z, Tang R, Yin W, Chen X, Hu Y, Liu X, Jiang C, Li J, Yang M, Song Y, Wang X, Gao Q, Zhu F. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2020 Nov 17:S1473-3099(20)30843-4. doi: 10.1016/S1473-3099(20)30843-4. Epub ahead of print. PMID: 33217362.