PINNACLECARE

Medical Intelligence Report

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Topic: Update on COVID-19 Research

At-Home COVID-19 Testing

Ellume

The FDA issued an Emergency Use Authorization (EUA) for the Ellume COVID-19 Home Test, which is an antigen test that can be performed at home without a prescription from a doctor (FDA Ellume, 2020 and Wu, 2020b). The over-the-counter test detects proteins produced by SARS-CoV-2 in nasal swab samples. The test is authorized for use in individuals over the age of two years, and the nasal swab can be self-administered in people over the age of 16 years. The test procedure gives results in about 20 minutes. Tests will be sold in pharmacies and online and are expected to cost around $30.

Ellume reports that they expect to produce more than three million tests in January 2021 and to ship around 100,000 tests per day.

Within the first half of 2021, the company is predicting they will be able to provide 20 million tests to the United States (Georgiou, 2020).

During clinical studies, the Ellume test correctly identified 96% of positive samples and 100% of negative samples in individuals **with symptoms**. Antigen tests are less accurate in people without symptoms because there are typically less viral particles present, making them harder to detect. Trials of the Ellume test showed that it correctly identified 91% of positive samples and 96% of negative samples in individuals **without symptoms**. The test was found to give invalid results, meaning the test did not work properly, in 8% of cases, or 17 out of 209 tests. Nine of the invalid results were due to inadequate amounts of the sample from the nasal swab to perform the test.

The test packet includes a nasal swab, a dropper, processing fluid, and a plastic cartridge that detects antigens. To perform the test, the nasal swab is attached to the dropper after a sample has been collected. Next, the processing fluid is poured into the dropper, and five drops of liquid are placed on the testing cartridge. The test cartridge contains a Bluetooth device that connects to a smartphone app to analyze the results of the test. The results of the test are shown on the phone, and a certificate of testing can be emailed if needed. The smart phone app will automatically send the results of positive tests to local health officials if needed along with the date of birth and zip code of the person taking the test.

The FDA also stressed that “all tests can experience false negative and false positive results. Individuals with positive results should self-isolate and seek additional care from their healthcare provider. Individuals who test negative and experience COVID-like symptoms should follow up with their healthcare provider as negative results do not preclude an individual from SARS-CoV-2 infection.”

Abbott

A second at-home test, the BinaxNOW COVID-19 Ag Card Home Test, was also granted EUA by the FDA (FDA Abbott, 2020 and Abbott, 2020). Unlike the Ellume test, use of BinaxNOW requires a prescription for use, but the BinaxNOW also detects antigens from the SARS-CoV-2 virus. The test is authorized for use at home with self-collected nasal swab samples from individuals who are 15 years or older within the first seven days of symptom onset. The test can also be used by individuals between 4 years and 14 years if the nasal swab is collected by an adult.

The test procedure is supervised through telehealth services from the company eMed.

The observer from eMed establishes the suitability of the individuals to use the BinaxNow test, guides the nasal swab self-collection process, and aids the individual in getting the test results. The telehealth provider will also report all test results to the relevant public health authorities in accordance with local, state, and federal requirements.

The overall performance of the BinaxNOW test had a 91.7% agreement with positive results (sensitivity) and 100% agreement with negative results (specificity) compared to PCR-based tests in people who were tested seven days or less from symptom onset.

In people with high levels of virus, as measured by PCR, there was a 100% agreement with positive results from PCR-based testing when the test was given seven days or less from the start of symptoms. Abbott officials suggest that this allows for reliable identification of people with the highest risk of transmitting SARS-CoV-2 to others, but this statement has not been fully validated with experimental data. The basis of the correlation stems from experiments performed at Abbott where nasal samples with viral RNA below a certain threshold were not able to infect cells grown in culture. The threshold of viral RNA in the experiments was the same as the cutoff where the BinaxNow test was 100% accurate.

The test takes about 15 minutes for results, and is expected to cost $25. To obtain a test, an individual contacts the eMed service through the NAVICA app, which is available on smart phones. After eligibility requirements are determined, the test kit is shipped to the home or a pick-up location that allows for continued quarantine of potentially infected individuals.

Abbott and eMed expect to deliver and administer 30 million BinaxNOW tests in the first quarter of 2021, with an additional 90 million in the second quarter.

Antibody Treatment

REGN-COV2 is an antibody cocktail developed by Regeneron for the treatment of COVID-19 in people 18 years or older who do not require hospitalization (Weinreich et al., 2020). The company has organized a Phase 1 to 3 trial that combines all three phases of investigation in order to increase the speed of the process. They published the interim results for the Phase 1 and 2 sections of the trial in the *New England Journal of Medicine*.

REGN-COV2 consists of a combination of two different neutralizing antibodies for SARS-CoV-2 that prevent the virus from binding to a cell and infecting it. The antibodies, called **casirivimab** and **imdevimab**, are present in equal amounts in the cocktail. The use of an antibody cocktail rather than a single antibody helps to prevent the virus from mutating to become resistant to the treatment.

The report describes the outcome of the first 275 symptomatic participants in the Phase 1 and 2 section of the trial who were treated between June 16 and August 13, 2020. To be eligible for the trial, participants must have received a positive test no more than 72 hours before treatment and have had symptoms for no more than seven days. The median age of participants was 44 years, and 49% were male, 13% identified as Black or African American, and 56% identified as Hispanic or Latino. The median number of days since symptom onset before treatment was three. Participants were screened to determine if they had begun producing their own antibodies towards SARS-CoV-2 in order to investigate a possible difference in outcomes based on timing of the treatment. Before treatment was started, 45% of the participants were positive for antibody, 41% were negative, and 14% had an unknown status.

Participants were randomly assigned to receive a placebo, a low dose of the antibody cocktail (2.4 g) or a high dose of the cocktail (8.0 g). The treatment is given as an intravenous infusion that takes about an hour. REGN-COV2 must be administered under medical supervision because some people have a strong immune response to the sudden rise of antibodies in the bloodstream, which is referred to as an **infusion reaction**.

As part of the trial, the researchers also investigated the general course of the disease without the use of medication to better understand changes that occur in people with mild COVID-19. They found that people who had not started producing their own antibodies had higher levels of virus present than those who had antibodies at the start of the trial. Also, participants with antibody production at the start of the trial who did not produce neutralizing antibodies had similar levels of virus to those not producing any antibodies, highlighting the importance of neutralizing antibodies in the immune response to SARS-CoV-2. The researchers also evaluated of the need for medical intervention for COVID-19 symptoms and found that people who were producing their own antibodies were less likely to require a medical visit for treatment of symptoms.

Efficacy of the antibody treatment was observed in participants receiving both the low and high dose of the antibody cocktail based on a reduction in the amount of virus present. As might be expected, the amount of virus declined in all of the participants regardless of treatment as the infection resolved, but the reduction was larger in those receiving the antibody cocktail compared to those in the placebo group. The majority of the reduction in virus levels occurred within 2 days of the infusion.

The researchers also evaluated the number of people who required medical treatment of COVID-19 from a provider. They found that 6% of participants who received the placebo required a visit to a healthcare provider compared to 3% of those who received the REGN-COV2.

The difference in the proportion of people requiring medical treatment for COVID-19 between the study groups was even larger when only participants who did not produce their own antibodies at the start of treatment were evaluated.

The researchers report that 15% of the participants in the placebo group who had not been producing their own antibodies at the start of the trial required a visit for treatment of COVID-19 symptoms compared to 6% of those in the REGN-COV2 group who were not producing their own antibodies at the start of the trial. There was not a difference in the time until symptoms resolved between the treatment groups and the placebo group.

The number of serious adverse events (e.g. infusion-related reactions and hypersensitivity reactions) reported during the trial were similar between the placebo and REGN-COV2 groups. Both doses of REGN-COV2 used in the trial had few adverse effects reported, and those that were observed were mainly categorized as low-grade. The amount of antibodies from the cocktail measured in the blood of participants was similar for both casirivimab and imdevimab, and the half-life (time it takes for the amount to reduce by one half) for both antibodies was estimated to be between 25 and 37 days.

Based on the results, the authors conclude that the antibody cocktail had the most benefit in participants who were not producing their own SARS-CoV-2 targeted antibodies at the start of the trial and use of REGN-COV2 enhanced clearance of the virus and reduced the number of participants who required a medical visit for treatment of COVID-19.

Contribution of Different Non-Pharmaceutical Interventions on Transmission

Researchers have constructed a model of the effects of non-pharmaceutical interventions (attempts to reduce transmission without the use of drugs) on COVID-19 transmission in 41 countries between January and the end of May 2020. Based on the evaluation, there were several interventions that led to a reduction in the reproduction number of SARS-CoV-2. The **reproduction number** is the number of people one person with SARS-CoV-2 will infect with the virus.

Effective interventions include:

- Business closures and gathering bans have been effective at reducing COVID-19 transmission.
- Closing most face-to-face businesses was only somewhat more effective than targeted closures of establishments with a high infection risk, such as bars, restaurants, and nightclubs
- Limiting gatherings to 10 people or less was more effective than limits of up to 100 or 1000 people.
- Issuing a stay-at-home order had a small effect when a country had already closed educational institutions, closed non-essential businesses, and banned gatherings.
- There was a large effect after closing both schools and universities at the same time, but it was not possible to distinguish between schools for younger children and young adults based on the available data.

Rate of Hospital Readmission or Death after Initial Discharge from COVID-19 Treatment

Researchers in the Veterans Affairs (VA) health care system published a report on the rate of readmission to the hospital after discharge of an individual who was treated for COVID-19 (Donnelly et al., 2020). The authors report on the outcomes of individuals after the initial hospitalization, including rate of readmission, reason for readmission, and rate of death after readmission.

Information on veterans from 132 hospitals around the United States was included with admission dates between March and June, 2020 and initial discharge dates between March and July, 2020. During this time period, 2,179 veterans were treated in VA hospitals for COVID-19. Within this group, 31.1% were treated in an intensive care unit, 12.8% required mechanical ventilation, 14.1% required use of drugs to control blood pressure due to septic shock (vasopressors), and 81.5% survived to discharge.

Within 60 days of being discharged from the hospital, 27% of individuals treated for COVID-19 were readmitted or died.

The researchers compared this rate to those observed for other serious conditions, including pneumonia from other sources or heart failure. Early after discharge, individuals who had been hospitalized for COVID-19 were more likely to require readmission or die than those who were treated for pneumonia from other causes (13.4% versus 9.7%) or heart failure (13.9% versus 8.8%). However, when evaluated over 60 days, the rate of death of readmission for individuals with COVID-19 was lower than the rate observed for individuals who were treated for pneumonia from other causes (26.1% versus 31.7%) or heart failure (27.0% versus 37.0%).

These results suggest that there may be a period of heightened risk of clinical deterioration in the first ten days after discharge from the hospital for treatment of COVID-19.

Excess Deaths in Individuals between the Age of 25 and 44 Years

An analysis of the excess mortality in adults from 25 to 44 years of age between March and July, 2020 in the United States was performed to determine the impact on this age group (Faust, et al., 2020). Normally, the largest cause of death in this age group is accidental opioid overdose, and for comparison, the researchers reported that there were a total of 10,347 unintentional opioid deaths among adults aged 25 to 44 years in the United States from March through July of 2018.

From evaluating the compiled data from the pandemic time period, the researchers found that there were 76,088 deaths from any cause in people from 25 to 44 years of age, which is 11,899 more deaths than during this timeframe in 2015 to 2019.

During the study period, there was an increased number of deaths in every month and in every region of the United States. Overall, deaths recorded from COVID-19 accounted for 38% of the excess deaths during the time period. However, in areas where there were surges in the number of cases in the community, the proportion of excess deaths attributed to COVID-19 was higher. For example, during the early surge in New York and New Jersey, 80% of excess deaths were related to COVID-19 in 25 to 44 year olds. In the early summer surges in Arkansas, Louisiana, New Mexico, Oklahoma, and Texas, 48% of excess deaths were related to COVID-19, and in Arizona, California, Hawaii, and Nevada, 40% of excess deaths were from COVID-19.

The study was not designed to determine if the 68% of the excess deaths not attributed to COVID-19 were due to under-reporting of COVID-19 deaths or if they occurred from some other cause such as increased opioid use or avoidance of treatment of serious conditions during the pandemic.

However, the number of excess deaths observed suggests that there is a noteworthy effect from the pandemic on this age group that has not been emphasized.

Differences between COVID-19 and Influenza

Researchers examined the characteristics of all people hospitalized for COVID-19 from March 1 to April 30, 2020 in France for a comparison with all people hospitalized for influenza between Dec 1, 2018, and Feb 28, 2019 (Piroth et al., 2020). In total, 89,530 patients with COVID-19 and 45,819 patients with influenza were hospitalized in France during the respective study periods and were included in the study.

It was found that individuals with COVID-19 were more likely to be obese or overweight than people hospitalized for influenza. Additionally, those with COVID-19 more frequently had diabetes, hypertension, and dyslipidemia (abnormal cholesterol levels) while hospitalized individuals with influenza were more likely to have heart failure, chronic respiratory disease, cirrhosis, and deficiency anemia. After admission, people with COVID-19 were more likely to develop acute respiratory failure, pulmonary embolism, septic shock, or hemorrhagic stroke

than patients with influenza, but they were less likely to develop atrial fibrillation or myocardial infarction.

Table 1. Characteristics of individuals hospitalized with COVID-19 or influenza in France.

Characteristic	Individuals with COVID-19	Individuals with Influenza
Median age	68 years	71 years
In-hospital mortality	16.9%	5.8%
Proportion of patients under 18	1.4%	19.5%
Proportion of patients younger than 5 years needing intensive care support	2.3%	0.9%
In-hospital mortality for adolescents (11–17 years)	1.1%	0.1%

COVID-19 was found to have a higher risk for respiratory problems during hospitalization, leading to more respiratory complications and to higher mortality. The analysis indicates that there is a 2.9-fold increase in the risk of death from COVID-19 compared to influenza overall. The increase for younger individuals was larger than for adults with a 10-fold increase in mortality for people age 11 to 17 with COVID-19 compared to influenza.

For children, the rate of hospitalization to treat COVID-19 is lower than for influenza, but in-hospital mortality is higher in those with COVID-19.

Similar findings were reported from a study evaluating the outcome of individuals treated at VA health centers throughout the United States (Xie et al., 2020). The records of 3,641 patients treated for COVID-19 between February 1 and June 17, 2020 were compared with 12,676 patients treated for influenza between 2017 and 2019.

The researchers found that people with COVID-19 had a higher risk of death, an increased need for mechanical ventilation, a higher requirement for treatment in the intensive care unit, and spent an extra three days in the hospital compared to people with influenza.

Importantly, both influenza and COVID-19 can cause damage to the lungs, but there was also a high rate of damage to other organs in people with COVID-19. For example, COVID-19 was associated with a higher risk of acute kidney injury, new need for dialysis, insulin dependency, severe septic shock, and the need for vasopressors to raise abnormally low blood pressure. There was also an elevated risk for pulmonary embolism, deep-vein thrombosis, stroke, acute inflammation of the heart muscle, heart rhythm abnormalities and sudden cardiac death, elevated troponin levels (indicating heart attack or damage), rhabdomyolysis (rapid muscle breakdown), and elevated levels of aspartate aminotransferase and alanine aminotransferase, which both are indicators of liver damage.

COVID-19 in Children

Researchers investigated the factors associated with children testing positive for COVID-19 to determine where they are most likely to be infected (Hobbs et al., 2020). This study compared the potential exposure from school, the community, or close contacts in 394 children under the age of 18 years who were tested for COVID-19 through the University of Mississippi Medical Center (UMMC) at either outpatient testing centers (including drive-up testing locations) or emergency departments between September 1 and November 5, 2020. From the entire group, 53% of the children were tested because they were experiencing symptoms.

Attendance at school or day care within the last 14 days was reported by 62% of participants who tested positive for COVID-19 and in 68% of participants who tested negative.

Based on the analysis, attendance at school or day care was NOT associated with a positive SARS-CoV-2 test result, but inconsistent use of masks while at school was associated with a positive SARS-CoV-2 test.

Based on the recollection of parents, the rate of mask use by children and staff while at school or day care was 64% for those with a positive test and 76% for those with a negative test.

In the two weeks before getting tested, children who received a positive test were more likely (compared to children testing negative) to have had close contact with someone who was positive for COVID-19, to have attended gatherings and social functions with persons outside their household, to have activities with other children outside of school, or to have had visitors in the home. Among those who tested positive for COVID-19 in this study, 69% reported close contact with a person with COVID-19, and most close contact exposures were to family members. The high number of cases from exposure to family members is consistent with previous reports of high levels of transmission within households.

Based on the results of the study, the researchers conclude that

- Close contacts with individuals with COVID-19 and gatherings contribute to SARS-CoV-2 infections in children and adolescents.
- Attendance at school with consistent mask use is not associated with receiving a positive COVID-19 test.
- Consistent use of face masks and social distancing continue to be important to prevent COVID-19 spread.

References

Abbott. Abbott's Binaxnow Covid-19 Rapid Test Receives FDA Emergency Use Authorization For First Virtually Guided, At-Home Rapid Test Using eMed's Digital Health Platform. Published December 16, 2020. Accessed on December 28, 2020 at https://abbott.mediaroom.com/2020-12-16-Abbotts-BinaxNOW-COVID-19-Rapid-Test-Receives-FDA-Emergency-Use-Authorization-for-First-Virtually-Guided-At-Home-Rapid-Test-Using-eMeds-Digital-Health-Platform

Brauner JM, Mindermann S, Sharma M, Johnston D, Salvatier J, Gavenčiak T, Stephenson AB, Leech G, Altman G, Mikulik V, Norman AJ, Monrad JT, Besiroglu T, Ge H, Hartwick MA, Teh YW, Chindelevitch L, Gal Y, Kulveit J. Inferring the effectiveness of government interventions against COVID-19. *Science*. 2020 Dec 15:eabd9338.

Ellume. COVID-19 Home Test. Published 2020. Accessed on December 28, 2020 at https://www.ellumehealth.com/products/consumer-products/covid-home-test

FDA. Coronavirus (COVID-19) Update: FDA Issues New Authorization for the BinaxNOW COVID-19 Ag Card Home Test. Published December 16, 2020. Accessed on December 28, 2020 at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-new-authorization-binaxnow-covid-19-ag-card-home-test

FDA. Coronavirus (COVID-19) Update: FDA Authorizes Antigen Test as First Over-the-Counter Fully At-Home Diagnostic Test for COVID-19. Published on December 15, 2020. Accessed on December 28, 2020 at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-antigen-test-first-over-counter-fully-home-diagnostic

Georgiou A. Where to Buy FDA-Authorized Ellume At-home COVID Test and How Much It Costs. *Newsweek*. Published December 16, 2020. Accessed on December 29, 2020 at https://www.newsweek.com/covid-test-ellume-fda-how-buy-cost-1555142

Jin J, Agarwala N, Kundu P, Harvey B, Zhang Y, Wallace E, Chatterjee N. Individual and community-level risk for COVID-19 mortality in the United States. *Nat Med.* 2020 Dec 11.

Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, Musser BJ, Soo Y, Rofail D, Im J, Perry C, Pan C, Hosain R, Mahmood A, Davis JD, Turner KC, Hooper AT, Hamilton JD, Baum A, Kyratsous CA, Kim Y, Cook A, Kampman W, Kohli A, Sachdeva Y, Graber X, Kowal B, DiCioccio T, Stahl N, Lipsich L, Braunstein N, Herman G, Yancopoulos GD; Trial Investigators. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. *N Engl J Med*. 2020 Dec 17.

Wu KJ. New At-Home Covid Test Gets Green Light From F.D.A. *The New York Times*. Published December 15, 2020. Accessed on December 28, 2020 at https://www.nytimes.com/2020/12/15/health/rapid-covid-test-ellume.html?smtyp=cur&smid=tw-nytimes