PINNACLECARE

Medical Intelligence Report

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Topic: Update on COVID-19 Research

COVID-19 Treatments

Development of treatments for COVID-19 remains an important focus because of the large number of individuals in the United States who currently have COVID-19, which in turn leads to a large number of hospitalized individuals. While the release of vaccines for SARS-CoV-2 infections is expected to gradually reduce the number of people infected with the virus, until this reduction occurs, treatments will still be needed to prevent COVID-19-related deaths.

Convalescent Plasma

The last PCI COVID-19 Research Update included the first randomized and controlled trial investigating the efficacy of convalescent plasma to prevent the progression to severe symptoms from COVID-19 (Libster et al., 2021). The study showed that use of convalescent plasma early in the course of disease along with use of plasma with high levels of neutralizing antibodies was effective in prevention of severe symptoms.

Another study has been published in the *New England Journal of Medicine* that compares the outcome of COVID-19 after use of convalescent plasma with differing levels of antibodies (Joyner et al., 2021). The information from the study was gathered from the United States national registry initiated at the Mayo Clinic for organizing the COVID-19 Convalescent Plasma Expanded-Access Program. The registry includes characteristics reported in the medical records of people who participated in the expanded access program and therefore does not allow a comparison to a control group. However, it is possible to compare the differences in outcomes based on the amount of antibodies in the plasma used, which is similar to the dose of a typical medication.

The study includes information on 3,082 individuals that received convalescent plasma in the first three months of the program, from the beginning of April to the beginning of July, 2020. The people eligible to participate in the program were 18 years of age or older with a high risk for progression to severe or life-threatening COVID-19 and were hospitalized for treatment. The individuals were separated into three groups based on the amount of antibodies in the plasma they received. The level of antibodies produced are measured based on a unit called titer, and therefore the three groups were called the high titer-group, the medium titer-group, and the low-

titer group. The researchers reported the number of deaths within 30 days after plasma transfusion for the three groups.

Table 1. Number of deaths in the 30 days after plasma transfusion.

	Number of participants	Number of deaths within 30 days of transfusion	Percentage of group that died within 30 days
High-titer group	515	115	22.3%
Medium-titer group	2006	549	27.4%
Low-titer group	561	166	29.6%

The reduction in the risk of death observed between the high and low-titer groups was only evident in those participants who received convalescent plasma **before** there was a need for mechanical ventilation.

This result is consistent with the previous report suggesting that early use of convalescent plasma with high levels of antibodies is associated with better outcomes.

The authors also stress that use of convalescent plasma was not beneficial in patients after they required mechanical ventilation regardless of the level of antibodies present. The rate of death was higher overall for those who required mechanical ventilation (1,068 participants) and ranged from 40.5% to 43.7% compared to 26.9% for the entire study group (3,082 participants). Additionally, participants who received plasma within 3 days after the diagnosis of COVID-19 had a lower risk of death than those who received a transfusion later in the disease course.

Overall, the authors conclude that the benefit of convalescent plasma was most apparent in patients who received plasma transfusions containing higher levels of anti–SARS-CoV-2 IgG antibodies early in the disease course.

Antibody Treatments

Researchers from Eli Lilly published a study investigating the use of two antibody treatments in individuals with mild to moderate COVID-19 (Gottlieb et al., 2021). The first treatment included bamlanivimab alone, and the second was a combination of bamlanivimab and etesevimab. Bamlanivimab has been authorized for emergency use by the FDA, but etesevimab has not. The use of the combination therapy was proposed to reduce the risk of new virus variants that are resistant to the treatment because the two antibodies included interact with different regions of the virus. The 613 participants in the study were staff and residents of 49 nursing homes who tested positive for SARS-CoV-2 but did not require hospitalization for treatment.

There were three groups of participants. One group received a single infusion of bamlanivimab, the second group had a single dose of the combination treatment, and the third group received a placebo. Individuals in the bamlanivimab only group received one of three different doses, 700 mg, 2800 mg, or 7000 mg. Individuals in the combination group received 2800 mg of bamlanivimab and 2800 mg of etesevimab. During the study, researchers measured the change

in the amount of virus produced by participants, symptoms, and clinical outcomes, such as the proportion of patients with a COVID-19–related hospitalization, an emergency department visit, or death.

Measurements showed that the combination treatment resulted in a statistically significant reduction in virus on day eleven after diagnosis. However, there was not a statistically significant difference in the viral production for bamlanivimab alone.

Table 2. The proportion of COVID-19 related hospitalizations or emergency department visits

	Number of events	Proportion of participants
Placebo	9	5.8%
Bamlanivimab, 700 mg	1	1.0%
Bamlanivimab, 2800 mg	2	1.9%
Bamlanivimab, 7000 mg	2	2.0%
Combination	1	0.9%

There were no deaths that occurred during the time period of the study. Another section of the trial is still underway to determine the outcome of treatment in participants at high-risk for progression of COVID-19 from mild symptoms to severe symptoms.

Prophylactic Use of Antibody Treatments

Both Eli Lilly and Regeneron announced the results of prophylactic use of their antibody treatments to prevent COVID-19 in press releases. The Eli Lilly study investigated the treatment's response when used early in an outbreak at a nursing home or long-term treatment facility. Regeneron is investigating the ability of the antibody treatments to prevent transmission within households after one member tests positive.

Eli Lilly and its partner Abcellera investigated the use of bamlanivimab to slow outbreaks at nursing homes when used as a treatment for infected participants or as a prophylactic to prevent infection with SARS-CoV-2 (Eli Lilly, 2021 and Herper, 2021). The study involved a fleet of vehicles that were deployed to nursing homes after an outbreak at the facility was identified. The vehicles were outfitted to allow researchers to prepare the drug, take the lab work of participants, and provide space for onsite infusion centers. The dose of bamlanivimab used in this study was six-fold higher than that used in previous studies in order to ensure a longer lived effect.

The study included 1,097 participants consisting of 300 residents and 797 staff. At the beginning of the study, 132 participants tested positive out of the entire group, and 41 of the positive cases were residents.

The researchers found that symptomatic infection was reduced by 57% with prophylactic use of the antibodies, and the reduction was larger in participants who were residents of the facilities at 80%.

There were four deaths in the study, and all four were residents who were in the placebo group.

Representatives from Eli Lilly stated that the development of antibody treatments was continuing even though vaccines are being distributed in order to address scenarios with active outbreaks where there would not be time for individuals to develop an immune response to a vaccine. The complete results of this study have not yet been released in a peer-reviewed journal, but the researchers are reportedly finishing the article as quickly as possible.

Regeneron also reported the interim results of their Phase 3 placebo-controlled trial on the prophylactic use of their antibody cocktail, which included the first 400 participants in the study (Herper, 2021 and Regeneron, 2021). There were 223 people in the placebo group of the study, and the remaining participants received the combination therapy that includes two antibodies, casirivimab and imdevimab. The participants in the study are people living in the same household as someone who has been diagnosed with COVID-19. People residing with someone with COVID-19, who are also referred to as household contacts, have a high risk of contracting the disease as well.

Use of the antibody cocktail prevented ALL cases of symptomatic COVID-19, and lowered the overall rate of infection by 50%.

In total, 23 individuals in the placebo group tested positive for COVID-19, and eight out of the 23 developed symptoms. In the group treated with the antibody cocktail, ten participants tested positive for COVID-19, and none developed symptoms. The participants who received the antibody cocktail who became infected also produced less virus and had a lower time period of viral release (or viral shedding), nine weeks versus 44 weeks. The duration of the infection was shorted in those who received the antibodies as well. Infections in participants receiving the antibody lasted no more than one week while around 40% of those in the placebo group that became infected lasted three to four weeks.

Importantly, the antibodies were administered via injections rather than as IV infusions, which would make it easier to use the treatment. Currently, available doses of the two authorized antibody treatments are reported to be underused, possibly due to difficulties from infusion of the treatments.

Tocilizumab and Sarilumab

A report was released as a preprint on January 7, 2021 describing the results of a study by researchers in the United Kingdom that indicates a beneficial response from the use of the anti-inflammatory medications tocilizumab and sarilumab in hospitalized individuals with COVID-19 that was included in the previous PCI COVID-19 Update (REMAP-CAP investigators, 2021).

A second report was published in the journal *BMJ* that describes a study in Brazil that compared the outcome of hospitalized individuals treated with tocilizumab or with standard care (Viega et al., 2020).

The trial was stopped early because it was found that there was an increase in the mortality in individuals who had received tocilizumab for 15 days.

When the trial was stopped, 129 people had been enrolled, and 65 participants had received tocilizumab while 64 were assigned to standard care. Analysis of the data from the trial indicated that 18 of 65 (or 28%) participants in the tocilizumab group and 13 of 64 (or 20%) in the standard care group required mechanical ventilation or died by day 15 of treatment.

Eleven participants who received tocilizumab had died after 15 days of treatment, corresponding to 17%, while 2 participants, or 3%, in the standard care group had died after 15 days.

An article from Reuters on the trial from Brazil included expert commentary on the results (Kelland, 2021). Several of those interviewed were surprised at the very low numbers of participants in the placebo group who had died during the trial. They suggested that rather than a negative effect from tocilizumab, there may be a random effect on the placebo group that would have gone away if the full number of participants had been enrolled and treated. However, there are other clinical trials on the class of anti-inflammatory medications that includes tocilizumab that have had mixed results as well.

Metformin

A second study has reported a potential protective effect for people with diabetes who were taking metformin **before** infection with SARS-CoV-2 (Crouse et al., 2021). The study evaluated the medical records from 25,326 people who were tested for COVID-19 between February 25, 2020 and June 22, 2020 at the University of Alabama at Birmingham Hospital. The study was investigating potential characteristics that are associated with mortality from COVID-19.

Based on the results of the study, the risk of contracting COVID-19 was higher for Black or African American individuals as well individuals of all races and ethnicities with hypertension, diabetes, or classified as obese. Individuals with diabetes also had dramatic increase in mortality from COVID-19 compared to other individuals, as has been reported previously. The increased risk for death from COVID-19 in people with either Type 1 or Type 2 diabetes was independent of a person's age, race, sex, level of obesity, and presence of hypertension.

The researchers also report that individuals who were taking metformin to treat their diabetes BEFORE they were diagnosed with COVID-19 had a statistically significant reduction in mortality from COVID-19.

This result is in agreement with a previous report from December about the potential protective effect of metformin use in people with diabetes. However, the protective effect was observed only in women in the previous study and not men (Paulsen, 2020).

Another study that was published in October, 2020 evaluated the medical records of 1,213 individuals who were taking metformin and were diagnosed with COVID-19 (Cheng et al., 2020). The researchers found that metformin was associated with an increased incidence of acidosis (increased amount of acid in the bloodstream). There was no increase in mortality for those taking metformin due to adverse reactions, and there was a reduction in heart failure and inflammation. Other reports have provided inconsistent results with some suggesting benefits

and others indicating no benefit in people with COVID-19 with an increase in negative side effects from use of the drug (Lui and Tan, 2020).

Based on the studies with positive results, some experts have suggested that metformin should be used for prevention of severe COVID-19 in people with diabetes or a BMI of at least 30 regardless of whether they would normally meet the prescribing criteria for the medication (Paulsen, 2020). However, the benefit, and potential adverse reactions, from this scenario and the potential magnitude of the effects cannot be predicted without randomized and controlled trials.

Use of Anti-Coagulation Treatments

The National Institutes of Health described the interim results of a Phase 3 trial on the use of anti-coagulation treatments (blood thinners) in a press release (NIH, 2021). The study is an adaptive platform study that allows for quicker results by using shared placebo groups and allows different drugs to be started, stopped, or combined during the study in response to emerging scientific data.

The results presented in the announcement describe the outcome for 1,000 participants who were moderately ill and being treated in the hospital for COVID-19. The study is designed to investigate if there is a benefit from different doses of an anti-coagulant treatment called heparin. One group in the study is receiving a smaller dose, which is the dose normally used to prevent blood clot formation in hospitalized individuals. However, observations early in the pandemic suggested that more aggressive use of anti-coagulants, at doses used in non-hospitalized individuals, may be more beneficial in preventing complications.

> **The interim results indicated that use of the full dose of heparin reduced the requirement of vital organ support, such as ventilation, compared to the smaller doses.**

There was also a possible improvement in the mortality rate in people receiving the higher dose, but final analysis of this component with the entire study population will be needed to determine if the change is statistically significant. The reduction in the need for intensive care measures were listed as being potentially helpful in reducing the strain on intensive care units around the world as the number of new infections starts to rise again.

COVID-19 Vaccine Development

Two more companies released interim data from Phase 3 trials on vaccines for COVID-19, Johnson & Johnson and Novamax.

Johnson & Johnson COVID-19 Vaccine

The Johnson & Johnson vaccine, which is produced by the subsidiary Janssen, has garnered interest because in its current form it only requires a single shot rather than two shots a month apart as with the currently authorized forms.

The Phase 3 ENSEMBLE trial has enrolled and evaluated the effect of the vaccine in 43,783 participants (Johnson & Johnson, 2021). The ENSEMBLE trial is a randomized, controlled trial for individuals over the age of 18, and 34% of the participants were over the age of 60 with 41% of the participants reporting chronic medical conditions that were associated with an increased risk of severe COVID-19. There were evaluations of efficacy of the vaccine on day 14 and 28 after vaccination.

There have been 468 symptomatic cases of COVID-19 reported from the entire group of participants, which corresponds to an efficacy rate of 66% in preventing moderate to severe symptoms 28 days after vaccination.

Moderate COVID-19 was defined as evidence of pneumonia, deep vein thrombosis, shortness of breath with abnormal blood oxygen saturation or respiratory rate, or two or more symptoms associated with COVID-19. Severe illness was defined as admission to an intensive care unit, respiratory failure, shock, organ failure, or death.

The overall efficacy rate is lower than that reported for the Pfizer-BioNTech and Moderna vaccines, but the study was conducted in the United States, South America/Latin America, and South Africa, and the presence of new SARS-CoV-2 variants in some of the regions is thought to have affected the efficacy.

When the efficacy for preventing moderate to severe disease was evaluated for participants living the United States, where the variant was not yet widespread, the Johnson & Johnson vaccine was 72% effective in the prevention of moderate to severe COVID-19.

The efficacy in prevention of moderate to severe COVID-19 was reduced in some regions where the trials occurred when compared to the overall efficacy rate or the rate observed in the United States.

Table 3. Efficacy by region.

Region	Efficacy Rate
Entire Trial Population	66%
South and Latin America	66%
South Africa	57%
United States	72%

There are SARS-CoV-2 variants that have been identified in Brazil and South Africa that have a specific mutation that is thought to be responsible for this reduction in efficacy of the vaccine. This mutation is not present in the variant that was first identified in the United Kingdom (B.1.1.7), suggesting that the efficacy against the B.1.1.7 variant should be similar to the efficacy observed in the United States section of the trial. It was determined that 95% of cases

of COVID-19 that occurred in participants in the section of the trial performed in South Africa had the new SARS-CoV-2 variant, which can be designated Y501.V2 or B.1.135.

Importantly, the vaccine was found to be 85% effective at preventing severe symptoms from COVID-19 in ALL of the regions included in the study, including those where new variants are widespread.

The efficacy in preventing severe disease increased over time, and there were no cases of severe disease reported in any of the vaccinated participants after 49 days from the time of their vaccination.

There were also no cases that resulted in death or need for medical intervention (defined as hospitalization, ICU admission, mechanical ventilation, extracorporeal membrane oxygenation, or ECMO) in vaccinated participants after 28 days from the date of vaccination.

The onset of protection from COVID-19 was observed as early as day 14. There were no reports of any significant safety concerns relating to the vaccine, and a single dose was generally well tolerated.

Novavax COVID-19 Vaccine

The Novavax vaccine is a protein-based vaccine, called NVX-CoV2373, that was evaluated in a Phase 3 trial conducted in the United Kingdom (Novavax, 2021). Similar to the Johnson & Johnson vaccine, NVX-CoV2373 contains a full-length version of the SARS-CoV-2 spike protein embedded in a nanoparticle that emulates the covering (or capsid) of the virus. However, unlike the Johnson & Johnson vaccine, two doses are required, administered 21 days apart, to stimulate a large enough immune response. NVX-CoV2373 is stable at refrigerator temperatures and can be distributed through existing vaccine supply chains.

The Phase 3 trial included 15,000 participants between 18 and 84 years of age, including 27% over the age of 65. At the first interim analysis, there were 62 cases of PCR-confirmed, symptomatic COVID-19, and 56 of the cases occurred in the group that received the placebo.

Based on the interim results, the efficacy of NVX-CoV2373 in preventing COVID-19 was 89.3%.

The only case with severe symptoms occurred in a participant in the placebo group, and all other cases had mild to moderate symptoms.

Because the trial took place in the United Kingdom, there was a high prevalence of the SARS-CoV-2 B.1.1.7 variant with over 50% of the confirmed cases in the trial attributable to B.1.1.7.

When the results were analyzed based on the variant-type, NVX-CoV2373 was found to be 95.6% effective against the original COVID-19 strain and 85.6% against B.1.1.7.

The safety of the new vaccine was considered good, and severe, serious, and medically attended adverse events occurred at low levels and were balanced between vaccine and placebo groups.

In the same press release, Novavax described the results from their Phase 2b clinical trial of NVX-CoV2373 that is being conducted in South Africa. This study has enrolled over 4,400 beginning in August of 2021. There have been 44 cases of COVID-19 reported in participants in the trial, and 92.6% of the cases with genome sequencing data available were found to be the Y501.V2 (also called B.1.135) variant. There were 29 cases in the placebo group and 15 cases in the vaccinated group with one case of severe symptoms in the placebo group, and all other cases were of mild to moderate severity.

> **These preliminary results suggest that NVX-CoV2373 is 60% effective against the Y501.V2 variant.**

The representatives from the company stressed that, in this study, around 33% of the participants had evidence of previous SARS-CoV-2 infection based on the presence of antibodies. Because of the timing of the trial, the previous infections would have been with the initial variant of the virus. The Y501.V2 variant is associated with a higher rate of reinfection compared to other versions of SARS-CoV-2, making it important to determine if a vaccine is able to provide protection from reinfection.

> **The company states that the data described in the press release "suggest that prior infection with COVID-19 may not completely protect against subsequent infection by the South Africa escape variant, however, vaccination with NVX-CoV2373 provided [statistically] significant protection."**

Novavax began development of new vaccine constructs against the emerging strains in early January, 2021, and identification of a booster or combination vaccine for the variants is expected within a week. Clinical testing of the updated vaccines is expected to begin in the second quarter of the year.

ICU Capacity Associated with Risk of Death from COVID-19

Research conducted before the emergence of SARS-CoV-2 showed that there is often an increase in mortality in hospitals when they reach their capacity, and this concept makes logical sense as providers struggling with limited resources will not be able to provide the best care. Researchers at the Department of Veterans Affairs (VA) hospital system investigated the contribution of a high number of patients in intensive care units on the mortality after the start of the pandemic (Bravata et al., 2021).

The overall load within a unit was described as the comparison between the number of individuals being treated at a specific time and the normal number of beds in the intensive care unit. The specific COVID-19 load included only individuals in the intensive care unit with COVID-19. The COVID-19 load could range from 0% to 100%, and if the facility increased the bed capacity due to demand the COVID-19 load was reported as over 100%.

Periods of low demand were defined as a COVID-19 load under 25%.

The study included individuals treated at any VA hospital between March and August of 2020 in the intensive care unit for COVID-19. The outcome of treatment for 8516 participants was followed up to November, 2020. Over the study period, the mortality rate of individuals with COVID-19 varied. When the mortality rate for the entire country was analyzed, the value decreased over the study period.

Table 4. Monthly mortality of all individuals treated for COVID-19 in a VA intensive care unit in the United States

Month	Total Individuals Treated	Number of Deaths	Mortality Rate
March	954	218	22.9%
April	1594	399	25.0%
May	920	142	15.5%
June	1314	179	13.6%
July	2373	297	12.5%
August	1361	174	12.8%

However, because surges occurred at different times in different regions, the mortality rates at different facilities changed in an independent fashion. Based on the evaluation, the researchers report that when COVID-19 load in an intensive care unit was between 25% and 50% there was no change in the risk of death compared to periods of low demand (under 25%).

However, the risk of death started to increase when the COVID-19 load increased over 50%, and when COVID-19 load rose to 75% to 100%, the risk of death was nearly twice that observed during periods of low use.

When the COVID-19 load increased to over 100%, the relative risk of death increased by 2.35-fold. This association between load and mortality was not observed for individuals being treated for COVID-19 in other sections of the hospital, meaning those who did not require intensive care.

Based on the results of the analysis the authors conclude that the strains on critical care capacity were associated with increased COVID-19 intensive care unit mortality.

The specific components of intensive care that could not be provided at the usual level that lead to an increased mortality during high use could not be identified in this study.

However, increasing the capacity of the intensive care unit (e.g. adding beds) during times of high demand did not help to reduce the mortality.

The authors suggest that this could be due to how well the expanded facilities compared to the original facility in the number of staff, experience of staff, and/or access to specialized equipment. The authors suggest that the information from the study can be used by hospital

administrators to set thresholds of COVID-19 load that trigger a collaborative use of resources, by transfer of patients for example, within a region to reduce the strain on specific facilities.

The increased mortality observed in the study may also have resulted from the concentration of people with more severe disease in the intensive care unit. People with less severe disease who would normally be treated in the intensive care unit when demand is low may be transferred to regular units in the hospital, leading to an increased mortality rate in the intensive care due to an increased proportion of more severely ill patients rather than changes in the level of care. This study was not set up to be able to assess this possibility.

In a commentary published with the original article, it was stated that the results of the study also reaffirm the concept of needing to "flatten the curve" to keep the number of people needing treatment at any one time low so as to not overload the health system. Initiating measures that can reduce the load and demand on intensive care units are easier to implement than changing the other characteristics associated with mortality from COVID-19, specifically chronic medical conditions and age. Authorities have used increasing load on intensive care units to trigger increased community-based restrictions, but the change in transmission from these interventions takes several weeks to have an effect, making them a cumbersome preventative measure.

Assessments of Antigen Testing

Use of antigen tests for rapidly assessing the COVID-19 status of individuals could be very helpful in situations such as schools, air travel, and other areas where it is difficult to maintain social distancing. However, antigen tests are less accurate in detecting infections in asymptomatic individuals and early in the course of an infection. This drawback has made it difficult to determine if they are useful for screening large groups. Three studies have been published that investigate the use of antigen-based tests in real-world situations to help define the efficacy in certain situations.

Overview of terms used to assess the validity of diagnostic tests:

Sensitivity- the ability of a test to correctly identify people with the disease or the **true-positive rate**. Sensitivity can also be expressed as the **false-negative rate**, or how many people are identified incorrectly as not being sick.

Specificity- the ability of a test to exclude those without the disease or the **true-negative rate**. Specificity can likewise be described as the **false-positive rate**, or how many people are identified incorrectly as having the disease.

If the test has a **low sensitivity**, individuals with a disease will erroneously be informed they are not sick, and if a test has **low specificity** more people will be erroneously informed they are sick.

Positive predictive value- the probability that the individual being tested actually **has** the disease.

Negative predictive value- the probability that the individual being tested actually **does not have** the disease.

Panbio COVID-19 Ag Rapid Test Device

In a report studying the use of the Panbio COVID-19 Ag Rapid Test Device, researchers evaluated how well the tests performed in the diagnosis of **symptomatic** individuals visiting primary healthcare centers (Albert et al., 2021). Individuals were tested with the antigen tests as described in the manufacturer's instructions with a reading after 15 minutes. The antigen test was followed up with a PCR-based test with results returned within 25 hours. If the antigen test indicated no infection and the PCR-based testing indicated a positive result, researchers used the testing samples to determine if virus would grow in cell culture, indicating that the participant would have been infectious.

The study included 412 individuals visiting primary care centers affiliated with the Clínico-Malvarrosa Health Department in Valencia, Spain. There were 43 individuals, corresponding to 10.4%, who tested positive for COVID-19 with both tests, and 358, corresponding to 86.9%, who tested negative by both methods. There were 11 tests, corresponding to 2.7%, that gave negative results with the antigen test and positive results from PCR-based testing. None of the samples with conflicting results were able to produce virus when grown in cell culture.

Based on the results, the authors concluded that the test performed well as a point-of-care test used for diagnosis of COVID-19, and importantly, that those who tested negative with the antigen test, but positive with the PCR-based test, were unlikely to be infectious.

Sofia SARS Antigen Fluorescent Immunoassay

Researchers investigated the ability of the Sofia SARS Antigen Fluorescent Immunoassay to identify individuals with SARS-CoV-2 at two universities in Wisconsin (Pray et al., 2021). The study occurred between September 28 and October 9, 2020 and involved paired testing of 1,098 individuals. The individuals tested were a mix of students, faculty, and other staff or affiliated individuals. Each participant was tested with PCR-based testing and the Sofia antigen test. Samples that tested positive for SARS-CoV-2 with either test were also tested for the presence of active virus by growth in cell culture.

Table 5. Results from antigen testing with the Sofia test

	Number tested	Proportion of the participants	Antigen test sensitivity	Antigen Test Specificity	Positive predictive Value	Negative Predictive Value
Asymptomatic Individuals	871	79%	41.2%	98.4%	33..3%	98.8%
Symptomatic Individuals	227	21%	80.0%	98.9%	94.1%	95.9%

The overall prevalence of COVID-19 in the study group was 5.2% based on PCR-based testing.

In the group of participants reporting symptoms consistent with COVID-19, the proportion of positive antigen tests was 15%, and the proportion of positive PCR-based tests was 17.6%. In the group that did not have potential symptoms at the time of testing, 2.4% were found to be positive with antigen testing, and 2.0% were positive with PCR-based testing. All false-negative results from symptomatic participants were from specimens collected less than 5 days after onset of symptoms.

Based on the evaluation of the accuracy of the Sofia antigen test in real-world conditions, the researchers found that the test was less accurate than reported in the company's tests used to obtain the Emergency Use Authorization from the FDA, which is often the case.

In real-world conditions, the sensitivity was 80.0% and the specificity was 98.9% while in the clinical trial results the sensitivity was 96.7% and the specificity was 100%.

Cell culture experiments showed that active virus could be isolated from 46.6% of the total number of testing samples that were positive for COVID-19, including both antigen and PCR-based tests (total of 73 cases). There were 18 paired tests in the study that had conflicting results between the antigen and PCR test, and two, or 11.1%, produced virus in cell culture experiments, suggesting the individuals were infectious. There were eight false-negative results from antigen tests in symptomatic individuals with antigen testing, and two of the specimens from these tests produced active virus in cell culture, suggesting that the antigen tests did not identify two infectious people.

In response to this outcome, the authors suggest that confirmatory testing with PCR-based testing should be considered following negative antigen test results in symptomatic persons.

The authors were also concerned about the low positive predictive value observed in asymptomatic individuals. The positive predictive value changes based on the prevalence of the disease in the population being tested. Therefore, in groups where there is a high level of infection, the positive predictive value should be higher than when there are few people infected. The population being tested in this study had a high likelihood of being positive, but the positive predictive value was still low at 33.3%. If this test was used in areas with a low prevalence of SRAS-CoV-2 infection, the positive predictive value would be even lower, making the test less useful.

Based on this poorer than expected result, the authors suggest that PCR-based testing should be used to confirm a positive result from a Sofia antigen test in asymptomatic persons.

There were **NO** cases where testing samples from negative antigen tests produced active virus in cell culture.

Therefore, asymptomatic persons with negative antigen results are unlikely to be infected with SARS-CoV-2 and would not require follow-up testing with PCR-based testing.

Overall, the authors suggest that use of serial testing using antigen based tests might allow for the rapid identification of infectious individuals thereby allowing for the control of new outbreaks as long as programs using antigen-based testing account for the lower sensitivity and lower positive predictive value associated with screening asymptomatic individuals.

Abbott BinaxNOW COVID-19 Ag Card

The Abbott BinaxNOW COVID-19 Ag Card, or BinaxNOW, antigen test was also investigated for accuracy when used in a real-world scenario (Prince-Guerra et al., 2021). Researchers investigated the use of the BinaxNOW at community testing centers between November 3 and 17, 2020 in Pima County, Arizona. A total of 3,419 paired tests were completed from individuals 10 years old or older. As in the other studies, testing-samples with positive results were used to determine if active virus was present and would grow in cell culture.

The overall rate of positive PCR-based tests in the group was 8.7%. At the time of testing, 24.2% of people receiving testing reported having at least one symptom that could be a result of COVID-19. In symptomatic individuals, 13.7% received a positive result from the BinaxNOW test, and 21.3% received a positive result from PCR-based testing. In individuals who did not report symptoms, 1.9% had a positive antigen test, and 4.7% received a positive PCR-based test.

Table 6. Results from antigen testing with the BinaxNOW

	Number tested	Proportion of the participants	Antigen Test sensitivity	Antigen Test Specificity	Positive predictive Value	Negative Predictive Value
Asymptomatic Individuals	2,592	75.8%	35.8%	99.8%	91.7%	96.9%
Symptomatic Individuals	827	24.2%	64.2%	100%	100%	96.9%

The positive predictive value for the BinaxNOW test was much higher than that reported in real-world scenarios for the Sofia antigen test (33.3% compared to 91.7%). The value of the positive predictive value is influenced by the prevalence of infections in the population being tested and the specificity of the test. The prevalence of COVID-19 in the group tested with the Sofia test was 5.2%. The authors of the study investigating the Sofia test reported that the prevalence was considered to be relatively high, suggesting that the Sofia test may not have a high enough specificity to prevent false positive results as was mentioned by the authors. Based on the author's statements in this study of BinaxNOW, the prevalence reported, 8.7%, is considered a moderate level of infection, and therefore, the main influence on the positive predictive value would also be the specificity of the test.

The differences in outcome between the Sofia antigen test and the BinaxNOW antigen test illustrate how seemingly small differences in specificity of a test (98.4% versus 99.8% in asymptomatic individuals) can lead to large differences in the performance of a test in a real-world scenario.

The researchers also looked at a sub-group of people who had testing within seven days of symptom onset. Antigen testing may be less accurate during the early course of the disease due to a limited amount of viral protein being produced. For these individuals the sensitivity was 71.1%, the specificity was 100%, the positive predictive value was 100%, and the negative predictive value was 92.7%.

There were four positive results with the BinaxNOW test that were negative with PCR-based testing that were defined as false-positives, and all of the false-positive results occurred in people who were asymptomatic. There were 142 negative results with the BinaxNOW test that were positive with PCR-based testing that were classified as false-negatives, corresponding to 47.5% of the 299 positive PCR-based tests. The false-negative tests occurred in 63 symptomatic individuals and for 79 asymptomatic individuals.

There were 274 positive test samples that could be evaluated for the presence of active virus using cell culture experiments. Out of the 274 samples, 35% contained active virus. There were eleven tests out of the 124 designated as false-negative BinaxNOW results that contained active virus, corresponding to 8.9%.

This means that if only the antigen tests were used for identification of infectious individuals, eleven (8.9%) infectious people would have been incorrectly categorized as negative for COVID-19.

Of the eleven infectious false-negative tests, five of the participants reported having symptoms and the remaining six were asymptomatic. No active virus was detected in the samples that had false-positive BinaxNow results.

The authors also analyzed the specificity and sensitivity of the BinaxNOW test in the sub-group of samples that produced active virus in cell culture, which would be a good representation of those individuals who were infectious. The sensitivity of the antigen test was higher in the group of people who could be considered infectious.

Table 7. Sensitivity of the BinaxNOW test in infectious individuals versus all people tested

	Sensitivity in Infectious Individuals	Sensitivity in Entire Study Population
Asymptomatic	78.6%	35.8%
Symptomatic	92.6%	64.2%

Overall, the BinaxNOW antigen test was still less accurate (had a lower sensitivity) than PCR-based testing in identifying people with COVID-19, but the sensitivity increased for potentially infectious individuals, allowing for good performance in detecting those who are most likely to transmit the virus.

The researchers also reiterated the cautions from the paper by Pray and colleagues about the limits of antigen testing and the need for confirmation of negative antigen tests in people with symptoms (e.g. an elevated probability of a positive test) and in asymptomatic individuals who

receive a positive result who are in settings with a high risk for adverse consequences (e.g. long-term care facilities).

Effect of COVID-19 on Pregnancy Outcome

Researchers evaluated the outcome of pregnancy in women with COVID-19 by investigating information from an insurance database (Jering et al., 2021). The database includes information on about 20% of hospitalizations in the United States, and information on 406,446 women who gave birth between April 1 and November 23,2020 . Within this group, 6,380 women were diagnosed with COVID-19, corresponding to 1.6%. Most were asymptomatic upon admission and were diagnosed through routine testing.

The overall mortality in the group was low for both those with COVID-19 and those without, but in-hospital mortality was higher for women with COVID-19, 141 deaths per 100,000 compared to 5 deaths per 100,000. The rate of myocardial infarction (0.1% versus 0.004%) and venous thromboembolism, or blood clots, (0.2% versus 0.1%) was higher in the group with COVID-19. There was also a higher risk of preeclampsia and preterm birth in women with COVID-19.

These results indicate that prevention of COVID-19 in pregnant women is important due to the higher rates of preterm birth, preeclampsia, thrombotic events, and death in women giving birth with COVID-19.

Long-Term Effects of COVID-19

While the acute phase of COVID-19 has been shown to last for around a week or two, more and more evidence suggests that the virus has longer-term effects on those who have become ill. Importantly, these long-term effects have been shown to not be associated with the severity of the initial illness so that individuals with mild symptoms that did not require medical treatment are just as likely to have symptoms that are present for weeks and months after resolution of the initial infection.

A study from Jin Yin-tan Hospital in Wuhan, China investigated the outcomes of 2,469 individuals who were discharged from the hospital between January 7 and May 29, 2020 after treatment for COVID-19 (Huang et al., 2021).

Of those who were discharged, 736 were excluded from evaluation in the study. Of those who were excluded, there were 460 who did not want to participate, who had moved out of the area, or could not be contacted. There were 214 people had mobility issues that made it difficult to participate, such as osteoarthritis, dementia or psychotic disease, residence in a nursing home, or were unable to move independently. The remaining 62 did not participate in the follow-up study for reasons that may have been associated with having COVID-19. For example, 33 individuals had died after discharge but before the study began (1.3% of the total number discharged), 25 individuals had been readmitted to the hospital, and 4 had experienced thrombotic events after discharge leading to difficulty in moving around. The cause of death for people after discharge but before the study began mainly included worsening of underlying pulmonary, heart, and kidney disease. Those that were readmitted to the hospital were treated

for complications from chronic diseases, and one individual had respiratory failure due to scarring in the lungs.

Information about the 1733 participants who were able to attend in-person appointments and were included in the study was gathered through questionnaires, physical examination, and blood tests. The median age of the participants was 57 years with a range from 47 to 65 years. The most common chronic conditions reported by the participants were hypertension (29%), diabetes (12%), and cardiovascular disease (7%). During treatment for COVID-19, 68% had required oxygen therapy, and 4% had been admitted to the intensive care unit.

The researchers found that six months after symptom onset 76% of patients still reported at least one symptom, and the proportion was higher in women.

The most commonly reported symptoms were fatigue or muscle weakness and sleep difficulties. There was also a high overall rate of depression and anxiety with 23% of the trial group reporting at least one of the conditions.

During the physical exam, 34% of the total group continued to have poor oxygen exchange in their lungs, a condition called diffusion impairment. When evaluated based on subgroups, diffusion impairment was detected in 21% of individuals who had not required oxygen during hospitalization for COVID-19, 29.1% of those who received supplemental oxygen, and 55.8% of those who needed ventilation of any kind or a similar procedure during treatment for COVID-19. The researchers also found that 13% of the participants with normal kidney function during the initial SARS-CoV-2 infection and who did not have a specific kidney injury after discharge showed signs of kidney damage at the follow-up exam, suggesting that there may be kidney damage during infection that becomes apparent over time.

Individuals who had had severe symptoms during the SARS-CoV-2 infection had an increased risk of pulmonary diffusion abnormality, fatigue or muscle weakness, and anxiety or depression compared to the other participants.

The authors conclude that those individuals who were treated in the hospital for severe symptoms of COVID-19 should receive regular check-ups after being discharged due to a large potential for long-term complications. One of the study's co-authors stated that he was "worried about the unknown future for these patients' recovery. At six months after symptoms onset, a considerable proportion of COVID-19 patients had physical and psychological problems" (Cooney, 2021). There are still questions on how long, or if, they will achieve a full recovery.

When discussing the results, a number of experts stated that the impact may be even larger than observed in the study (Lancet, 2021 and Belluck, 2021). One reason is that many of the sickest individuals discharged, e.g. those who lived in nursing homes or were readmitted to the hospital, were not included in this study. The exclusion of this population was due to difficulties in mobility, and the exclusion was implemented to allow for easier collection of information. Subsequent studies can be designed to include more of the entire group discharged as time and resources allow. Additionally, it was noted that only 4% of the study population required treatment in the intensive care unit, which makes the conclusions from the study less robust due to a small number of participants. As there are many people who have required intensive care

during treatment for COVID-19, evaluation of the larger groups may expose higher levels of long-term disability for this group.

Rates of Infection in Children

Researchers from the CDC have updated their evaluation of COVID-19 incidence in the United States and the testing volume for individuals between the ages of zero and 24 years (Leidman et al., 2021). For the purposes of the study, the children and young adults were grouped by school level. The groups were those between zero and four years (preschool), five to ten years (elementary school), 11 to 13 years (middle school), 14 to 17 years (high school), and 18 to 24 years (college or higher education).

Based on the most recent analysis, during the time period from March 1 to December 12, 2020, there were 2,871,828 confirmed cases of COVID-19 in people aged 0 to 24 years in the United States.

Table 8. Proportion of COVID-19 cases by age group.

Age Group	Proportion of COVID-19 Cases
Preschool (0-4 years)	7.4%
Elementary school (5-10 years)	10.9%
Middle school (11 to 13 years)	7.9%
High School (14 to 17 years)	16.3%
College (18 to 24 years)	57.4%

When the percentage of children with COVID-19 was evaluated based on race or ethnicity, 50.2% were white, non-Hispanic individuals, 27.4% were Hispanic/Latino, and 11.7% were Black, non-Hispanic. Unlike the general trend, children of Hispanic or Latino descent had the highest percentage of cases in the youngest group (34.4%), and the proportion of cases decreased with increasing age with 24.6% of COVID-19 case among those between 18 and 24 years.

When the researchers looked at the incidence rate over the study period, they found that the weekly incidence was the highest in the week of December 6 in all age groups.

The trends in increasing weekly incidence mirrored those observed in adults starting in June except for the week of September 6 where young adults aged 18 to 24 experienced a prominent peak in the number of weekly cases. This peak corresponded to the start of school for many individuals in this age group at colleges and universities.

Over the course of the study period, the number of tests in individuals from age zero to 24 increased greatly. From May 31 to December 6, 2020, the weekly testing increased by 423.3%. The peak of testing occurred during the week of November 15, and tests performed on individuals from age zero to 17 during this week made up 9.5% of the total number of tests

performed in the United States. During this same time period, the tests for individuals aged 17 to 24 represented 15.3% of the tests performed in the United States.

The information on hospitalizations, intensive care unit admission, and death was not complete with data available for only 41.9%, 8.9%, and 49.1% of the respective categories.

Based on the available data, the rate of serious disease was low, and 2.5% of individuals aged zero to 24 who were diagnosed with COVID-19 required hospitalization, 0.8% required treatment in the intensive care unit, and less than 0.1% died.

The highest proportion of children and young adults that experienced severe symptoms were in the zero to four year age group, and 4.6% of hospitalizations in individuals under the age of 25 were in young children aged zero to four with 1.8% of intensive care admissions. For comparison in the same time period, 16.6% of adults aged 25 years or older diagnosed with COVID-19 required hospitalization, 8.6% were treated in the intensive care unit, and 5.0% died. The proportion of children and young adults with COVID-19 and at least one underlying, chronic medical condition was 30.3% while 60.4% of adults age 25 or older with COVID-19 had at least one underlying, chronic medical condition.

When the timeline of COVID-19 incidence was evaluated, there was no indication that the increase in incidence or percentage of positive test results among adults was preceded by increases among children and adolescents as would occur if children were driving transmission.

Instead, increases and peaks in incidence in young adults aged 17 to 24 were found to precede increases among all other age groups, suggesting that young adults might contribute more to community transmission than do younger children.

This lack of transmission from children under the age of 17 that was observed occurred even though 62% of kindergarten through grade 12 schools in the United States offered full or partial in-person instruction. One explanation for the low rate of transmission that has occurred in K through 12 schools is that schools are a structured environment that can help to support adherence to mitigation measures. An opposite role in transmission has been the case with colleges and universities that were open for in-person instruction.

The authors conclude that “success in preventing introduction and transmission of SARS-CoV-2 in schools depends upon both adherence to mitigation strategies in schools and controlling transmission in communities.” Additionally, this paper indicates that there is a lower incidence of COVID-19 among younger children aged zero to 17. When taken together with evidence from previous studies, the risk for COVID-19 transmission among children from reopening child care centers and elementary schools appears to be below than that for reopening high schools and institutions of higher education. Current CDC guidelines suggest that K through 12 schools be the last settings to close if community-wide interventions are needed, and suspension of in-person instruction should be employed only after all other mitigation measures have been implemented, such as restrictions of gatherings, indoor dining, etc.

SARS-Cov-2 Transmission in K through 12 Schools

A growing number of research studies suggest that transmission of SARS-CoV-2 in schools for children in kindergarten through grade 12 might not significantly contribute to COVID-19 spread nationwide. Researchers from the CDC released a study that investigated the number of COVID-19 cases, transmission of the virus, and compliance with mask use between August 31 and November 29, 2020 in 17 schools in Wisconsin (Falk et al., 2021). The schools were a mix of public schools, independent private schools, and private-school districts. There were eight elementary schools and nine middle/high schools.

The study included 4,876 students and 654 staff members, and the communities where the schools were located were found to have high rates of community transmission based on the positivity rate of COVID-19 testing that ranged between 7% and 40%. At the time of the study, 12.4% of students were attending school using virtual platforms.

Use of masks for staff and students was mandatory, and student mask use was reported to be higher than 92% with similar levels of compliance in older and younger children.

The schools in the county had received a grant that allowed them to purchase 2 or 3-layer cloth masks for students, and each student received three to five masks through the program. The rules for mask use at school included requirements to wear masks when within 6 feet of another person outdoors and at all times indoors. Classes were organized into cohorts of between 11 and 20 students, and all classes and lunch were held indoors.

The case rate in students and staff was lower than observed in the population of the whole county, and COVID-19 incidence in schools conducting in-person instruction was 37% lower than that in the surrounding community. There were 191 cases identified at the schools during the study period with 58 staff members and 133 students testing positive for COVID-19.

There was no in-school transmission identified amongst the staff members of the schools.

There were seven cases amongst the children at the schools that were found to have occurred through in-school transmission.

Cases of in-school transmission were 3.7% of the total 191 COVID-19 cases identified during the study period.

Five of the seven cases of in-school transmission were in elementary schools and two were identified in middle/high schools. Three of the cases were within one class at an elementary school while the other four occurred at four different schools. None of the cases of in-school transmission occurred between different class-cohorts. Based on the evidence from this study, the authors concluded that most transmission of SARS-CoV-2 occurred outside of required school activities.

Even with the higher rate of asymptomatic infection for children that might lead to a lower rate of identifying cases in students, the absence of identified child-to-

staff member transmission during the 13-week study period suggests in-school spread was uncommon.

Other research studies have reported consistent results that indicate that the transmission from asymptomatic individuals within a household, where unmasked close contact often occurs, is relatively low at 0.7%. Other studies have suggested that there is also a lower rate of transmission from children to adults in households.

Another point that the authors stressed was that the percentage of positive COVID-19 test results in the community was high, ranging from 7% to 40%, and the transmission rate within the schools was still low. Based on this observation, the authors stated that attending in-person school, where recommended mitigation strategies are implemented with high compliance, does not produce an environment with higher risk for transmission of SARS-CoV-2 between children than that in the community outside of the school. Monitoring while in school can increase compliance to behaviors that reduce the risk of transmission, such as mask wearing and physical distancing.

Overall, the authors conclude that allowing children to gather in school settings has not been shown to increase the risk of transmission if mitigation strategies are enforced, and in fact the risk outside of school, where there is less structured monitoring of compliance to these strategies, may be higher.

Effect of New Variants on Transmission in Schools

The spread of new, and more transmissible, variants of SARS-CoV-2 around the world has again complicated the question of the safety of sending children back to in-person classes. While the current research suggests that transmission in school has been low since the start of the new school year in 2020, parents and researchers are struggling with how a more transmissible strain could change that (Lewis, 2021).

The research available on the new variants is still scarce because of how recently they were identified. The most information is available on the B.1.1.7 strain, which was first detected in the United Kingdom.

B.1.1.7 has been shown to be more transmissible in all age groups when compared to earlier variants of SARS-CoV-2.

There were initial reports that children may no longer have a lower rate of transmission, when compared to adults, with the new variant. This would mean that the protection previously observed for children would no longer be provided.

However, as more information has become available, researchers have found that children are still less likely to transmit B.1.1.7 than adults are.

Because they were identified more recently, there is less information known about the variants first identified in South Africa and Brazil. Initial reports suggest similar characteristics to B.1.1.7

in terms of transmissibility where the variants are more transmissible across all age groups but remain less transmissible from children when compared to adults.

The B.1.1.7 variant has caused several outbreaks in primary schools in the Netherlands, and the scenario shows how the increased transmissibility might change discussions on sending more children back to in-person classes in the United States (Vogel, 2021). Until late November, 2020 students attended schools in the Netherlands full-time with normal class sizes, and transmission in the community was low enough that use of masks were not required to prevent transmission at schools.

The first affected school in the Netherlands enrolled children aged 4 to 12 and experienced an outbreak in late November. Health officials were surprised by the number of cases being reported in young children as previous school-related outbreaks had involved mainly high-school aged children or those at universities. By December 16, 40% of the students and almost 50% of the staff at the school were reporting respiratory symptoms, and cases had spread to nearby and associated schools. The first case of B.1.1.7 was identified in the town the school is located in on December 23, and the case was traced back to contacts within the school. By December 26, 818 staff, students, and family members associated with the school had been tested for COVID-19, and 123 cases were identified, corresponding to 15% of the school community. All of the cases associated with the outbreak at the school that have had the genome sequenced were the B.1.1.7 variant.

> **As of January 15, more than 80% of the B.1.1.7 cases in the surrounding community can be linked to the school.**

However, studies in areas where there have been high levels of community transmission, for example in the United States, suggest that even when transmission is high, use of strict measures to control transmission lead to a low level of risk at schools. Research on school outbreaks in North Carolina have shown that strict mask requirements and small class sizes even in areas with a 14-day incidence of more than 900 cases per 100,000 residents provide protection that keeps school outbreaks rare. Similar results were described above in this report for schools in Wisconsin.

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