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Medical Intelligence Report

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Topic: COVID-19 Research Update

Increases in COVID-19 Cases and Deaths

There are preliminary signs that the number of new cases in the United States may have started to plateau, but the level of newly infected people each day is still higher than during the previous peak of infection in April that was located in New York City and surrounding areas (JHU, 2020). The United States has the highest total daily incidence of SAR-CoV-2 infections in the world and has the 5th highest per capita daily incidence rate in the world. **Over the weekend of July 25, the United States had two of the highest daily incidence totals with a new record high of 74,818 new cases in one day**. As of July 28, 2020 California (over 516,851 cases), Florida (491,884 cases), and Texas (456,624) have surpassed the total number of people who have been infected in New York state (416,843 cases) the site of the initial peak of the outbreak. Evaluation of the number of total infections adjusted for population (cases per 100,000 people) shows that Louisiana, Arizona, and Florida have moved ahead of New York in this metric as well (JHU Coronavirus Resource Center, 2020).

Table 1. Highest confirmed cases per 100,000.

State	Confirmed Cases per 100,000 population
Louisiana	2593
Arizona	2503
Florida	2309
New York	2133
New Jersey	2050
Mississippi	2047
Alabama	1896
Georgia	1858
South Carolina	1828
Rhode Island	1820

There were 10 days between July 21 and August 4 where there were **more than 1,000 deaths a day from COVID-19** in the United States, and the country is now averaging more than 1100 deaths per day as of the August 4 report from Johns Hopkins University. The number of deaths per day is increasing in areas such as California, Texas, and Florida where there are large outbreaks as well as in a number of other states where infections have been rising. The number of people dying in Texas each day from COVID-19 is estimated to be approximately 250, while

Florida reports more than 150 and California has more than 100 deaths each day from COVID-19. On a per capita basis, Arizona has the highest number of deaths each day with 1 death per 100,000 population per day, compared to approximately 0.5 for Florida and Texas and 0.25 for California.

The United States has **three times more total deaths** than any other country, except Brazil. Evaluation of reported cases shows that the United States has 22% of the global deaths and 26% of the global cases while representing only 4.3% of the global population. In terms of per capita cumulative deaths, the United States is eighth in the world.

The number of people who have died from COVID-19 so far this year as of July 31 is over 150,000.

> **Based on reports from previous years from the CDC, death from COVID-19 is the 6th leading cause of death in the United States having surpassed Alzheimer's disease, diabetes, and influenza/pneumonia.**

Based on projections made by the CDC, it is expected that the total number of deaths in the United States from COVID-19 will be between 160,000 and 175,000 by August 15th (CDC, 2020). That would move **COVID-19 into the 3rd leading cause of death in the United States behind heart disease and cancer.** The current number three is unintentional injury with 167,127 deaths reported in 2018, the most recent year for which information has been released (Howard, 2020). The number of new deaths from COVID-19 in the United States over the next four weeks is expected to exceed the number reported for the previous four weeks. When regions of the country were examined separately, researchers from the CDC estimated that the number of deaths are expected to increase in a similar manner in 25 states and one territory (CDC, 2020).

Resource Shortages

Shortages have begun to occur again as areas of the country see large increases in new cases of COVID-19 and the associated high hospitalization rates. As observed during the first peak in cases, hospitals are running short on personal protective equipment, and there are shortages of staff and medications leading to an inability to treat patients.

Hospitalization Rates

Hospitalization rates in several areas of the country have reached the capacity of local hospitals, leading to a need to transfer patients to other facilities hundreds of miles away while making tough choices about rationing care. The associate medical director of the emergency department at Tampa General Hospital in Tampa, Florida told the *Washington Post* that "We can withstand a surge. We can withstand a disaster. But we can't withstand a disaster every single day. How many jumbo jet crashes can you handle before you run out of capacity? That's what we're facing."

Houston and rural areas in the south part of the state have been the hardest hit regions in Texas. In Houston, patients are being treated for COVID-19 in the emergency room for days because there is nowhere else to move them. There are reports that Houston-based hospitals are telling emergency responders that they cannot accept new patients due to a lack of space and resources (Ornstein and Hixenbaugh, 2020). The situation is especially dire in Starr County, Texas, which is a small rural area that normally has eight intensive care unit beds at the Starr County Memorial Hospital, the only hospital in the community (Chavez, 2020 and Koop, 2020). They were able to increase the number of beds to 29, but they have run out of space for new patients. The only option is to transfer patients to hospitals in other areas, but those hospitals are also reporting that they are nearly full. Due to the deteriorating situation, Jose Vasquez, the county health authority, announced the formation of a committee to help medical workers determine ways to allocate scarce medical resources to patients with the best chance to survive. **If a patient is likely to die based on the criteria approved by the committee, they will be sent home to be cared for by relatives**. Vasquez stated at the press conference that "those patients that most certainly do not have any hope of improving, they are going to be better taken care of within their own family in the love of their own home rather than thousands of miles away dying alone in a hospital room." The governor of Texas, Greg Abbott announced that medical teams from the United States Navy would arrive to assist with the situation in the southern part of Texas, which includes Starr County.

Southern California hospitals are also having to divert patients to other facilities, some as far away as 600 miles (Witte and Weiner, 2020). In Imperial County, which is along the Mexican border, hospital officials are sending people to Sacramento in northern California, which is a nine hour drive. The mayor of the city has reported that hospitals in Miami, Florida are at 95% capacity as of July 16. The average length of stay in the hospital at the University of South Florida for people needing care for COVID-19 is 12 days, and doctors are being transferred from other specialties to treat those with COVID-19. Regular patient visits are being conducted remotely or canceled. Mississippi is also reporting similar strains on hospital resources, and a state Health Officer reported that the lack of capacity is harming patient care.

Due to the large number of individuals needing treatment, teams across Texas are beginning to organize crisis-care models that allow hospitals to triage resources based on patients' likelihood of survival as mentioned in Starr County. Arizona has already enacted similar crisis-care models, but as of yet there has been capacity to transfer people to hospitals in Phoenix. Officials in Arizona report that they are running short on staff, but would still have physical space for more beds if there were more staff to care for all the patients using the beds. Because the many of cases are occurring in a specific geographical area, hospitals are not able to utilize the normal protocols put in place to accommodate an emergency increase in the number of patients. Facilities throughout the Southwest region of the United States are being affected at the same time so that coordination is not possible.

Staffing Issues

Staffing is reported to be the biggest concern of hospital administrators, and hospitals are competing against each other to hire contract workers (Witte and Weiner, 2020). Nurses are being offered twice the normal rate by some facilities, which many hospitals do not have the resources to accommodate. Federal help is beginning to arrive from the Defense Department

and FEMA, but local doctors and nurses are reaching the breaking point according to Saskia Popescu, a University of Arizona epidemiologist who described the falling morale of staff from the climbing death toll in the state. It is unknown if the addition of more health providers will improve the situation because it was not effective when applied to New York City. During the New York outbreak, federal help was not implemented fast enough or in the right way to ease the burden, and it remains to be seen if federal groups will be able to scale up more efficiently this time.

The lack of staff is also being affected by a number of hospitals furloughing healthcare workers, including nurses and doctors (Fadel et al., 2020). The United States Labor Department reports that 1.4 million health care workers lost their jobs in April with an additional 42,000 laid off in March. Of those who were furloughed, 135,000 were employed at hospitals. The administration of the healthcare systems site the reduction in revenue generating procedures and appointments that patients are not scheduling due to the pandemic.

A review of the medical leave associated with COVID-19 for emergency responders and firefighters in New York City showed that there were high levels of infection for those responding to calls during the outbreak in New York City (Prezant et al., 2020). The authors of the study investigated medical leave between March 1 and May 31. In previous years, the baseline level of EMS and firefighters on medical leave was 6.1% and 6.8%, respectively. **The peak of individuals on medical leave occurred in April of 2020 with 19.3% of EMS and 13.0% of firefighters**. The mean duration of medical leave was 25.3 days for those with confirmed cases of COVID-19 and 19.8 days for those with suspected cases that were not able to be tested. As of March 31, 40.7% of EMS responders and 34.5% of firefighters who were on medical leave had suspected or confirmed COVID-19. Of those who were sick with COVID-19, 1.2% required hospitalization, and 4 out 8281 individuals had died. The high amount of personnel affected reduced the available workforce as there was a surge in cases in New York City and a surge in the demand for services. In previous reports, the COVID-19 infection rates for health care workers in China was 1.1% and between 14% and 18% in the Netherlands.

Amnesty International reports that an estimated **3,000 healthcare workers from 79 different countries have died from COVID-19** (Van Beusekom, 2020c). The majority of those who have died were located in the United State, the United Kingdom, and Russia. It is estimated **that 507 healthcare workers in the United States have died from COVID-19**. Another report by Kaiser Health News estimated that the number of medical personnel who have died in the United States is closer to 600 as of July 29, and that **in some areas medical personnel are 20% of known coronavirus cases** (Kaiser Health News, 2020). The International Council of Nurses has estimated that 230,000 healthcare workers have been sickened throughout the world during the pandemic and more than 600 nurses have died. Healthcare workers throughout the world are also reporting incidents of discipline, violence, arrest, unfair or no pay, and discrimination while working to treat patients, and whistleblowers who have brought attention to problems at facilities have been fired and arrested.

Hospital Costs

The non-profit Fair Health uses their database of health care claims to investigate costs of healthcare and information about healthcare usage, and they have access to 30 billion private

healthcare claim records. The researchers have produced a report about the health insurance claims submitted between January and May of 2020 (Fair Health, 2020). Based on their analysis, the median charge for in-patient treatment for COVID-19 in **people aged 23 to 30 was $34,662** and **$45,683 for those aged 51 to 60**. The amounts for use of systems that were in-network ranged from $17,094 to $24,012. They found that most people (33%) had their first contact for treatment of COVID-19 from a health provider's office while 23% were first treated as in-patients in a hospital setting. As age increased, however, individuals were more likely to have their first encounter in an in-patient setting, and **people over the age of 61 were most commonly first seen for treatment of COVID-19 at inpatient centers**.

The researchers also projected the total costs of hospitalization for COVID-19 based on estimates of incidence rates from epidemiologists at Harvard University. It has been projected that between 20% and 60% of the adult global population will be infected by SARS-CoV-2. Based on the current United States population, this means that between 66 million and 198 million adults in the United States could be infected. At the time of the analysis, 50% of those with COVID-19 were not requiring medical care. Of those with symptoms requiring medical attention, **15% to 20% required treatment in the hospital**. This means that between 33 million and 100 million will seek medical care. Calculations based on the lower incidence rate and the lower rate of people requiring hospital care indicate that 5 million people could be treated in the hospital during the pandemic. Using the highest incidence rate and the highest rate of people requiring care for the calculation, it was estimated that up to 20 million people could be treated in the hospital for COVID-19. They estimated that the total average charge per COVID-19 patient requiring an inpatient stay would be $73,300 and the total average estimated allowed amount per commercially insured patient is $38,221.

> **Using the database of health insurance claims, the researchers found that the total costs for all hospitalized COVID-19 patients could range from a low of $362 billion in charges to a high of $1.449 trillion in charges, depending on the incidence rate of the infection in the US population.**

Personal Protective Equipment

Nurse's unions in the United States are reporting that healthcare providers are being instructed to reuse protective gear, and doctor's associations stated that physicians' offices have needed to close because they cannot get masks and other supplies (Mulvihil and Fassett, 2020). Individuals at larger facilities report that supplies are adequate and their staff has good access, but facilities not associated with academic institutions and rural facilities have reported limited supplies. The American Medical Association has stated that they have learned that the material used to make protective gowns for staff is "not available at any price," which suggests problems in the supply chain may soon occur. A nonprofit group started in March that distributes donated protective gear said they had a 200% increase in requests for supplies from health providers in Texas in the first weeks of July, suggesting that facilities cannot get supplies on their own. They had initially only expected to be in operation for a few weeks early in the course of the pandemic, but they are still getting hundreds of thousands of requests a week.

Alex Azar from the United States Department of Health and Human Services mentioned on a call on July 7 that it was important to continue to reuse and repurpose protective gear to stretch

the stocks and avoid shortages, and the official in charge of coronavirus-related supplies for the White House reported that one fourth of states have less than a 30-day supply available. FEMA has stated that they are replenishing the federal stock of supplies with a goal of having a two-month supply on hand. Most states have needed to acquire their own supplies, reporting that federal supplies make up a small part of their stockpiles. In June, FEMA was still delivering faulty equipment that could not be used in response to requests. A New Hampshire association that represents nursing homes said that supplies that were delivered from FEMA included only child-sized gloves, surgical masks with ear loops that broke when stretched, and isolation gowns with no arm openings. Members of Congress have expressed concerned about the potential of severe shortages in the fall if the expected increase in the number of cases occurs. There is currently no national strategy to assure that supplies will be sufficient.

Testing

The massive increase in the number of new cases has also led to another shortage of testing across the United States. Even in areas that have not experienced a surge in cases, testing in private labs such as Quest and CVS Pharmacy involves wait-times of over a week, and there have been some reports that results can take over two weeks to be returned. According to the assistant secretary for health at the United States Department of Health and Human Services, **about half of the tests in the country are performed by large, commercial labs that are experiencing long delays** (Cole, 2020). He also stated that the average turnaround for all testing in the country is 4.2 days with about a quarter of the tests using point-of-care machines that give a result in around 15 minutes. Another quarter of the tests are performed in local laboratories or hospitals and have results in around 24 to 48 hours. He has suggested that tests that take over ten days are “outliers,” but the number of people reporting at least weeklong waits and some upwards of 20 days suggests that it is not an uncommon occurrence (Edwards, 2020).

On July 16, **labs in the United States were able to perform 831,900 tests in one day, which was an all-time high** (O’Donnell and Alltucker, 2020). The average number of tests performed is about 550,000 a day (Madrigal and Meyer, 2020). This amount is five times the number of tests processed in the middle of April. However, the Harvard Global Health Institute had suggested that the United States should reach 500,000 tests a day by May with an ultimate goal of least 1.2 million people a day, suggesting that the United States is well behind in testing capacity again.

At the same time that labs are able to perform a record number of tests per day, Quest Diagnostics estimates that the average turnaround time for nonpriority patients was seven days or more because the number of cases continues to rapidly escalate. They are guaranteeing single day turnaround only for hospitalized individuals, patients facing emergency surgery, and symptomatic health-care workers. Quest estimates that their orders for tests has grown by 50% over the last three weeks (Madrigal and Meyer, 2020). LabCorp reports that they are having large increases in testing demand, leading to a strain on supplies and equipment so that the average turnaround time for patients not in the hospital ranges from four to six days (O’Donnell and Alltucker, 2020). CVS sends test samples to third-party labs that process kits and return results, and a representative reported that during times of high demand, it may take six to 10 days to receive the results with some people waiting even longer. If the results are returned over

the weekend, people awaiting the results have to then wait until Monday, which adds a further delay.

Public health experts have stated that the delays make the tests irrelevant because most people reach the end of the quarantine period before getting the results to their tests, and the transmission of the virus from asymptomatic people leads to continued increases in the spread of the outbreak.

Michael Mina, an epidemiologist from Harvard University, stated that "Our modeling efforts more or less show that if you don't get results back in a day or so, outbreaks really can't be stopped without isolating and quarantining all contacts preemptively" (Madrigal and Meyer, 2020).

A research group in Germany published a modeling study in *Lancet Public Health* on the effects of testing delays on the effectiveness of contact tracing (Kretzschmar et al., 2020). The group has also studied the components that influence the effectiveness of contact tracing in other pandemics, including the influenza pandemic in 2009. **In all of their previous investigations, the key factor in implementing an effective public health response was the length of time of each step in the monitoring chain.** In this study, the researchers modeled the effectiveness of contact tracing for SARS-CoV-2 infections. If 80% of infectious people who develop symptoms are tested and isolated within 1 day after symptom onset, the reproduction number, or number of people that they infect, declines from 1.2 to 1.0 without contact tracing. When the **reproduction number** falls below one, it means that the spread of the virus will slow because not everyone who is sick infects someone else.

The researchers feel that the "best case scenario" that could potentially be attained in real-life situations would be

- 80% testing coverage
- No testing and tracing delays
- Tracing coverage of 80%

If this best case scenario is modeled, the reproduction number is reduced by 30% to 0.8. As delays in the process occur, the contact tracing coverage must stay high in order to keep the reproduction number below one. For example, if the testing delay extends to 2 days, then either the tracing delay can be only one day at most or the tracing coverage needs to remain at 80% to keep the reproduction number below one.

Once the testing delay becomes three days or longer, even perfect contact tracing (i.e., 100% testing and tracing coverage with no tracing delay) cannot bring the reproduction number below one.

From their study, the researchers conclude that reducing the testing delay, or shortening the time between symptom onset and a positive test result, with immediate isolation after a positive test is the most important factor for improving contact tracing effectiveness.

As well as reaching the capacity of the staff and machines at many testing labs, a shortage of supplies for running tests and collecting samples is occurring again. Chemical reagents used in the testing reactions are running low and the vendors and suppliers have not been able to meet demand (Madrigal and Meyer, 2020). USA Today reported on July 20, that states and local labs have started bidding against each other again in order to obtain limited supplies (O'Donnell and Alltucker, 2020). The CEO of American Society for Clinical Pathology stated that states are fighting over access to the same supply chains. Compounding the problem is that there are numerous different platforms used to process COVID-19 tests, and each one utilizes proprietary supplies that can only be obtained from the manufacturer of the platform. Different manufacturers are encountering problems at different times, and resolving the bottlenecks and shortages on a national scale becomes more difficult because resources cannot be easily shared by those with an excess.

Solutions to Testing Delays

Joshua Sharfstein, a professor and vice dean at Johns Hopkins Bloomberg School of Public Health suggested that insurance programs could penalize labs that did not produce results within 48 hours or increase payment to the lab for quick turnaround times (O'Donnell and Alltucker, 2020). This strategy was used in April when Medicare began paying labs twice as much for "high-throughput" tests (tests were $51 and increased to $100 for quick turnaround). Dr. Sharfstein also mentioned that increasing government funding to provide a guaranteed market would be an incentive for firms to invest in increasing their capacity over time.

Experts from the Rockefeller Foundation have suggested that there is a need for an increase to 30 million tests a week, and that the United States government should allocate $75 billion towards COVID-19 testing to ensure access to all people who need them, including people with low incomes and those who are ethnic or racial minorities (Edwards, 2020). They stress that increasing the testing capacity is crucial as flu season approaches due to the overlap in symptoms between the two diseases. The president of the foundation, Rajiv Shah, stated that "There will be 100 million cases of the sniffles. If everybody believes that that's COVID-19, it's going to strangle our economy, shut down our critical institutions, and introduce so much fear and crisis into the American system of government, education, health services, and food services that it will be a disaster that looks much worse than what we experienced in the spring." The Rockefeller Foundation has committed $100 million to the effort.

Better coordination of efforts has also been mentioned as a way to increase capacity (O'Donnell and Alltucker, 2020). In New York, the number of cases has declined, and testing is now plentiful leading to turnaround times of about 12 hours while shortages of supplies and staff have led to delays of a week to ten days in Phoenix, Arizona. However, there is not a way for labs to determine if there are areas with an abundance of supplies that can be transferred to improve turnaround time. There are also smaller labs that have been given emergency-use authorization from the FDA to test for COVID-19 but are processing far under their capacity. For example, a lab in Colorado can process 1,500 tests a day with results within 48 hours of receiving the testing sample, but they are only performing 200 tests a day. They have attempted to reach out on their own to organizations who are testing people, but they haven't been able to connect.

Pooled testing is another method that could help to stretch the resources for PCR-based testing. In pooled testing, laboratories combine the samples obtained from several people and test the multiple specimens together in the same test run (Erman, 2020). If the batch is negative for SARS-CoV-2 infections, then all of the people from that batch are negative. If someone has a positive test, the individual samples from the batch are reprocessed individually to determine who is infected. Pooled testing is most effective when the expected number of positive results is low. When there are a large amount of positive results, the likelihood of someone in the batch being positive for infection is higher, and it is more likely that the individual tests will need to be re-done. When a batches are likely to contain a positive test, there is no savings in resources.

There has also been an increase in recommendations for using other forms of testing (Edwards, 2020 and Carroll, 2020). For example, **antigen tests** that detect protein components of the virus rather than genomic components as with PCR-based testing. Antigen tests are routinely used in healthcare provider's offices to test for influenza and have been developed and tested to diagnosis SARS-Cov-2. Antigen tests can use either respiratory fluids from the throat, nose, and mouth or saliva to test for the virus. This is an advantage because inserting a swab into nose and throat, as is needed for PCR-based tests, increases the chance of the person being tested coughing or sneezing. With less invasive collection methods, the tester is safer and less personal protective equipment is required during the testing procedure and collection can be done more quickly. Antigen tests can also be processed quickly, with results in 15 to 20 minutes, but they are less accurate than PCR-based tests, which are currently used for diagnosis. It is estimated that antigen tests would miss about 25% of positive cases compared to a false negative rate of around 20% for PCR-based testing (Herper, 2020). Based on previous public health research, getting control of transmission of a viral outbreak when there is not a vaccine available can only be accomplished with frequent testing of large groups of people (Carroll, 2020). While antigen tests are less precise, they can be more easily produced than PCR-based tests. This makes antigen tests more readily available and allows for testing of large groups using quicker collection techniques with minimal supplies or at home by the patients themselves. Some rapid antigen tests allow for the processing of more than 50 an hour and do not need to be processed in a lab setting. While the tests are less precise, they still have the potential to identify more people with COVID-19 simply due to the volume that can be performed. Interventions to reduce transmission would still be required to prevent new cases from incorrect results, but accurate testing that takes too long will also promote spread of the virus.

The National Institutes of Health (NIH) has developed a program called the Rapid Acceleration of Diagnostics (or RADx), which expands the typical format for NIH support of research for the development, production scale-up, and deployment of accurate, rapid tests across the country with a focus on meeting the needs of those who are currently being underserved (Tromberg et al., 2020). **The goal of the program is to expand capacity so that by December, 2020 approximately 2% of the U.S. population (6 million persons) can be tested per day, with more tests ready for rapid deployment in response to demand**. Applications have already begun with 600 full applications by July 13, and many of the groups are simultaneously preparing submissions to the FDA for emergency use authorization of the tests. The effort is being funded by $1.5 billion from the federal stimulus acts (Dunn, 2020).

Remdesivir

Hospital pharmacists are reporting that there is not enough remdesivir at Houston hospitals to treat all of those who may benefit (Boodman, 2020). As far back as June, Houston Methodist hospital restricted the antiviral drug to those who did not yet require mechanical ventilation in order to stretch their supply. The hospital received a second shipment of 200 doses in the first week of July. However, as of July 10, they already expected to completely run out of the medication by the next day.

On July 1, Jackson Health System in Miami, Florida had exhausted its supply of remdesivir, but a new shipment was expected within a day. The new shipment was able to treat patients for four days before being exhausted again. Remaining supplies were used to finish the treatment of those who had already started therapy, and new patients were not being treated.

The 940,000 doses donated to the United States government by the manufacturer, Gilead Sciences, have been used, and a new supply for around 500,000 patients has been purchased by federal officials for distribution to states. Hospitals and patients will be billed for use of the new stock. This supply was initially expected to last until September, but with the increase in the number of cases, it is not expected to last that long.

The recent increase in cases has increased demand for the drug, leading to shortages, but there are still problems with the government's system for allocating remdesivir throughout the country according to physicians around the United States that are compounding the problem. The current system is not able to adapt to new hot spots, and also does not track the amount of drug being used in different areas to determine where there might be extra doses available and where there are shortages. Officials from the Department of Health and Human Services have stated that each week's allocation is based on the previous week's numbers. Hospital administrators and pharmacists would prefer allocation be based on predicted numbers that would account for expected changes in the number cases.

Antiretroviral Medications

The WHO has stated that 73 countries have reported that they are at risk for running out of antiretroviral medications to treat HIV due to complications from the COVID-19 pandemic (Stephenson, 2020). Of those 73, 24 countries report that they are critically low on supplies and expect to have disruptions in their ability to supply them. In the 24 countries, it is estimated that 8.3 million people, or about one-third of all people receiving HIV treatment worldwide, were receiving antiretroviral medication in 2019. The problems have stemmed from the failure of suppliers to deliver the medications on time, difficulties with land and air transport services, limited access to health services within countries, a shortage of the material used to produce the active ingredients in the medication, and a sharp reduction in air and sea transport slowing the distribution of the raw materials and packaging needed to produce the medications.

Shipping has been a major issue for drug production in general because the number of flights has been greatly reduced, and shipments by sea are occurring at a slower pace than normal. Shipping freight by sea has been affected by a lack of customs personnel, shortages of workers to load and unload ships, and a reduced availability of road transport to move goods to ports.

Additionally, the shutdown of factories in China at the beginning of the pandemic interrupted the pipeline for many raw ingredients for medications, and the disruptions are still being felt even though the factories have reopened for production.

The WHO has produced a predictive model to determine potential outcomes of a six-month disruption in HIV therapies, and the results suggest that the number of HIV-related deaths could double over a one-year period, which would cause more than 500,000 extra deaths from AIDS-related illnesses in sub-Saharan Africa in 2020 and 2021.

The prices for antiretroviral medications are also expected to increase from production difficulties, and predictions from the manufacturing sites in India suggest that there could be a 10% to 25% increase in cost due to the pandemic. This level of increases would mean that the drugs manufactured in India would cost between $100 million and $225 million more per year than previous years.

Thrombolytic Therapies for Stroke Treatment

Thrombosis, or clot formation, has been found to be a key component contributing to mortality during the inflammatory phase of COVID-19, and the use of anticoagulant medications has been shown to be an effective treatment for some seriously ill individuals. The anticoagulant alteplase is being used to treat people with COVID-19 that have developed acute respiratory distress syndrome (ARDS), but there have been reports of a lack of adequate supplies. Additionally, supply chain disruptions mean some centers and regions in the world have not had access to alteplase for the treatment of stroke (Lou, 2020).

Another medication called tenecteplase had been replacing the use of alteplase for the treatment of stroke in some centers because it can be administered more quickly, using a five second IV injection versus a one hour IV transfusion. Experts are suggesting that centers may need to switch to tenecteplase more quickly than anticipated in order to effectively treat strokes should the shortages of alteplase continue. Complicating the issue, is that tenecteplase has not yet been approved for the treatment of strokes, but it is available for off-label use. Previous clinical trials have shown that it is “non-inferior to,” or works the same as, alteplase in safety and efficacy. It may also be advantageous for use in stroke patients with an unknown SARS-CoV-2 status due to the shorter interactions times between healthcare staff and the patients during administration of anticoagulant medication, which would lead to a lower risk of transmission of the virus.

Lack of Regular Medical Care

Physicians and other officials are also becoming more concerned about the reduced access to regular healthcare for individuals in the United States and the possible long-term consequences of putting off medical procedures and screening. As mentioned above, in areas with high rates of COVID-19, medical personnel are being re-tasked to care for people with COVID-19. Other medical procedures are being canceled, including surgeries and regular office appointments. The number of screening visits for cancer or other chronic conditions has largely decreased. When a region is able to open up to regular medical care again after a surge in SARS-CoV-2

cases, there remains a large backlog of people who were not previously treated and the new people who now need to be treated, suggesting that long wait times and overburdened staff will continue.

Cancer

A study in the United Kingdom modeled the effect of delays in getting a cancer referral to a specialist during the pandemic to determine if there will be a change in outcome of cancer treatments (Sud et al., 2020). In the United Kingdom, there is a pathway for getting an urgent evaluation by a specialist in the case of certain aggressive cancer types called the two-week-wait pathway. During the peak of the outbreak in the United Kingdom (March through May), there was an 84% reduction in the number of people seen through the program. Now that transmission of the virus has fallen, there is a large backlog in the number of people in need of the service. The investigators used information from earlier clinical trials to quantify the potential effect of the delay in diagnosis or in the initiation of treatment. Table 2 lists the information from earlier clinical trials describing the reduction in the survival rate that is expected from a three-month delay. Based on the information, the researchers calculated the total number of lives that may be lost and the number of years of life that could be lost from premature death in England due to a delay ranging between one and six months in the initial inspection, diagnosis, or treatment of cancer.

Table 2. Reduction in the 10-year survival rate from a 3-month delay for the most common tumor types. The types of cancer with the largest decreases are highlighted in red.

Cancer Type	Age in Years					
	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	Over 80
Bladder	15.79%	14.95%	14.29%	15.48%	17.15%	17.03%
Brain	11.75%	14.15%	**17.82%**	**18.24%**	16.64%	16.70%
Breast	4.88%	3.27%	2.49%	2.14%	3.71%	7.70%
Cervix	5.59%	9.03%	12.20%	15.73%	**17.98%**	15.52%
Colorectal	10.22%	11.38%	10.82%	10.59%	13.10%	16.36%
Kidney	5.01%	6.50%	8.53%	10.53%	13.10%	**17.41%**
Larynx	11.07%	14.29%	13.45%	14.94%	15.86%	16.79%
Liver	16.68%	**17.29%**	16.17%	14.67%	11.89%	14.78%
Lung	16.87%	**18.26%**	16.80%	15.37%	11.78%	6.70%
Melanoma of skin	3.13%	3.96%	4.89%	5.66%	7.32%	12.56%
Esophagus	16.85%	16.21%	16.12%	15.18%	12.28%	4.59%
Oral cavity	12.83%	16.98%	**18.27%**	**18.28%**	**17.88%**	16.62%
Oropharynx	11.79%	14.48%	16.77%	**18.31%**	17.08%	13.73%
Ovary	7.24%	13.87%	**17.38%**	**18.28%**	17.08%	15.86%
Pancreas	12.86%	11.76%	12.11%	9.00%	7.18%	10.74%
Prostate	0.68%	0.67%	0.32%	0%	0%	3.69%
Stomach	**18.58%**	**18.54%**	**18.03%**	**17.34%**	16.11%	8.85%
Testis	0.58%	0.36%	0.76%	0.35%	0.63%	1.62%
Thyroid	0.11%	0.63%	1.33%	0.22%	2.57%	0%
Uterus	2.43%	5.27%	6.04%	8.68%	11.83%	14.43%

Between 2013 and 2019, an average of 6281 patients with stage I to III cancer were diagnosed via the two-week-wait pathway per month. The number of deaths from cancer expected to occur in this group based on historical data was 6281 (or 27%) within 10 years.

The difference in treatment outcomes was assessed for a lockdown period of three months that led to a delay of two months before individuals were first evaluated for cancer. **The type of cancer that would lead to the most lives lost from a delay was colorectal cancer, and the most years of life lost occurred with breast cancer.** The researchers investigated the differences if there was a 25% increase in the usual patient volume, a 50% increase, and a 75% increase after the end of the lockdown period. If a lockdown led to a backlog of patients that was 25% more than usual, 181 deaths are expected to occur with a loss of 3,316 years of life, which corresponds to around 18 years per person. If the increase was 50% of the normal patient volume, 361 deaths would be expected with a loss of 6,632 years of life. In this scenario, more people are affected, but the average number of years lost per person is the same. If there were 75% more patients than usual, 542 people would be expected to die with a loss of 9,948 years.

An expansion of the capacity of the program that increased the number of people who could be seen was found to minimize the number of deaths that are expected from delays caused by the pandemic. The researchers calculated how much extra capacity would be needed if all of the delayed patients were seen within the first month after the end of the lockdown. If there was a 25% increase of the normal patient volume, the capacity of the system would need to be increase by 175% of the normal conditions. If the patient volume was 50% higher, the capacity would need to be 250% higher, and a 75% increase in the patient volume would require an increase in capacity of 325% to accommodate all of the patients in the program. The average number of people per month whose cancers are diagnosed in the two-week-wait program is 8024. A 175% increase in the number of patients seen each week would correspond to approximately 14,000 more people. Such massive increases in capacity are most likely not possible. If the time for addressing the backlog is extended from one month to three months, 90 more deaths than previous years would be expected for a 25% increase in patient volume with a loss of 1,662 years of life, which corresponds to about half of the levels expected if no action was taken. The same trend was observed for the higher levels of patient volume as well.

They also found that **all delays in diagnosis should be avoided in people who are less than 70 years of age**. However, for older individuals, the risk of contracting SARS-CoV-2 could be higher than the risks from a delayed cancer diagnosis, especially those types of cancer with a slow rate of progress, such as prostate cancer, or types of cancer with generally poor prognosis where treatment is not expected to improve in the outcome.

Heart Attack

After a local disaster like a tornado or hurricane, the risk of cardiac events has been shown to increase from the added stress associated with uncertainty (Wessler et al., 2020). There are changes in the cardiac tissue that hasten the onset of acute coronary syndromes by increasing both the clumping of platelets (blood cells involved in clot formation) and the risk of plaques in the blood vessels breaking loose from the blood vessel walls. After Hurricane Katrina in Louisiana, researchers observed a three-fold increase in the rate of hospitalization for

myocardial infarction at Tulane Health Sciences Center in New Orleans, Louisiana compared to the rates before the hurricane, and increased rates persisted for years after the storm. Researchers estimate that a similar increase from the COVID-19 crisis will lead to an additional two to three million coronary events through 2021.

They worry that this increase will be compounded by the fact that people are avoiding treatment for cardiac symptoms due to a fear of catching SARS-CoV-2 through contact with healthcare providers. During the peak of infections in April, there was a 40% drop in the number of patients treated at nine high-volume centers that perform catheterization for myocardial infarction in the United States. If not treated in a timely manner, sudden death, stroke associated with left ventricular thrombus, and mechanical complications are common outcomes from myocardial infarction. If a reduced rate of treatment is coupled with an increased rate of incidence, there could be large increases in the risk of death or permanent injury.

The researchers also compared the risk of acquiring a SARS-CoV-2 infection from the hospital and subsequently dying from COVID-19 with the risk of dying from myocardial infarction due to a lack of treatment. Based on current information, the risk of being infected with SARS-CoV-2 in the hospital is estimated at less than 1%, and the risk of death from COVID-19 is emerging as less than 1%. When combined, the risk of dying from an infection acquired at the hospital is very small. The known probability of dying from myocardial infarction that is not treated is 30%, and the risk of dying decreases to 5% with use of revascularization techniques (catheterization) and modern medications coupled with critical care.

Based on the comparisons, the risks associated with cardiac events are substantially greater than the risk of infection with SARS-CoV-2 at the hospital, and the benefits of evidence-based therapies outweigh, by orders of magnitude, the small potential risk of infection in patients having acute cardiac symptoms.

SARS-CoV-2 Transmission

The CDC and local governments are conducting an ongoing serological study to measure the number of people who have antibodies to SARS-CoV-2 in their blood (CDC, CDC Seroprevalence, 2020).

There are 3 types of serological surveys being coordinated by the CDC:

- **Large-scale geographic seroprevalence surveys**- the CDC has partnered with commercial labs to use blood collected for other tests, such as cholesterol tests, to check for antibodies to SARS-CoV-2 in Connecticut, South Florida, the New York City metro area, Missouri, Utah, and Western Washington State with ongoing efforts to expand to California, Louisiana, Minnesota, and Pennsylvania.
- **Community-level seroprevalence surveys**- State and county health departments are testing households in select counties using epidemiological sampling methods to obtain community-wide information on areas where there might be clusters of infections.
- **Special-populations seroprevalence surveys**- There are efforts to collect information on groups that may be at increased risk from the pandemic, such as healthcare workers or pregnant women, to prevent future exposure to the groups.

The CDC published the results from the information collected thus far in the large-scale survey, spanning the time period from March 23 to May12 (Havers et al., 2020). The information was collected from two commercial labs with locations in the San Francisco Bay area, California; Connecticut; south Florida; Louisiana; the Minneapolis-St Paul-St Cloud metro area, Minnesota; Missouri; the New York City metro area, New York; the Philadelphia metro area, Pennsylvania; Utah; and western Washington State. The test that was used had a 96.0% sensitivity (true positive rate) and 99.3% specificity rate (true negative rate). Samples were tested from 16,025 people, and 55.2% were female, 7.5% were under the age of 18, and 36.2% were over the age of 65. Most of the samples tested at each site contained no antibodies to SARS-CoV-2. The proportion of people with antibodies ranged from 1.0% in the San Francisco area (between April 23 and 27) and 6.9% in New York City (collected between March 23 and April1). Within the entire group, the estimated number of actual infections was between six and 24 times higher than the number of confirmed cases, which was 3.8 million as of July 21. Seven of the sites had greater than ten times more cases identified than the number of previously confirmed cases.

The authors conclude that even though the actual number of people who had been infected with SARS-CoV-2 was much higher than the reported values, most people in the geographic areas had not been infected with the virus and were still susceptible.

The Washington Post spoke with a number of experts about the study, and they all stressed that attaining herd immunity by allowing the population to become exposed to the virus is not a reasonable idea based on the results of the investigation (McGinley, 2020). Even in areas where there was significant transmission occurring, such as New York City, the level of people exposed was well below that needed to slow the spread of the virus in the community, and the exposure of 24% of New York City came at a great cost in lives with a breakdown of the healthcare system that led to an inability to treat everyone who needed care.

Another study reported by the CDC from the Indiana State Department of Health investigated the prevalence of SARS-CoV-2 in Indiana (Menachimi et al., 2020). The residents who were tested were randomly selected, and all were over the age of 12 years. The testing occurring at the end of April. Of the total group, 2.79% had either a current infection based on PCR-based testing or a previous infection based on serological testing. Of those who had an active infection, 44% reported having no symptoms. Based on the survey, there were ten times the reported number of SARS-CoV-2 infections in Indiana.

A similar study in Atlanta and the surrounding areas conducted by the Georgia Department of Public Health was also reported by the CDC (Biggs et al., 2020). The people tested lived in randomly chosen census blocks in two counties and represented 420 households with 696 people. Antibodies were detected in 2.7% of the group, which was used to calculate an area-wide prevalence of 2.5% during the time period from April 28 to May 3.

These reports support the information shared by the CDC director in June about the estimates of actual cases compared to reported cases. However, while there was undercounting in each geographic area, there was a large range in the local levels, showing that separate outbreaks have been occurring across the country. The time frame for the reports corresponds to the peak of infections in the Northeast that were centered on New York City, but noteworthy, silent transmission was also occurring in other areas that were reporting low overall rates of COVID-19.

The large number of excess cases indicates that there may be high levels of people with unnoticed or no symptoms that can spread the virus without knowing it. The fact that many individuals do not know they are infected is one of the main reasons that using face masks in public, keeping distance between people, and staying home when you have even mild respiratory symptoms is important for slowing the transmission of the SARS-CoV-2.

Modeling of Transmission during the Wuhan Outbreak

Researchers in China have been able to analyze the information from the outbreak of COVID-19 in Wuhan, China to get a better picture of the transmission dynamics of SARS-CoV-2 (Hao et al., 2020). The study covers the time period between January 1, 2020 and March 8, 2020 and includes information on 32,583 laboratory-confirmed cases. The authors report that there were two key features to the outbreak, high covertness and high transmissibility. The covertness of infectious was evident in that it was calculated that **87% of the infections that occurred before March 8 were unreported due to asymptomatic or mildly symptomatic individuals**. The authors point out that this low rate of reporting of actual cases was during a period where there was a large, active surveillance program in place with investigators going door-to-door to identify unreported cases. The large number of unidentified infections of SARS-CoV-2 suggests that intervention strategies must differ from those used in previous coronavirus outbreaks.

During the early period of the outbreak, the reproduction number was 3.54, which means that each sick person infected three and half other people. This reproduction number is much higher than the value observed during the SARS and MERS outbreaks. Implementation of multi-pronged interventions, with a largescale lock down for all residents on February 2, had a large

effect on transmission, and by March 8, the reproduction number had been lowered to 0.28. This corresponds to a projected 96% reduction in the total number of infections in Wuhan.

The authors concluded that even with low levels of detection of actual cases, transmission from people with unreported cases could be controlled through interventions that included wearing face masks, social distancing, and quarantining close contacts.

Aerosol Transmission

Researchers at several academic centers around the country contributed to a study on whether infectious SARS-CoV-2 is carried by aerosol sized particles (Santarpia et al., 2020). The study was published as a preprint, which means that it has not been peer-reviewed, but several experts have mentioned the results from the study and it took place at institutions well-versed in the study of infectious disease such as the University of Nebraska, University of Illinois, and Harvard University. The researchers collected aerosol samples in the rooms of six patients admitted for COVID-19 during the month of April. The samples were assessed for the presence of viral RNA and infectious virus in aerosol particles that ranged from larger than 4.1 micrometers, between one and four micrometers, and less than one micrometer. RNA from the virus was detected in all three sizes of particles in all six rooms. **Infectious virus was obtained from three samples of aerosols that were less than one micrometer in size**. There was also evidence of infectious virus in the aerosols between one and four micrometers, but the result was not statistically significant. Additional analysis of samples of this size indicated that RNA and proteins from the virus as well as intact virus particles were present in the mid-sized aerosols. A lack of statistical significance for this results could be due to the small size of the study, and a larger number of participants could help to determine if infection is possible from this type of aerosol.

Even with the uncertainty observed for the one category of aerosols, there was evidence of the presence of infectious SARS-CoV-2 in the smallest aerosols indicating that airborne transmission of COVID-19 can occur.

Airborne transmission can be prevented by the use of masks in public areas, increased ventilation in enclosed spaces, and systematic surveillance testing in the community to identify clusters of infections (Prather, 2020).

In a viewpoint published in *JAMA*, three physicians from the public health department of Harvard University discuss what is known about the mode of transmission of SARS-CoV-2 (Klompas et al., 2020). The debate about airborne versus droplet transmission in respiratory viruses has been ongoing for a number of years, and even with the well-studied influenza virus, definitive evidence is still lacking due to the difficulty in studying the matter. The Harvard researchers acknowledge that experimental evidence for aerosol transmission suggests that it can occur with SARS-CoV-2, but they also interpret the available data on infection rates and transmissions in populations during normal daily life and find that long-range aerosol transmission does not appear to be common.

Transmission from measles virus is through the air, and measles can stay suspended at face-level for long periods of time so that it is more easily inhaled than viruses that are found in droplets. Compared to the reproduction number of measles, which is around 18, the reproduction numbers of SARS-CoV-2 have been reported at around two to three. Based on the relatively long length of time that people with COVID-19 are infectious (up to a week), airborne transmission of SARS-CoV-2 would be expected to result in higher reproduction numbers. The lower reproduction number could occur in combination with airborne transmission if the amount of virus required to infect someone with SARS-CoV-2 is be much higher than the amount needed for transmission of measles.

The secondary attack rate on an infection can also help to differentiate the modes of transmission. The **secondary attack rate** describes the rate of infection of people in close contact with a person confirmed to be infected. Airborne infections have a higher secondary attack rate and contacts do not need to be in close proximity for long periods of time to become infected. The **secondary attack rate of SARS-CoV-2 is currently reported to be around 5%**, which is considered a low value. The secondary attack rate increases for people who live in the same household and ranges between 10% and 40% for SARS-CoV-2. Activities such as sharing a meal have been found to have a secondary attack rate of 7%, and the secondary attack rate for passing interactions, such as between people shopping in the same store, is 0.6% for SARS-CoV-2. The secondary attack rate calculated for healthcare workers who unknowingly care for a patient with COVID-19 while either wearing only a face mask (not an N95 respirator) or without any personal protective equipment is less than 3%.

> **Based on the observed secondary attack rates for SARS-CoV-2, the researchers suggest that SARS-CoV-2 is likely spread most often through "secretions that fall rapidly to the ground within a narrow radius of the infected person rather than with virus-laden aerosols that remain suspended in the air at face level for hours where they can be inhaled by anyone in the vicinity."**

In a recent statistical analysis of ten separately published studies on the effectiveness of medical grade masks compared to N95-type respirators to prevent infection, the authors report that there were lower rates of infection with N95 respirators than the less protective masks, which could indicate the occurrence of airborne transmission. However, the Harvard researchers call into question the validity of the analysis due to the poor quality of the initial studies used for the generation of the comparison, the lack of a direct comparison between the two types of masks, and the fact that many of the studies did not describe SARS-CoV-2, but the other coronaviruses that cause SARS and MERS.

There are documented cases that support the possibility of airborne transmission, however, and numerous incidences have been reported showing that prolonged exposure to an infected person in a poorly ventilated space can allow otherwise insignificant amounts of virus-laden aerosols to accumulate. Superspreader events, such as infection during choir practice, occurred under very specific conditions that can be preemptively identified and avoided.

Based on their experience and examination of the evidence, the researchers conclude that people produce both droplets and aerosols, and transmission may take place along a spectrum of modes rather than a strict delineation between the two.

Currently available evidence based on transmission data suggests that long-range aerosol-based transmission is not the dominant mode of SARS-CoV-2 transmission.

Transmission from College Students

There have been reports of large numbers of college students being infected with SARS-CoV-2 as administrators are deciding whether to conduct classes online or in person (Cai et al., 2020).

A recent study of transmission rates based on age suggests that children over the age of ten have similar transmission rates to adults, and that people between the ages of 20 and 29 had the highest amount of contacts both inside and outside of their household (Park et al., 2020). This suggests that college-aged individuals may be a large contributor to transmission in a community even if they do not experience serious symptoms from the infection.

The *New York Times* did a survey of four-year colleges in the country as well as private institutions that competes in Division I sports or are a members of an elite group of research university to determine the extent of spread that has already occurred before the start of school (Cai et al., 2020). They found that there have been **at least 6,600 cases linked to about 270 colleges since the start of the pandemic**. The cases occurred in student athletes, in students who stayed at their college over the summer, and in faculty and staff at the schools. There have also been at least 14 COVID-19 related deaths at the schools.

A study by researchers at the Yale School of Public Health in New Haven, Connecticut modeled the effects of different testing strategies on the transmission of the virus (Nature, 2020). They found that if five new cases were brought to campus a week in a school of 5,000 students, each infected student would infect 2.5 others. Testing students every two days with a rapid, antigen-based test would keep infections to around 135 over a semester of 80 days. If testing were stretched to once a week, there would be “explosive” growth on campus. If there were higher amounts of transmission from off campus, controlling the infections on campus would require daily testing and double the costs of the testing program.

Another research group has determined the medical vulnerability of young adults aged 18 to 25 years based on the prevalence of risk indicators from the CDC, including sociodemographic characteristics, health status and behavior indicators, activity limitations, injuries, health insurance coverage, and access to and utilization of health care services (Adams et al., 2020). It was determined that medical vulnerability was 32% for the whole group and lower for those who did not smoke (16%). In the full group, more men (33%) were medically vulnerable than women (30%), but when only nonsmokers were evaluated, women (19%) were found to be more medically vulnerable than men (14%). As people with increased medical vulnerability are more likely to experience severe symptoms associated with COVID-19, these results indicate that a relatively large number of the individuals on a college campus would be at higher risk of poor outcomes from infection. This is contrary to the commonly held belief that individuals in this age range have little risk from COVID-19.

The study highlights the increased risk to individuals in this age range due to smoking. Because younger individuals typically have fewer chronic conditions than older individuals, the rates of

smoking could more predictive for the risk of severe COVID-19 for this age group. Smoking is associated with a higher likelihood of COVID-19 progression, including increased illness severity, ICU admission or death. Recent trends suggest that college aged individuals are starting to smoke at higher rates than previously (UCSF, 2020).

COVID-19 Characteristics

Thrombosis

The formation of clots has been well-documented in cases of severe COVID-19, but there is less information about the incidence of the condition in those with less severe disease (Bilaloglu et al., 2020). Researchers have compiled the information from all 3334 patients hospitalized with COVID-19 that were treated at the four hospitals associated with NYU Langone Health in New York City between March 1 and April 17. The thrombotic events reviewed included clots in both venous and arterial clots, such as deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke, and other systemic thromboembolism. Specific screening for thrombotic events was not used, and events were identified during routine clinical care. In total, **16% of participants had at least one event**, 6.2% were venous, and 11.1% were arterial. The events were further classified with 3.2% PE, 3.9% DVT, 1.6% ischemic stroke, 8.9% MI, and 1.0% systemic thromboembolism. **The overall mortality rate of the entire group was 24.5%, and mortality was higher in participants who had a thrombotic event (43.2% compared to 21.0%) with both venous and arterial contributing**. In individuals who required treatment in the intensive care unit, 29.4% had a thrombotic event while 11.5% of individuals who did not require treatment in the intensive care unit had a thrombotic event.

Risk Factors Associated with Mortality from COVID-19

The disease severity observed on chest x-rays is associated with a higher risk of disease progression and poorer outcomes from COVID-19 (Joseph et al., 2020). Researchers recently reported that non-white individuals who were admitted to the hospital with a confirmed case of SARS-CoV-2 were more likely to have indications of severe disease on chest radiographs and an increased likelihood of adverse clinical outcomes. There were 326 participants in the study who were treated at Massachusetts General Hospital between March 27 and April 10. The cause of the more severe disease progression in ethnic and racial minorities was thought to be due to a delay in accessing healthcare compared to white individuals.

Researchers utilized the Coronavirus Disease 2019-Associated Hospitalization Surveillance Network (COVID-NET), a CDC operated surveillance system that collects information on individuals who have been hospitalized from laboratory confirmed COVID-19 in one of 250 hospitals across 14 states (Kim et al., 2020). Based on the information they were able to identify risk factors that were associated with severe outcomes in adults with COVID-19. Between March 1 and May 2, the records of 2,491 individuals were evaluated. Based on the evaluation, 92% of participants had at least one chronic condition. Individuals with three or more conditions had 1.3-fold increase in the risk of admission to the intensive care unit compared to those with no underlying conditions, and those with three or more chronic conditions had 1.8 times the risk of death while in the hospital compared to those without chronic conditions. After admission to

the hospital, 32% required treatment in the intensive care unit, 19% required mechanical ventilation, and 17% died. Of those who needed mechanical ventilation, 53% died. Many of the people in the study were older, and 75% of the participants were over the age of 50. **The highest predictor of mortality while in the hospital for COVID-19 was increasing age**.

As has been observed in other studies, people who were Black were more likely to be admitted to the hospital, but once in the hospital individuals of African descent did not have an increased risk of poorer outcomes compared to other ethnic and racial groups who were hospitalized.

Factors associated with ICU admission for COVID-19 in the United States included

- Age over 50 compared to age below 39
- Male sex
- Obesity
- Immunosuppression
- Diabetes

Factors associated with mortality from COVID-19 while in the hospital in the United States included

- Age over 50 compared to age below 39
- Male sex
- Immunosuppression
- Renal disease
- Chronic lung disease
- Cardiovascular disease
- Neurologic disorders
- Diabetes

While there was a high prevalence of hypertension in participants in the study, the condition was not associated with the need for treatment in the intensive care unit. Other studies of COVID-19 cases in the United States have also not seen an association between hypertension and mortality that was reported in studies from China.

An evaluation of the risk factors associated with death in people with COVID-19 who were treated in the intensive care unit in Lombardy, Italy has also been published (Grasselli et al., 2020). In the study, 3,988 critically ill individuals with laboratory-confirmed COVID-19 were admitted to the intensive care unit between February 20 and April 22. The median age of the individuals in the study was 63 years, and 79.9% were men. A majority of the group also had at least one chronic condition, 60.5%, but the proportion was smaller than the group from the United States. At the time of admission to the intensive care unit, 87.3% required the use of mechanical ventilation. The median time from symptom start to admission to the intensive care unit was a median of 10 days with a median length of stay of 12 days. By May 30, 50.4% had been discharged from the intensive care unit, 48.7% had died while in the intensive care unit, and 53.4% died while in the hospital.

Risk factors associated with mortality for patients in the ICU in Lombardy, Italy included

- Older age
- Male sex
- Need for high levels of oxygen
- High positive end-expiratory pressure on ventilation
- Low ratio of the level of arterial oxygen compared to the amount of inspired oxygen (PaO2/FiO2)
- Chronic obstructive pulmonary disease
- High cholesterol
- Type 2 diabetes

The National Health Service (NHS) in England has created a secure health analytics platform (OpenSAFELY) covering 40% of all the patients in England, which corresponds to 17,278,392 adults. A total of 11% of the individuals included in the database are descended from non-white individuals. This database was used to determine the risk factors associated with death from COVID-19 in the country (Williamson et al., 2020). Of the people in England who have died, researchers were able to link 10,926 related deaths to the records in the OpenSAFELY database.

COVID-19-related deaths in England were associated with

- Male sex
- Older age
- Deprivation
- Diabetes
- Severe asthma
- Respiratory disease
- Chronic heart disease
- Liver disease
- Neurological diseases
- Reduced kidney function
- Autoimmune diseases and immunosuppressive conditions

As observed in numerous other studies, those of South Asian descent and Black individuals who live in England were at higher risk of death than white individuals. One notable difference in the list of associated factors in England is asthma. Other studies have not identified this condition as having a higher risk of death from COVID-19, and there has been an underrepresentation of hospitalized asthma patients with COVID-19.

Researchers have also compiled the information on 2,215 adults in the United States who were admitted to the intensive care unit of 65 different hospitals across the country for treatment of COVID-19 between March 4 and April 4 (Gupta et al., 2020). The mean age of the group was

60.5 years, and 64.8% were male. When the outcomes of the individuals were assessed 28 days after admission to the intensive care unit, 35.4% had died, 37.2% were discharged, and 27.4% remained hospitalized.

Factors associated with death in patients with COVID-19 in the ICU in the United States included

- Older age
- Male sex
- Higher body mass index
- Coronary artery disease
- Active cancer
- The presence of hypoxemia
- Liver dysfunction
- Kidney dysfunction

As observed in other studies, race was not associated with the risk of death in the intensive care unit even though a higher number of Black individuals were admitted to the hospital than white individuals. Hypertension, diabetes, and lymphocyte count were also not associated with an increased risk of death. **The researchers also observed a correlation with the number of beds in the intensive care unit, and individuals admitted to hospitals with fewer intensive care beds had a higher risk of death.** Of the included hospitals, the proportion of individuals who died varied considerably between different institutions, and the number who died ranged from 6.6% to 80.8%. The information used in the evaluation did not include data describing ventilator management strategies, hospital or intensive care unit volume, physician and nurse availability, or the potential strain on the available resources for the hospital even though these factors may have contributed to the outcomes in the study.

Compared to the information from Lombardy, Italy discussed above, the researchers found that the characteristics of the people treated in the intensive care unit were similar. There was a higher mortality in the United States (35.4%) than in Italy (26%). However, a larger number of the group in Italy were still being treated in the intensive care unit at the end of the study. The mortality rate reported here was lower than that reported for Wuhan, China (62%) and the Seattle area (50%). One major difference between the other studies, it that only 10.4% experienced a thrombotic event, which is compared to between 15% and 42% reported in Europe. The lower rate observed here is closer to the rate reported for critically ill patients without COVID-19.

Additionally, while increasing age was associated with a higher risk of death, at least 15% of all patients from in every age group died from COVID-19, including those under the age of 40 year.

Age-Adjusted Case Fatality Rate

A study of the case fatality rate (the number of diagnosed people who die) can vary greatly between countries due to differences in the demographics of the population if age is a risk factor

for death (Sudharsanan et al., 2020). This group of researchers calculated the case fatality rate for the reported number of individuals with COVID-19 in China, France, Germany, Italy, the Netherlands, South Korea, Spain, Switzerland, and the United States as of April 19 (1,223,261 cases). The overall case fatality rates were the highest in Italy (9.3%) and the Netherlands (7.4%) with the lowest case fatality rates in South Korea (1.6%) and Germany (0.7%).

> **Adjustment of the case fatality rates for the age distributions in the country explains 66% of the variation across the countries, and the age-standardized median case fatality rate was 1.9%**.

Before standardizing the case fatality rates for the age of the population, South Korea and China appeared to have much lower rates, but after adjustment, the gap is much smaller. The highest adjusted case fatality rates were observed in Italy, Spain, and the Netherlands with the lowest rates in France, the United States, and Germany. This suggests that prevention of illness would reduce the number of people dying in the United States to the level of other European countries.

A complete comparison with the countries was not possible because many did not report the ages of those who had died, but the researchers found that the observed variation in case fatality rates across 95 countries is 13 time larger than would be expected based on the age of the population.

Identification of the Contribution from Toll-Like Receptors

One method scientists use to identify important components of a disease is to track the incidence in family groups, which allows for the discovery of potentially linked genes. Researchers have determined from laboratory experiments that proteins in the cell called **Toll-like receptors (TLR)** may be involved in the severe symptoms of COVID-19 that affect some people. TLR have a role in the innate immune system, and recognition of viral RNA within the cell by TLR leads to production of inflammatory molecules such as cytokines and interferons (Plenge, 2020). The role of TLRs in COVID-19 has been further implicated by mutations found in two unrelated sets of brothers (van der Made et al., 2020).

A mutation in the TLR-7 gene was identified in a 32-year-old man and his 29-year-old brother who both contracted COVID-19. The older brother required mechanical ventilation in the intensive care unit, and his younger brother died from complications from COVID-19. Based on the changes that would occur to the protein produced from the gene, it is thought that the mutation likely led to a complete loss of function of the protein, which was confirmed through laboratory experiments with the men's cells. The mutation is found on the X-chromosome, and therefor passed from mothers to their offspring with men being more often affected.

Another family was identified with a mutation in TLR-7 after a 21-year-old man and his 23-year-old brother were both admitted to the intensive care unit for treatment of COVID-19. The mutation detected in this set of brothers differed from the one described above, but it also led to a form of the TLR-7 protein that was completely non-functioning.

The lack of a functional TLR-7 protein led to a lack of production of type 1 interferon genes in the affected men. As discussed in the previous COVID-19 Research Report from PCI, interferons (IFNs) are a small protein-based molecule that participates in the control of the immune response to microbial infections (Ivashkiv et al., 2015). There are numerous types of interferons that have been identified that have differing roles in the cascade of events that occurs upon identification of a foreign body by the immune system. When a cell interacts with a type I IFN, they are alerted to potential infectious threat, and there are changes to the cell that make it more difficult for infectious agents, and especially viruses, to infect the cell. Researchers have found that there is a correlation with low levels of type I IFNs and cases of severe COVID-19 (Hadjadj et al, 2020 and Lee et al., 2020). The researchers have found that the type I IFN response plays a large role in the promotion of inflammation in severe COVID-19. Additionally, it has been discovered that type I IFN deficiencies as measured by blood tests may be indicative of a risk of severe COVID-19. When cells from the men were tested, it was found that both mutations cause a complete deficiency in IFN-gamma production in response to molecules that normally stimulate the TLR-7 pathway.

Genomic analysis of both mutations suggest that they are extremely rare occurrences in the general population. As the authors of the report state, “The presence of 2 independent, rare mutations in a single gene (TLR-7) in two different families with an unusual presentation of COVID-19 (severe disease in young, previously healthy males) is statistically unlikely to have occurred by chance alone.” Along with the previous laboratory evidence, the identification of the mutation suggests that TLR-7 may have an important role in determining the severity of COVID-19 symptoms. As the mutations are extremely rare, **there is little chance that similar mutations are the cause of severe symptoms in the general population**. However, with the knowledge of the systems that may be malfunctioning, it may be easier to develop treatments. For example, therapies that boost the innate immune system early during infection with SARS-CoV-2 may be beneficial in preventing severe symptoms, and the use of different forms of IFNs are being tested for treatment of COVID-19.

Potential Treatments for COVID-19

Interleukin 7 (IL-7)

Interleukin 7, or IL-7, is a cytokine that regulates the survival and growth of lymphocytes, such as T and B cells, and it has been used in previous clinical trials for both cancer and infectious diseases as a treatment to increase the amount of lymphocytes and promote their functional activity (Laterre et al, 2020). It has been shown to reduce viral loads in trials of viral infections by increasing the numbers of both helper T cells and cytotoxic T cells up to three fold while increasing activation of the cells without increasing the levels of cytokines that promote inflammatory responses. The use of IL-7 was investigated for the treatment of 12 critically ill individuals with COVID-19 and severe lymphopenia (lack of lymphocytes). The outcome of the treatment was compared to 13 individuals being treated at the same hospital with the usual hospital care who had similar characteristics. The treatment was well tolerated, and no observed treatment-associated adverse effects were noted. Pro-inflammatory cytokines were measured before and after treatment, and there were no increases in the amount of several different cytokines. There were changes in IL-6 levels, but the timing of the changes seemed correlated to the participant’s health rather than administration of IL-7, according to the authors.

When the participants were assessed 30 days after treatment, mortality was 42% for those treated with IL-7 and 46% in the group receiving usual hospital care, but the authors did not report if this different was statistically significant or not. This could be due to the small group of participants, of the lack of a true control group for comparison. Additionally, the use of IL-7 was associated with a restored lymphocyte count, with the participants taking IL-7 achieving levels more than 2-fold greater than the group that did not. There was also not an increase in secondary infections in the participants taking IL-7.

The researchers conclude that that IL-7 can be safely administered to critically ill patients with COVID-19 without exacerbating inflammation or pulmonary injury, and IL-7 was associated with an increase in the level of lymphocytes, appearing to reverse a hallmark of severe COVID-19.

RECOVERY Platform

A **platform trial** is a trial protocol that allows for efficient, less expensive designs by enrolling populations quickly and collecting minimal data to answer more than one question (Normand, 2020). The WHO has organized the RECOVERY platform to test different therapies for COVID-19 in a manner that is faster and more efficient than a traditional clinical trial. Hospitalized individuals with COVID-19 were assessed for mortality within 28 days of starting a treatment. The four treatments being tested dexamethasone, hydroxychloroquine, lopinavir–ritonavir, or azithromycin, which were compared to usual hospital care. In total, 11,303 participants were enrolled, and the results from the dexamethasone arm of the trial were reported in the New *England Journal of Medicine* (RECOVERY Collaborative Group, 2020). Both oral and intravenous forms of dexamethasone were investigated, and 2104 participants were assigned to receive dexamethasone with 4321 receiving usual care. Based on evaluation of the outcomes of treatment at 28 days after initiation, 22.9% of individuals taking dexamethasone died and 25.7% who received usual hospital care died. There was a difference in the effect of dexamethasone based on the level of respiratory support of the participant at the start of the trial. **Participants using mechanical ventilation who were taking dexamethasone had a lower incidence of death (29.3%) than those receiving the usual care (41.4%).** Those receiving oxygen without invasive mechanical ventilation who took dexamethasone also had a lower incidence of death (23.3%) than those receiving usual care (26.2%), but while the difference was statistically significant, the magnitude of the difference was small. There was no benefit from dexamethasone in participants who did not require respiratory support at the start of the trial.

Based on their results, the researchers concluded that the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.

Additional Negative Results for Hydroxychloroquine

A number of trials were also published that showed that **hydroxychloroquine has no beneficial effects for people with COVID-19**.

In a trial performed by researchers from the University of Minnesota, the University of Manitoba, and McGill University, 491 participants with laboratory-confirmed COVID-19 or those with probable COVID-19 from a high-risk exposure were randomly assigned to receive either hydroxychloroquine or placebo within four days of symptoms onset. The main goal of the study was to determine if early use of the medication led to a reduction in symptom severity or duration and prevention of hospitalization (Skipper et al., 2020). Approximately 50% of the participants were enrolled within one day of symptoms starting. The researchers found that there was not a difference in symptom severity between the two groups during 14 days of observation of the participants. There was also no statistically significant difference in the number of participants with ongoing symptoms after 14 days between the two groups. There were also a statistically significant increase in the number of participants experiencing adverse effects in the group taking hydroxychloroquine (43%) compared to the group taking the placebo (22%). There was also no difference between the groups in the number of people hospitalized, which was generally low (ten and four participants hospitalized)

A study in Spain investigated the early treatment of adults with mild COVID-19 symptoms (Mitjà et al., 2020). The study enrolled 293 participants for a randomized and controlled trial of the use of hydroxychloroquine in non-hospitalized adults with confirmed SARS-CoV-2 infection who had had less than five days of symptoms compared to a placebo. There was no statistically significant difference in the reduction of viral load at day three or seven after the start of treatment as measured by PCR testing of nasopharyngeal swabs. There was also no difference in the risk of hospitalization or the time to complete resolution of symptoms between hydroxychloroquine and the placebo.

A reporter at *CIDRAP News*, spoke with Jason Gallagher who is a clinical professor and specialist in infectious diseases at Temple University School of Pharmacy about the trials (Dall, 2020). **Dr. Gallagher stated that these trials add to the growing evidence that hydroxychloroquine is not an effective treatment for COVID-19, either for hospitalized patients or those in the early stages of the infection.** Based on the number of clinical trials that have been published he remarked that “it has been conclusively found to be ineffective." He also feels like it is time to move on to other potential treatments and expend the resources elsewhere.

After publication of a purportedly positive report on the use of hydroxychloroquine from the Henry Ford Health System in Detroit, Michigan, numerous researchers published rebuttals in the journal that released the initial paper, *International Journal of Infectious Diseases* (Cohen, 2020). Based on experts reading of the report, they concluded that due to “flaws in the analysis the conclusions reached in [the study] are invalid." The main problem with the study is that patients were assigned to the treatment based on their underlying medical conditions, which would introduce a bias in the information from the study. The researchers from Henry Ford Health System also made adjustments to the death rates that were inappropriate and led to skewing of the data. Individuals treated with hydroxychloroquine in the study were also more likely to have received additional treatment with steroids (between 79.9% and 74.3%) while only 35.7% of those in the placebo group were also treated with steroids. As steroids produce an anti-inflammatory effect that has been shown in other clinical trials to improve the outcome of severe cases of COVID-19, the unequal use in the two trial groups would lead to effects that cannot be attributed only to the use of hydroxychloroquine.

A laboratory-based study of the effect of chloroquine on SARS-CoV-2 infection of cell cultures also did not observe an effect of the drug on viral infection (Hoffman et al., 2020). The anti-viral function of chloroquine, and the related hydroxychloroquine, functions to change the pH of the compartment (called an endosome) used by viruses to gain entry into a cell. In some cells, SARS-CoV-2 utilizes the protein CatL to gain entry into cells. This process is dependent on the change in pH in the endosome. In the cells that make up the lining of the respiratory system, SARS-CoV-2 interacts with an enzyme in the cellular membrane called TMPRSS2 because there are very low levels of CatL. The interaction and activity of TMPRSS2 in the entry of SARS-CoV-2 is not dependent on a change in pH in the endosome. To recreate this environment, the researchers grew two types of cells, one similar to respiratory cells that contain TMPRSS2 but little CatL and another type that produces only CatL. In the respiratory system-like cells, there was **no inhibition of SARS-CoV-2 entry into the cells in the presence of chloroquine**. In the cells that only produce CatL, the entry of SARS-CoV-2 was effectively stopped.

> **Based on their results, the researchers state that "chloroquine targets a pathway for viral activation that is not operative in lung cells and is unlikely to protect against SARS-CoV-2 spread in and between patients."**

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