PINNACLECARE

Medical Intelligence Report

Date: September 29, 2020

Topic: Update on COVID-19 Research

Potential Treatments for COVID-19

Baricitinib Antibody Treatment

Eli Lilly and researchers from the Adaptive COVID-19 Treatment Trial (ACTT-2) sponsored by the National Institute of Allergy and Infectious Diseases announced their initial, interim findings from the trial of an antibody treatment called baricitinib in a press release. Baricitinib is an orally administered antibody that is currently approved for treatment of rheumatoid arthritis. The antibody targets a protein called Janus kinase (or JAK), which is involved in the regulation of pro-inflammatory cytokines.

The clinical study is a Phase 3 trial investigating the outcome of baricitinib plus remdesivir versus remdesivir alone in 1000 hospitalized patients with COVID-19 (Lilly, 2020). **Analysis of the interim data indicates the combination of baricitinib and remdesivir led to a reduction in the median recovery time of one day compared to participants receiving only remdesivir.** There were also beneficial effects based on the assessment of participant health on day 15 after the start of treatment. The details of the study have not yet been released, and the information has not been made available for perusal by experts outside the trial. Lilly has stated they are planning to use the information from the trial to discuss Emergency Use Authorization for baricitinib from the FDA.

Neutralizing Antibody Treatment

A second trial sponsored by Lilly, called BLAZE-1, is a Phase 2 clinical trial investigating the effect of a neutralizing antibody against SARS-CoV-2 that was developed by the company (Lilly, 2020). Lilly and the sponsors of the trial announced the interim results in a press release. The trial involves testing of three different doses of the antibody, called LY-CoV555, in participants recently diagnosed with mild-to-moderate COVID-19. The effect of the antibody was compared to a placebo.

The efficacy of the treatment was evaluated by measurement of the amount of viral RNA present eleven days after the start of treatment. Most of the participants, including those who received the placebo had nearly complete clearance of the virus by the assessment point on the eleventh day, making it difficult to observe any difference of an effect with the treatment.

Additionally, only the middle dose of the three tested resulted in a reduction in the amount of viral RNA by day eleven when compared to the levels of the placebo group. The lack of a response of the higher dose has raised some concerns because usually an increased dose leads to a corresponding increase in effect from a medication (Herper and Garde, 2020). Lilly suggested that the manner used to assess recovery, measurement of viral RNA, may have had difficulty detecting the low amounts in some participants leading to what seemed to be a lack of effect.

The researchers' design of the trial was based on known clearance rates of the virus, but the time period utilized may have been too long so that all of the participants recovered regardless of treatment status.

Earlier assessment at three days after the start of treatment indicated that use of LY-CoV555 reduced the proportion of participants with high levels of virus.

Another outcome measurement had a more definitive positive effect. The researchers also indicated that the use of LY-CoV555 led to a reduction in the risk of hospitalization. The company reported that 6% of participants taking the placebo went to the emergency room or were hospitalized, but only 1.7% of those taking LY-CoV555 required treatment at a hospital or emergency room.

Use of LY-CoV555 led to a 72% relative reduction in the risk of hospitalization or need for an emergency room visit.

These results are preliminary because they only include some of the participants from the total expected enrollment of the final study. For example, the data used to calculate the reduction in risk of hospitalization included only five of the 302 participants receiving LY-CoV555 and nine of the 150 participants in the placebo group. The smaller number of individuals included in the analysis, the less likely it is that the effect will still be evident in a larger population.

Nasal Spray and Oral Rinses

Because the initial point of infection for COVID-19 is in the nose and mouth, it is possible that nasal and oral rinses could affect the infectivity of the virus.

Researchers have been investigating use of a povidone-iodine nasal antiseptic solution at three concentrations (0.5%, 1.25%, and 2.5%) for use in clinical situations to reduce the possibility of transmission to healthcare personnel (Frank et al., 2020). Providers in otolaryngology (ear, nose, and throat specialists) are more likely to be exposed to virus during exams or surgery due to the proximity to the nose and mouth of individuals. Previous research of SARS-CoV-1 and MERS-CoV has indicated that use of povidone-iodine solutions are effective at inactivating the virus, allowing for sterilization of the nasal cavity before procedures.

In this study, researchers tested the effect of the solutions on infected cells grown in a laboratory setting. Experiments were performed to determine the number of virus particles inactivated by povidone-iodine, water (a negative control with no effect), and ethanol (a positive control known to inactivate the virus). The tested concentrations of povidone-iodine greatly

reduced the amount of infectious virus in the samples without damage to the cells themselves when applied for either 15 or 30 seconds. In fact, the povidone-iodine solution worked better than the ethanol solution utilized as a positive control for the tests. Rinsing the cells with water had no effect on the amount of infectious virus as expected.

However, use of high concentrations of povidone-iodine have been shown to cause inhibition of mucous clearance in the nasal and respiratory tracts due to disruption of the movement of cilia in the system.

Cilia are long, thin protrusions from the surface of a cell that functions to sweep material out of an area. Clinical studies reported previously indicate that lower concentrations of povidone-iodine can be administered either for a single procedure or over a period of months with no adverse effects to the function of the cilia.

Based on the information from this study, the researchers conclude that contact for 15 seconds with 1.25% povidone-iodine formulations is sufficient for viral inactivation prior to intranasal procedures, and the process is expected to decrease risk of virus transmission via droplets or aerosol formation for healthcare providers.

Other potential applications of the povidone-iodine nasal rinse include nasal decontamination before individuals arrive at the provider's office to decrease the amount of virus in the upper respiratory system and potentially prevent spread in waiting areas and other common areas. Providers with exposure to the upper respiratory tracts of individuals during treatment may also consider use of nasal decontamination when putting on or taking off a mask. It is estimated that the decontamination effect after a 15 second spray continues for four hours.

Occasional use of povidone-iodine nasal sprays has been shown to be safe, but excess use can lead to absorption of iodine and cause thyroid disease.

This type of preventive treatment should not be used for individuals who are allergic to iodine, pregnant women, those with active thyroid disease, and individuals undergoing radioactive iodine therapy. **Additionally, it is not recommended that individuals prepare their own nasal preparations from commercially available iodine antiseptics because most are formulated for use on skin and contain additives that are toxic for nasal use**. Povidone-iodine solutions degrade quickly and are only good for a single day and need to be refrigerated once opened.

Researchers have also investigated the possible reduction in transmission with use of oral rinses (Meister et al., 2020). The theory of the practice is to lower the number of active virus particles from the nasal passages and oral cavity of **infected individuals** to reduce their capacity to transmit SARS-CoV-2. There are several commercially available dental mouthwashes that contain additives known to damage the external surface of the virus, but it has not been determined if applying mouthwash is sufficient to inactivate the virus in a real-world situation. In this study, the researchers investigated the efficacy of eight commercially available mouthwashes to inactivate SARS-CoV-2 in conditions that mimic nasal secretions. Three viral strains obtained from circulating virus in Germany were used in the tests. The mouthwash brands, active ingredients, and the effect on SARS-CoV-2 are listed in Table 1.

Table 1. Effect of commercially available mouthwash on SARS-CoV-2 inactivation.

Mouthwash Name	Active Ingredients	Effect on SARS-CoV-2
Cavex Oral Pre Rinse	Hydrogen peroxide	Moderate inactivation
Chlorhexamed Forte	Chlorhexidinebis (D-gluconate)	Moderate inactivation
Dequonal	Dequalinium chloride, benzalkonium chloride	Reduced viral infectivity to limit of detection
Dynexidine Forte 0.2%	Chlorhexidinebis (D-gluconate)	Moderate inactivation
Iso-Betadine mouthwash 1.0%	Polyvidone-iodine	Reduced viral infectivity to limit of detection
Listerine Cool Mint	Ethanol, essential oils	Reduced viral infectivity to limit of detection
Octenident mouthwash	Octenidine dihydrochloride	Moderate inactivation
ProntOral mouthwash	Polyaminopropyl biguanide (polyhexanide)	One virus strain moderately reduced and other two reduced to limit of detection

Based on the results of the experiments, the researchers conclude that multiple different SARS-CoV-2 strains can be efficiently inactivated with commercially available oral rinses under biologically relevant conditions mimicking respiratory secretions.

Three of the formulations reduced the viral load to below detectable limits. Clinical trials to reproduce the effects in human volunteers have been organized, which will compare the effects of three solutions after rinsing or gargling in individuals with confirmed cases of COVID-19.

Officials Have Questions about AstraZeneca Vaccine Trials

AstraZeneca voluntarily suspended their COVID-19 vaccine trial due to detection of a potentially serious neurological disorder in a participant in the United Kingdom. The safety review board of the study determined that the incident was unrelated to administration of the vaccine, and the trial was resumed.

However, officials from the National Institutes of Health in the United States have voiced concerns about continuing the vaccine trial in the United States due to limited information provided by the researchers in the United Kingdom (Allen and Szabo, 2020 and Grady et al., 2020). Even the diagnosis of the affected participant has yet to be officially reported to researchers in the United States although unofficial reports from those associated with the case have stated that it was transverse myelitis. Officials were also upset that the FDA was not specifically alerted when the United Kingdom trial was paused. There is particular interest for researchers involved in the trial in the United States to be allowed to review the details of the decision to continue the trial in the United Kingdom.

On September 19, AstraZeneca released more details about the vaccine trial, including information that normally is not available until the end of the trial (Grady et al., 2020). In the protocols of the trial, the company describes that the goal is to determine if the vaccine is 50% effective, the threshold set by the FDA. The plan also includes an interim analysis of the collected data at the halfway point of the trial. The more interim evaluations that are planned into a trial, the less rigorous it is. This occurs because an interim analysis includes fewer participants than the full trial, and data calculated from fewer individuals can lead to a false appearance of efficacy and safety not observed with the full dataset. Rarer side effects might also be missed when fewer people are included in the workup. Because this vaccine would potentially be given to the entire world population, the presence of rare side effects is an important factor and can lead to injury of a substantial number of people.

Caution should be used when deciding to approve a vaccine or treatment using only interim results because fewer people are included in the calculations.

Johnson & Johnson Begins Phase 3 Trial of Potential COVID-19 Vaccine

Johnson & Johnson announced they are beginning the Phase 3 trial of their potential COVID-19 vaccine in which they plan to enroll 60,000 participants (Zimmer and Thomas, 2020). The company also stated that results from the study would be expected to be available by the end of the year. The vaccine is an adenovirus-based vaccine that carries genes for specific proteins from SARS-CoV-2, which are inserted into cells in the vaccinated individual, and the genes are used by the cell to produce viral proteins that are detected by the immune system to initiate an immune response.

SARS-CoV-2 Infection Effects and New Potential Treatments

Researchers have performed an assessment of the differences in gene expression in cells obtained from the bronchial fluid of individuals from Wuhan who were infected with SARS-CoV-2 (Garvin et al., 2020). Based on their analysis, earlier reports were confirmed that infection with the virus leads to dysregulation of the system responsible for modulating blood pressure in the cells of the lungs (Roche and Roche, 2020).

After a cell is infected with SARS-CoV-2, a protein produced by the virus inhibits the production of a key molecule within in the cell (called **NF-kappaB**) that is involved in regulation of numerous functions. This reduction in the amount of NF-kappaB by SARS-CoV-2 is a pivotal alteration to the cell that seems to set off a string of changes associated with COVID-19. For example, when less NF-kappaB is produced, there is also a reduction in the amount of interferon produced by the cell. **Interferon** is released from a cell after infection by a virus to alert neighboring cells, and when the nearby cells interact with interferon there are changes to those cells that make it more difficult for a virus to gain entry. Previous studies have shown there is a reduction in the levels of interferon in people with COVID-19, and the lower amounts were correlated with higher virus levels, an increased inflammatory response, and an overall reduction in the immune response to SARS-CoV-2 infection (Lee et al., 2020 and Blanco-Melo et al., 2020).

NF-kappaB is also part of the **renin angiotensin system**, or **RAS**, and the interplay between proteins of this system controls the permeability of the blood vessels to fluid and molecules thereby changing blood pressure. Two of the main opposing components of the RAS are the **ACE and ACE-2 receptors**. Increased activity of the ACE receptor leads to an increase in blood pressure while an increase in ACE-2 lowers blood pressure.

It was observed that infection with SARS-CoV-2 leads to a reduction in the amount of ACE receptor produced on the surface of cells as well as a 200-fold increase in the amount of ACE-2 receptor produced.

As has been mentioned before, SARS-CoV-2 utilizes the ACE-2 receptor on the surface of a cell to attach to and infect the cell.

With the increased production of ACE-2 receptor, there is was also an increase in the production of one of the RAS-coupled proteins called bradykinin. **Bradykinin** causes dilation of blood vessels and allows fluid to cross the vessel walls. The increase in fluid outside of the blood vessels from this process leads to swelling of the tissue and an increased inflammatory response. In the normal process of blood pressure regulation, the amount of bradykinin is controlled by the ACE receptor, which functions to degrade the protein and remove it from circulation. The site where ACE is normally most active in removing bradykinin is the lungs. When the amount of ACE receptor is suppressed, as with SARS-CoV-2 infection, the amount of bradykinin is higher than usual and blood pressure is reduced (hypotension).

Based on the changes in gene expression observed, the researchers suggest that the broad variety in COVID-19 symptoms may stem from systemic effects of increased levels of circulating bradykinin and the eight-fold reduction of ACE in the lung that would normally degrade it.

Another system that was found to have an altered level of gene activation after SARS-CoV-2 infection was the production of hyaluronic acid, which is a complex sugar molecule normally present in connective tissue and joints. Hyaluronic acid is used as a shock absorber in joints, and the molecule can absorb up to 1,000 times its weight in water, forming a stiff substance like gelatin. After infection by SARS-CoV-2, cells in the lungs were found to greatly increase the production of hyaluronic acid and decrease the production of proteins used to remove the molecule.

The increased fluid in the lungs from excess bradykinin combined with high levels of hyaluronic acid in the internal space of the lungs leads to the formation of a viscous gel that impedes the exchange of gases.

Autopsies of individuals who have died from COVID-19 indicate that the lungs weigh 4.6 times as much as expected due to the formation of hyaluronic acid gel inside.

A correlation between SARS-CoV-2 infection and vitamin D deficiency was also addressed in this study. The vitamin D receptor, a protein on the surface of cells that binds vitamin D, was found to be produced at half the normal level when the cell was infected by SARS-CoV-2, and

proteins that metabolize vitamin D are produced at higher levels. Vitamin D also is part of the RAS and deficiencies are associated with an increased risk of severe lung complications.

Potential Treatments Revealed from Analysis of Gene Activation with SARS-CoV-2

There are several medications that target the systems identified in the gene expression study that are readily available for testing as a treatment for COVID-19. These potential treatments are listed in Table 2 (Garvin et al., 2020 and Roche and Roche, 2020).

Table 2. Potential COVID-19 treatments identified by Garvin and colleagues

Drug	Predicted Effect	Approval Status
Danazol, Stanozolol	Reduce bradykinin production	FDA approved for other disease
Icatibant	Reduce bradykinin signaling	FDA approved for other disease
Ecallantide	Reduce bradykinin production	FDA approved for other disease
Berinert, Cinryze, Haegarda	Reduce bradykinin production	FDA approved for other disease
Vitamin D	Reduce renin production	FDA approved as supplement
Hymecromone	Reduce hyaluronic acid	Approved in Asia for other diseases
Timbetasin	Increase breakdown of blood clots	In Phase 3 trials for other diseases

Icatibant is currently part of the I-SPY COVID-19 trial, which is one of the platform trials designed to rapidly screen potential treatments. It is a Phase 2 trial enrolling critically ill participants who have been diagnosed with COVID-19.

A longer-term goal suggested by the authors of the study would be to design inhibitors of the viral protein that initiates the above effects on NF-kappaB when SARS-CoV-2 infects a cell. This protein is called $3CL^{pro}$. While the time frame required to design and test such a treatment may not lead to treatments for the current SARS-CoV-2 pandemic, the authors propose that it seems likely that there will be future coronavirus outbreaks where such a treatment would be useful.

Transmission of SARS-CoV-2

A representation of how transmission of SARS-CoV-2 can affect both individuals and the community has been reported in a cluster that occurred after a wedding in Maine that occurred

in August (Kornfield, 2020). The wedding included around 65 guests to an indoor ceremony and reception even though local mandates restricted gatherings to under 50. As of September 16, 175 cases have been traced to attendees of the wedding as well as seven deaths of individuals who did not attend. The so-called superspreader event occurred even though the community rate of infections was low and the area is not densely populated

One instance of spread within the community occurred through the pastor who officiated the ceremony. Ten cases were later identified at the church where he preaches. Other outbreaks that have been connected to attendees at the wedding include outbreaks at a county jail in York County, which was more than 200 miles from the site of the wedding, and a nursing home 100 miles from the wedding where six people have died.

The event is a reminder that between 10% and 20% of infected people are responsible for 80% of the spread of SARS-CoV-2 through superspreader events, and that infections can quickly spread to others in the community.

Use of Personal Protective Equipment

As the pandemic initially unfolded, two of the world's major health organizations, the WHO and CDC, both stated that use of masks was not helpful and may even be worse than not using a mask. Since then, they have both reversed their positions and suggest that individuals should cover their mouth and nose with a mask when around others (CDC_Overview, 2020). The reversal was based on the fact that many people do not exhibit symptoms while they are infectious and from experiments that showed that even masks that were not medical grade were able to prevent droplets from being spread (Fischer, 2020). In other words, masks were able to keep those who were infectious from transmitting the virus to others.

A new report in the CDC publication, *Emerging Infectious Diseases*, presents evidence that use of a mask also protects wearers from infection from close contact with individuals who are infected with COVID-19.

The study was performed in Thailand, and involved contact tracing of 1049 people who had a known exposure to someone with COVID-19 (Doung-ngern et al., 2020). The exposures occurred within three clusters, a group of nightclubs, boxing stadiums, and a state office building. The participants in the study were asymptomatic when tested, but 84% of the people involved were considered to have had a high-risk exposure to COVID-19. Subsequent testing revealed that 211 had COVID-19, and 839 never tested positive. The secondary attack rate, which is the probability of infection among susceptible people in a group, for each scenario was calculated and is listed below.

The secondary attack rate for each scenario

- 86% at the boxing stadiums
- 18.2% at the nightclubs
- 16.5% within households
- 4.9% within workplaces
- 1.4% at other places

The characteristics of the participants during exposure were evaluated by phone interviews that included questions about whether participants wore a mask during the contact with the infected individual, the type of mask worn, and the frequency of wearing a mask during the contact. Other questions included the frequency of handwashing while with the infected individual, if they practiced social distancing, or if they had physical contact with the infected person.

Wearing a mask at all times during contact with an infected individual was found to be associated with a lower risk for infection with SARS-CoV-2.

Wearing a mask sometimes during contact with an infected person did not lower the infection risk. The type of mask worn was not associated with the risk of infection, and both medical grade masks and cloth masks were found to reduce the risk. The authors also reported that handwashing and social distancing were associated with a lower risk of infection in the settings investigated in the study.

The researchers conclude that the evidence from the study supports recommendations to wear a mask correctly and at all times while in public in order to reduce the risk of infection with SARS-CoV-2 after contact with an infected person.

Transmission on Commercial Airplane Flights

Two studies were published in the CDC sponsored publication *Emerging Infectious Diseases* that detail instances of COVID-19 transmission on commercial flights.

In the first, researchers performed an in-depth assessment of the risk for transmission from infected passengers to other passengers or crew members during the course of a flight on March 2 that began in London, United Kingdom and flew to Hanoi, Vietnam (Khanh et al., 2020). A cluster of infection was identified after the flight that involved 16 individuals. A single passenger seated in business class was the first identified case in the group (or the index case) and was experiencing a sore throat and cough during the flight. It was determined that the index case was infected during travels in Italy and other areas in Europe, and her traveling partner, who resides in London, was also diagnosed with COVID-19 in London after departure of the flight to Hanoi. There were 217 passengers and crew aboard the flight, and contact tracing was conducted for all passengers and crew that remained in Vietnam (168 individuals). Thirty-three passengers had continued on to other countries and were not available to the researchers for evaluation.

It was determined that 12 passengers in business class were infected with SARS-CoV-2 in addition to two travelers and a flight attendant who were in economy class during the flight. Of the 15 cases that were acquired in-flight, 80% were seated in business class. The secondary attack rate in business class was found to be 62%. Proximity to the index case during the flight was strongly associated with an increased infection risk, and 92% of passengers within two meters of the index case, which corresponds to about two seats away or closer, were infected. Those in business class who were more than two meters away had a lower risk of infection, and 13% of the individuals in this group were infected.

There were some questions about the infection source for the crew member and passengers in economy class because two passengers next to the two who tested positive continued their travel out of Vietnam and were not available for assessment. Because of the separation from the known index case in business class, the cases in economy class could potentially be a separate index case that was infected before boarding with transmission while on board. The potential role of surfaces on the plane containing infectious particles or intermingling during boarding or arrival could not be evaluated but may also have been associated with transmission of SARS-CoV-2 to the individuals in economy class. The researchers were not able to sequence the virus transmitted on this flight to confirm the same strain was involved in all passengers, but information on the timing of diagnosis, symptoms, and previous potential exposures indicate that the 15 people who tested positive after the flight were infected while on board.

The authors indicate that their results suggest additional interventions, beyond wearing a mask, may be needed for international air travel because of the longer duration of the flights.

They propose increasing the distance between passengers and skipping the middle seat in rows. Additionally, they mentioned that screening measures for symptomatic individuals proved to be inadequate as they did not identify the index case on this flight even though passengers were evaluated for fever before boarding.

The second case of inflight transmission was reported from a flight originating in Boston, Massachusetts and ending in Hong Kong on March 9 through March 10 (Choi et al., 2020). The index cases were a married couple seated in business class during the flight, and SARS-CoV-2 infection was transmitted to two flight attendants who were in close contact with the couple during the flight. Both of the index cases developed symptoms after the flight on March 10, including fever, productive cough, and sore throat. The couple had visited Toronto, Canada, New York City in New York, and Boston during their travels spanning February 15 to March 9.

The first flight attendant was asymptomatic and was tested on March 16 after being informed of close contact with the index cases during the flight. The second flight attendant developed fever and a cough on March 18 and was later hospitalized for COVID-19. A secondary attack rate for the flight could not be calculated because not all the passengers on the flight were tested, but no other cases were known to have been associated with this flight.

The researchers were able to sequence the virus from the four individuals, and it was found that the samples were 100% identical. The strain of virus collected from individuals on the flight had not previously been observed in Hong Kong, but was identified in individuals in Toronto, New York City, and Massachusetts.

This is the first case of inflight transmission that could be corroborated by genetic sequencing of the virus from infected individuals, and both the genetic evidence and timing of diagnosis, symptoms, and previous potential exposures indicate that transmission of SARS-CoV-2 occurred during the flight from Boston to Hong Kong.

Nursing Homes

A report from the CDC publication *Morbidity and Mortality Weekly Report* indicates that nursing homes with higher ratings on the Centers for Medicare and Medicaid Services (CMS) star quality ratings had a lower risk of having a COVID-19 outbreak than facilities with lower ratings (Bui et al., 2020). The study included information on COVID-19 cases from all CMS-certified nursing homes in West Virginia as of June 11, and an outbreak of COVID-19 was defined as two or more cases within 14 days. The star ratings were assigned based on inspections conducted between December 13, 2018 and February 26, 2020.

There were outbreaks in 11%, or 14 facilities, of the 123 nursing homes evaluated for the study with a total of 226 cases among residents and 140 cases among staff. The outbreak status of the facilities by the star rating is listed in Table 3.

Table 3. Outbreak status by star rating

Facility Ranking	Proportion of Facilities with Ranking	Number (Proportion) of Facilities with an Outbreak	Number (Proportion) of Facilities without an Outbreak
One star	16%	7 (50%)	20 (12%)
Two star	28%	0	34 (31%)
Three star	23%	5 (36%)	23 (21%)
Four Star	18%	1(7%)	21 (19%)
Five Star	14%	0	18 (17%)

The analysis showed that the odds of a COVID-19 outbreak at a one-star facility was seven times higher than the odds at a two to three-star facility and 17 times higher than at four to five-star facility.

There was also a higher level of community transmission in counties where there was a nursing home outbreak (178 per 100,000 people) compared to those without outbreaks (105 per 100,000 people). For each additional 10 cases per 100,000 in the county, there was a 5% increase in the odds of a nursing home in that county having an outbreak.

Effect of Racial Injustice Protests on Transmission

Researchers evaluated the anonymous cell-phone tracking data from May 25 to July 7 in 315 cities with a population over 100,000 people as well as the prevalence of COVID-19 in the weeks after the protests to determine if there was increased transmission of the virus (Dave et al., 2020). Of the 315 cities included in the analysis, 286 had protests and 29 did not. Of the

cities where protests occurred, 74.5% had protests for three or more days, and 47.2% of the cities included protests with crowds over 1,000 people.

Based on the cell-phone information, the researchers found that there was a net increase in social distancing due to community members who did not attend the protests increasing their social distancing behaviors.

The increase in social distancing behaviors in the community became evident three days from the start of the initial protests and peaked a week after the start of the protests. By the end of the study time-period, social distancing behavior had returned to the levels observed before the protests. On average, people in the counties where the protests occurred remained at home for 12.5 hours per day, corresponding to 89.6% of the time.

While the general trend was for increased social distancing, there is concern that individual protesters may have transmitted the virus within their homes and lead to increased community spread. Evaluation of data from county health departments showed that there was no difference in SARS-CoV-2 transmission rates for 35 days after the start of protests between counties that had protests and those that did not. Expansion of the analysis to bordering counties also indicated no increase in transmission after protests.

Based on the available information, there was no evidence of an increase in net COVID-19 case numbers or growth in mortality after racial injustice protests in the counties where they occurred.

The authors also state, “while it is possible that the protests caused an increase in the spread of COVID-19 among those who attended the protests, we demonstrate that the protests had little effect on the spread of COVID-19 for the entire population of the counties with protests.” While there was no net effect, the available data was not able to determine if there were adverse outcomes in subsets of the population, such as attendees, however.

COVID-19 and Pregnancy

Testing of women admitted to labor and delivery units in New York City, New York; Boston, Massachusetts; and Philadelphia, Pennsylvania indicates the rate of asymptomatic pregnant women ranged from 1.5% to 13% during early periods of the pandemic. The lowest rate (1.5%) was reported for Boston between April 18 and May 5 (Goldfarb et al., 2020). New York City reported 13% between the end of March and first part of April (Sutton et al., 2020 and Vintzileos et al., 2020). Philadelphia reported a rate of 9.6% between April and May (Cronin et al., 2020).

The authors of the report from Philadelphia suggest that there is a high rate of asymptomatic, pregnant women who could potentially infect staff in labor and delivery units, making the use of personal protective equipment necessary.

They also suggest that the low levels reported in Boston may be an outlier, and the reasons for the lower rate are not easily identifiable.

A report published in the CDC's *Morbidity and Mortality Weekly Report* includes information from a longer time range and includes clinical characteristics as well as birth outcomes (Delahoy et al., 2020). The study investigated hospitalized women with laboratory confirmed SARS-CoV-2 from March 1 to August 22.

There were 7,895 hospitalized women aged 15 to 49 years with COVID-19 during the study period, and 26.5% were pregnant. The majority of the pregnant women (74.7%) were hospitalized for obstetric indications, which includes labor and delivery, while 18.8% were in the hospital for COVID-19 related illness and 6.5% were hospitalized for other reasons. It was found that 2.3% were hospitalized in the first trimester, 10.2% were in their second trimester, and 87.4% were in their third trimester.

There was a much higher proportion of pregnant women with COVID-19 who were asymptomatic (54.5%) in this study than in previous reports. Women who were in the first or second trimester of pregnancy were more likely to have symptoms associated with COVID-19 (84.0%). Of the symptomatic, pregnant women with COVID-19, 16.2% required treatment in the intensive care unit, 8.5% required mechanical ventilation, and 0.7% (corresponding to two women) died. None of the pregnant women with COVID-19 who did not have symptoms were admitted to the intensive care unit, required mechanical ventilation, or died.

At the time of discharge from the hospital, 76.6% had completed pregnancies consisting of 97.8% live births. Loss of pregnancy was observed in both symptomatic and asymptomatic women. 87.4% of the live births were delivered at 37 weeks or greater (considered full term). The proportion of pre-term births was higher in the group of women experiencing symptoms (23.1%) than in the group of asymptomatic women (8.0%). There were two deaths of newborns, and both were born to women experiencing symptoms from COVID-19 who required mechanical ventilation.

Importantly, the prevalence of preterm delivery during COVID-19 associated hospitalizations (12.6%) was higher than the rate in the general U.S. population in 2018 (10.0%), and preterm birth was three times as likely for women with symptoms of COVID-19.

Additional losses of pregnancy associated with COVID-19 may be occurring during the earlier stages of pregnancy, but the information used for this study included only medically attended pregnancy loss.

The authors conclude that severe illness and adverse birth outcomes were observed among hospitalized pregnant women with COVID-19, and that pregnant women should continue to limit their exposure to infection through stringent use of social distancing and mask use.

Testing

The CDC updated their recommendations for testing, and the overview of testing on the CDC website again suggests that asymptomatic persons, including close contacts of a person with

documented SARS-CoV-2 infection, should be tested for COVID-19 (CDC-Overview of Testing, 2020).

Indicators for School Opening

The CDC released more specific indicators that can be used to evaluate the risk of having students attend school (CDC-Indicators, 2020). Generally, the indicators are the number of new cases in the community in the last 14 days, the percentage of tests that are positive in the last 14 days, and the ability of the school to implement certain mitigation strategies.

Key mitigation strategies for schools recommended by the CDC

- Consistent and correct use of masks
- Social distancing to the largest extent possible
- Hand hygiene and respiratory etiquette
- Cleaning and disinfection
- Contact tracing in collaboration with local health department

The primary indicators from the recommendations are listed below in Table 4. The CDC also listed secondary indicators that they suggest that schools should adopt to the extent possible, practical, and feasible, which are shown in Table 5.

Table 4. Specific indicators to determine the risk of students attending school.

Indicators	Lowest Risk	Lower Risk	Moderate Risk	Higher Risk	Highest Risk
Number of new cases per 100,000 persons within the last 14 days	Less than 5	5 to less than 20	20 to less than 50	50 to less than 200	More than 200
Percentage of RT-PCR tests that are positive during the last 14 days	Less than 3%	3% to less than 5%	5% to less than 8%	8% to less than 10%	More than 10%
Ability of the school to implement the 5 key mitigation strategies	All 5 strategies used correctly and consistently	All 5 strategies used correctly but inconsistently	Used 3-4 strategies correctly and consistently	Used 1-2 strategies correctly and consistently	Used no strategies

While there are five key mitigation strategies that are included in the CDC indicators, they also have a larger list of recommendations that are expected to reduce the risk of transmission in schools.

Full list of mitigation strategies recommended by the CDC to reduce transmission of SARS-CoV-2 in schools:

- Encourage consistent and correct use of face masks, by all students, teachers, and staff.
- Maintain a distance of at least 6 feet between people.
- Teach and reinforce handwashing with soap and water for at least 20 seconds and increase monitoring to ensure adherence among students and staff.
- Clean and disinfect frequently touched surfaces.
- Systematic contact tracing of infected students, teachers, and staff in collaboration with local health department.
- Create smaller groups, or cohorts, within the school that are kept separate during the school day.
- Making sure individuals stay home when ill and educating everyone on procedures to return to school after being ill.
- Stagger school arrival and drop-off times or locations by cohort, to limit contact between cohorts and direct contact with parents.
- Alternate schedules with cohorts of students and staff to decrease class size and promote social distancing to prevent wide scale transmission.
- Limiting outside visitors to the school.
- Ensure ventilation systems operate properly and increase circulation of outdoor air as much as possible.
- Take steps to ensure that all water systems and features (e.g., sink faucets, decorative fountains) are safe to use after a prolonged facility shutdown.
- Install partitions in areas where it is difficult for individuals to remain at least 6 feet apart.
- Halt shared use of spaces such as eating areas and playgrounds.
- Avoid self-serve food or drink options.

Based on the CDC website, the indicators are meant to be used as broad guideposts to inherent risk to inform decision-making. They do not specify precise cutoffs based on the category of risk for reopening schools, but instead state that “the risk of introduction and subsequent transmission of SARS-CoV-2 is higher and the school could consider alternative learning models.” The CDC website also states that even if a school meets all of the indicators, there could still be transmission of COVID-19 and cases of infected individuals who caught the virus in the community. Reducing the risk of transmission in schools involves both a low rate of community transmission and adherence to school and community mitigation strategies.

Table 5. Secondary indicators that should be used to determine risk for school if feasible.

Secondary Indicators	Lowest Risk	Lower Risk	Moderate Risk	Higher Risk	Highest Risk
Percent change in new cases per 100,000 population during the last 7 days compared with the previous 7 days (negative values are improving trends)	Less than -10%	-10% to less than -5%	-5% to less than 0%	0% to more than 10%	More than 10%
Percentage of occupied hospital inpatient beds in the community	<80%	<80%	80 to 90%	>90%	>90%
Percentage of occupied intensive care unit beds in the community	<80%	<80%	80 to 90%	>90%	>90%
Percentage of hospital inpatient beds occupied by patients with COVID-19 in the community that are	<5%	5% to <10%	10% to 15%	>15%	>15%
Localized community or public setting COVID-19 outbreak	No	No	Yes	Yes	Yes

There has been some concern about the ability of parents to get their children tested, however (Kliff and Sanger-Katz, 2020). The community sites often do not allow testing of children due to potential problems such as differences in health insurance, medical privacy rules, holes in test approval, and concerns over difficulty in performing tests on reluctant children. Many physician's offices have limited testing available for children, and the number of tests available are not adequate to test children who are not symptomatic or have not had a known interaction with a confirmed case, which is the type of testing that would be required for monitoring cases in schools.

A number of districts around the country have re-opened to onsite learning, but there has been difficulty in determining the extent of cases because of varying reporting in different states (Avila et al., 2020). The New York Times attempted to compile the available information though their efforts were hampered by the fact that eleven states do not publish information on school cases. The report published on September 21 included the officially reported information when available as well as information collected from state and local health and education agencies and through directly surveying school districts in eight states.

While it is possible in some cases to determine the number of COVID-19 cases occurring in students and staff, the effect of these cases on community spread cannot yet be evaluated. There are indications that some larger clusters include transmission in the schools rather than identification of cases acquired in the community.

Administrators are reporting that there is some difficulty with staffing due to the need to quarantine staff exposed to people with COVID-19 and isolated staff with COVID-19. In one Kentucky district, there have been only 21 cases identified in the 10,300 students and 17 cases among staff members. However, 59 staff members have also been quarantined due to exposure. The organization within the district is set up to accommodate for 50 staff members being absent on any day, but substitutes are in short supply because they are typically retired teachers who would be at increased risk due to their age. School closings of elementary and high schools were necessary not because of a transmission but due to staff shortages.

References

Allen A, Szabo L. NIH 'Very Concerned' About Serious Side Effect in Coronavirus Vaccine Trial. *Kaiser Health News*. Published September 14, 2020. Accessed September 17, 2020 at https://khn.org/news/nih-and-fda-examine-serious-side-effect-that-surfaced-in-covid-vaccine-trial/

Avila Y, Cai W, Harvey B, Love J, Lutz E, Matthews AL, Taylor K. What We Know About Coronavirus Cases in K-12 Schools So Far. *The New York Times*. Published September 21, 2020. Accessed on September 22, 2020 at https://www.nytimes.com/interactive/2020/09/21/us/covid-schools.html

Blanco-Melo D et al., SARS-CoV-2 launches a unique transcriptional signature from in vitro, ex vivo, and in vivo systems. *bioRxiv*. Published March 24, 2020. Accessed on August 11, 2020 at https://www.biorxiv.org/content/10.1101/2020.03.24.004655v1

Bui DP, See I, Hesse EM, et al. Association Between CMS Quality Ratings and COVID-19 Outbreaks in Nursing Homes — West Virginia, March 17–June 11, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1300–1304.

CDC. CDC Releases Indicators for Dynamic School Decision-Making. Published September 15, 2020. Accessed on September 18, 2020 at https://www.cdc.gov/media/releases/2020/s0915-dynamic-school-decision-making.html

CDC. How to Protect Yourself & Others. Published September 11, 2020. Accessed on September 22, 2020 at https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html

CDC. Indicators for Dynamic School Decision-Making. Published September 15, 2020. Accessed on September 18, 2020 at https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/indicators.html

CDC. Overview of Testing for SARS-CoV-2. Published 18, 2020. Accessed on September 18, 2020 at https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html

Choi EM, Chu DKW, Cheng PKC, Tsang DNC, Peiris M, Bausch DG, et al. In-flight transmission of severe acute respiratory syndrome coronavirus 2. *Emerg Infect Dis*. 2020 Nov.

Cronin S, Piacquadio M, Brendel K, Goldberg A, Goldberg M, White C, Jaspan D, Goldberg J. RE: Universal SARS-CoV-2 testing on admission to the labor and delivery unit: Low prevalence among asymptomatic obstetric patients. *Infect Control Hosp Epidemiol*. 2020 Jul 30:1. doi: 10.1017/ice.2020.382. Epub ahead of print. PMID: 32729454; PMCID: PMC7438617.

Dave DM, Friedson AI, Matsuzawa K, Sabia JJ, Safford S. Black Lives Matter Protests, Social Distancing, and COVID-19. *The National Bureau of Economic Research*. Published August, 2020. Accessed on September 16, 2020 at https://www.nber.org/papers/w27408

Delahoy MJ, Whitaker M, O'Halloran A, et al. Characteristics and Maternal and Birth Outcomes of Hospitalized Pregnant Women with Laboratory-Confirmed COVID-19 — COVID-NET, 13 States, March 1–August 22, 2020. *MMWR Morb Mortal Wkly Rep*. ePub: 16 September 2020.

Doung-ngern P, Suphanchaimat R, Panjangampatthana A, Janekrongtham C, Ruampoom D, Daochaeng N, et al. Case-control study of use of personal protective measures and risk for SARS-CoV-2 infection, Thailand. *Emerg Infect Dis.* 2020 Nov

Fischer EP, Fischer MC, Grass D, Henrion I, Warren WS, Westman E. Low-cost measurement of face mask efficacy for filtering expelled droplets during speech. *Sci Adv*. 2020 Sep 2;6(36):eabd3083. doi: 10.1126/sciadv.abd3083. PMID: 32917603.

Frank S, Brown SM, Capriotti JA, Westover JB, Pelletier JS, Tessema B. In Vitro Efficacy of a Povidone-Iodine Nasal Antiseptic for Rapid Inactivation of SARS-CoV-2. *JAMA Otolaryngol Head Neck Surg.* 2020 Sep 17. doi: 10.1001/jamaoto.2020.3053. Epub ahead of print. PMID: 32940656.

Garvin MR, Alvarez C, Miller JI, Prates ET, Walker AM, Amos BK, Mast AE, Justice A, Aronow B, Jacobson D. A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm. *Elife*. 2020 Jul 7;9:e59177. doi: 10.7554/eLife.59177. PMID: 32633718; PMCID: PMC7410499.

Goldfarb IT, Diouf K, Barth WH, Robinson JN, Katz D, Gregory KE, Ciaranello A, Yawetz S, Shenoy ES, Klompas M. Universal SARS-CoV-2 testing on admission to the labor and delivery unit: Low prevalence among asymptomatic obstetric patients. *Infect Control Hosp Epidemiol*. 2020 Sep;41(9):1095-1096. doi: 10.1017/ice.2020.255. Epub 2020 May 27. PMID: 32456729; PMCID: PMC7287300.

Grady D, Wu KJ, LaFraniere S. AstraZeneca, Under Fire for Vaccine Safety, Releases Trial Blueprints. *The New York Times*. Published September 19, 2020. Accessed on September 21, 2020 at https://www.nytimes.com/2020/09/19/health/astrazeneca-vaccine-safety-blueprints.html

Herper M, Garde D. Lilly's Covid-19 antibody helps some patients rid their systems of virus sooner in early analysis. *STAT News*. Published 16, 2020. Accessed on September 17, 2020 at https://www.statnews.com/2020/09/16/lilly-covid-19-antibody-helps-patients-rid-their-systems-of-virus-sooner/

Khanh NC, Thai PQ, Quach H-L, Thi NA-H, Dinh PC, Duong TN, et al. Transmission of severeacute respiratory syndrome coronavirus 2 during long flight. *Emerg Infect Dis*. 2020 Nov

Kliff S, Sanger-Katz M. It's Not Easy to Get a Coronavirus Test for a Child. *The New York Times.* Published September 8, 2020. Accessed on September 17, 2020 at https://www.nytimes.com/2020/09/08/upshot/children-testing-shortfalls-virus.html

Lee JS, Park S, Jeong HW, et al. Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19. *Sci Immunol*. 2020;5(49):eabd1554. doi:10.1126/sciimmunol.abd1554

Lilly. Baricitinib in Combination with Remdesivir Reduces Time to Recovery in Hospitalized Patients with COVID-19 in NIAID-Sponsored ACTT-2 Trial. Published September 14, 2020. Accessed on September 17, 2020 at https://www.prnewswire.com/news-releases/baricitinib-in-combination-with-remdesivir-reduces-time-to-recovery-in-hospitalized-patients-with-covid-19-in-niaid-sponsored-actt-2-trial-301129865.html

Lilly. Lilly announces proof of concept data for neutralizing antibody LY-CoV555 in the COVID-19 outpatient setting. Published 16, 2020. Accessed on September 21, 2020 at https://www.prnewswire.com/news-releases/lilly-announces-proof-of-concept-data-for-neutralizing-antibody-ly-cov555-in-the-covid-19-outpatient-setting-301131785.html

Kornfield M. Maine wedding 'superspreader' event is now linked toseven deaths. None of those people attended. *The Washington Post*. Published on September 16, 2020. Accessed on September 24, 2020 at https://www.washingtonpost.com/health/2020/09/15/maine-wedding-covid/

Meister TL, Brüggemann Y, Todt D, Conzelmann C, Müller JA, Groß R, Münch J, Krawczyk A, Steinmann J, Steinmann J, Pfaender S, Steinmann E. Virucidal Efficacy of Different Oral Rinses Against Severe Acute Respiratory Syndrome Coronavirus 2. *J Infect Dis*. 2020 Sep 14;222(8):1289-1292. doi: 10.1093/infdis/jiaa471. PMID: 32726430; PMCID: PMC7454736.

Peccia J, Zulli A, Brackney DE, Grubaugh ND, Kaplan EH, Casanovas-Massana A, Ko AI, Malik AA, Wang D, Wang M, Warren JL, Weinberger DM, Arnold W, Omer SB. Measurement of SARS-CoV-2 RNA in wastewater tracks community infection dynamics. *Nat Biotechnol*. 2020 Sep 18. doi: 10.1038/s41587-020-0684-z. Epub ahead of print. PMID: 32948856.

Roche JA, Roche R. A hypothesized role for dysregulated bradykinin signaling in COVID-19 respiratory complications. *FASEB J.* 2020 Jun;34(6):7265-7269. doi: 10.1096/fj.202000967. Epub 2020 May 2. PMID: 32359101; PMCID: PMC7267506.

Sutton D, Fuchs K, D'Alton M, Goffman D. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. *N Engl J Med.* 2020 May 28;382(22):2163-2164. doi: 10.1056/NEJMc2009316. Epub 2020 Apr 13. PMID: 32283004; PMCID: PMC7175422.

Vintzileos WS, Muscat J, Hoffmann E, John NS, Vertichio R, Vintzileos AM, Vo D. Screening all pregnant women admitted to labor and delivery for the virus responsible for coronavirus disease

2019. *Am J Obstet Gynecol.* 2020 Aug;223(2):284-286. doi: 10.1016/j.ajog.2020.04.024. Epub 2020 Apr 26. PMID: 32348743; PMCID: PMC7194835.

Zimmer C, Thomas K. Johnson & Johnson's Vaccine Advances, Sparking Optimism in Race. *The New York Times*. Published September 23, 2020. Accessed on September 24, 2020 at https://www.nytimes.com/2020/09/23/health/covid-19-vaccine-johnson-and-johnson.htm