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Medical Intelligence Report

Date: September 15, 2020

Topic: Update on COVID-19 Research

Factors Associated with SARS-CoV-2 Infections

The CDC released a report investigating the community contacts that potentially contribute to the spread of SARS-CoV-2 (Fisher et al., 2020). Transmission was determined by interviews with symptomatic adults who either had a SARS-CoV-2 infection confirmed by PCR-based testing or symptomatic adults from the same health care facilities who had negative SARS-CoV-2 test results. There were 154 individuals with positive tests included in the study and 160 individuals who tested negative. The time period of the study was between July 1 and July 29, and testing occurred at eleven sites across the country in California, Colorado, Maryland, Massachusetts, Minnesota, North Carolina, Ohio, Tennessee, Utah, and Washington.

People with a positive test for SARS-CoV-2 were more likely to have had contact with a person with a confirmed case of COVID-19 (42%) compared to the group who was negative for SARS-CoV-2 (14%). Most close contact exposures were family members, leading to household transmission of SARS-CoV-2. As a group, those with COVID-19 in the study were also 2.4 times as likely to report that they had dined at a restaurant in the two weeks before the onset of illness.

> **When the activities of individuals with COVID-19 who had not interacted with someone with a known case were evaluated, those with COVID-19 were 2.8 times more likely to have gone to a restaurant, bar, or coffee shop in the past two weeks than those who had negative tests for SARS-CoV-2.**

Additionally, when the participants in the study who reported going to a bar, coffee shop, or restaurant in the 14 days before the onset of symptoms were asked about the adherence to mask use and social distancing, those positive for SARS-CoV-2 were less likely to describe almost all patrons adhering to recommendations than those with a negative test for SARS-CoV-2. The area in the restaurant where participants sat was not included in the study (e.g. indoor or outdoor dining).

The researchers also recorded the participants' descriptions about close contact (within 6 feet for more than 15 minutes) with a person with known COVID-19, workplace exposures, and mask-wearing behavior. Other potential community contacts that were assessed included gatherings with less than 10 or more than 10 persons in a home; shopping; dining at a restaurant; going to an office setting, salon, gym, bar/coffee shop, or church/religious gathering;

or using public transportation. The researchers did not find an association with having COVID-19 and shopping; gatherings with less than 10 persons in a home; going to an office setting; going to a salon; gatherings with more than 10 persons in a home; going to a gym; using public transportation; going to a bar of coffee shop (for the entire group); or attending church/religious gathering.

Based on the evaluation, the researchers conclude that study participants with and without COVID-19 reported generally similar community exposures, with the exception of going to locations with on-site eating and drinking options.

One possible explanation the authors present is that masks cannot be worn while eating and drinking, whereas shopping and numerous other indoor activities allow for mask use.

Evaluation of Everyday Risks and Risk from COVID-19

As more information becomes available about transmission of SARS-CoV-2, public health officials are continually reassessing the risks to specific individuals and the risk of different activities. A researcher from the University of Cambridge, Winton Centre for Risk and Evidence Communication assessed the “normal” risk of a person dying each year compared to the risk of dying from COVID-19 (Spiegelhalter, 2020).

When the typical risk of dying in a given year is plotted out by age, there is an initial increase due to birth defects and birth trauma followed by a period with the lowest risk of death until around nine years of age. After nine years, the risk of death begins to increase in a linear manner, except for a sharper increase in risk around age 20 from accidental deaths. The annual hazard of death increases 9.7% a year for men and 10.4% a year for women. The average annual risk for death under normal circumstances doubles with every seven years of age.

Based on an evaluation of the death certificates registered in England and Wales between March 7 and June 26, there were 218,354 deaths in the regions. The average number of deaths during this time period over the last five years was 159,595. Therefore, there were an excess of 58,759 deaths compared to the last five years. This is an increase of 37% in the number of deaths. Assessment of the excess deaths indicates that 84% were attributed to COVID-19.

When deaths from COVID-19 are plotted similarly to the information from all causes of death, there is a similar linear increase with age. The death rate from COVID-19 is around 12% to 13% higher for each year older a person is. Therefore, the risk of death doubles for every 5 to 6 years of age.

Comparison with the average annual risk of death indicates that catching the virus roughly doubles the risk of dying this year.

Table 1. The additional risk of dying from COVID-19 (Adapted from Spiegelhalter, 2020)

Age	Number of COVID-19 Deaths	Population	COVID-19 Rate/100,000	Percentage Increase in Risk of Death from COVID-19
0-4	3	3515430	0.1	0
5-14	3	7159102	0	2
15-24	33	6988755	0.5	5
25-34	128	7998302	1.6	10
35-44	369	7460856	4.9	14
45-54	1283	8142528	15.8	20
55-64	3476	7019590	49.5	27
65-74	7319	5906928	124	28
75-84	16043	3476922	461	35
85-89	10160	918437	1110	35
90+	10790	528959	2040	32
All	49607	59115809	83.9	31

The calculations show that those aged over 90 have around 4300 times the risk of dying from COVID-19 compared with 15 to 24 year olds, highlighting the different risks for different age groups.

The actual risk for an individual differs from the risk calculated for a hypothetical person based on the average of the entire population. The risk of dying from any cause, or COVID-19, is higher for those who are already chronically ill. For the large majority of healthy people, the risk of either dying from COVID-19, or something else, is much lower than the “average” person. The reverse is also true, and a frail individual who normally has a 60% risk of dying in a given year would have an 84% chance of dying if they were infected with COVID-19.

The author also emphasizes that while death is an easily recorded outcome in studies, there is increasing evidence that many individuals experience prolonged and debilitating symptoms from COVID-19, which while short of death, greatly affect their quality of life after infection.

The risk of long-term complications from COVID-19 are not addressed in this analysis and may greatly change the assessment of risk for different age groups that have a lower risk of death.

Low Transmission in Children’s Programs with Appropriate Distancing Measures

There have been two examples of successful opening of children’s programs published by the CDC. The first was in Rhode Island where childcare facilities were able to re-open when COVID-19 cases and hospitalizations fell below the pre-determined threshold (Link-Gelles et al., 2020). The Rhode Island Department of Human Services mandated that both licensed center and home-based programs reduce enrollment to 12 persons initially and increase the limit at a later time to 20 people (including staff members) while maintaining small groups of staff and students that remained together throughout the day in physically separated spaces. Staff were

required to wear masks at all times, and symptom checks were done on a daily basis for both staff and children. As of July 31, the Department of Human Services had approved 666 programs to re-open out of 891 in the state (corresponding to 75%). Based on the number of children enrolled, 74% of the state's child care program population that had been enrolled during January 2020 returned. Programs were monitored through unannounced visits, and officials reported high compliance with the requirements. A class with a symptomatic person was required to close for 14 days or until a negative PCR-based test result was available. Contacts of sick individuals were quarantined and monitored by weekly phone calls from the Department of Human Services to ask about any new symptoms.

The capacity for the re-opened programs was 18,945 children, and there were 101 possible childcare-associated COVID-19 cases between June 1 and July 31. After evaluation of potential cases, 49% of those reporting symptoms that can be associated with COVID-19 had negative PCR-based tests, 33% had a confirmed case based on a positive test, and 19% were classified as having a probable case. Probable cases were defined as people with clinical symptoms and exposure to confirmed cases that were unable to access official testing. Of the group of positive and probable cases, 58% were children, and the remaining were adults, including both teachers (22 individuals) and parents (2 individuals). Most of the cases occurred at the end of the study period in late July when the number of cases in the state was rising. Test results were available within a median of two days with a range between zero and eleven days after collection of the test sample. The identification of the 101 potential cases led to closure of 89 classes and quarantine of 687 children and 166 staff members.

There were 29 programs that reported a potential case, and 69% of these programs had only a single case without secondary spread.

This suggests that cases were mainly originating in the community and not through transmission in the childcare programs.

Of the programs with more than one potential case, 15% had between two and five cases. When the timing of the onset of symptoms was investigated by local public health officials, it was determined that in most of the programs, childcare-related transmission had not occurred. There were four programs where officials were not able to rule out in-program transmission. In one, there were ten cases, and inspections showed that there was poor adherence to regulations, particularly switching between classrooms. The other potential transmissions at the program sites all occurred late in July when community spread had increased as well.

The conclusions of the authors were that secondary transmission in childcare programs can be controlled, but there was a large impact on the children, staff, and parents who had to quarantine until test results were available to rule out potential cases.

Another important point was that secondary transmission was well contained during periods with low community spread, but increased as the number of cases in the state increased.

The second report of successful children's programs involved four overnight camps located in Maine (Blaisdell et al., 2020). The camps had 1,022 attendees that came from 41 states and international locations between June and August of 2020. Attendees included 642 children and

380 staff members with a range of attendee age from 7 to 70 years. The camp sessions ranged from 44 to 62 days with only a single session rather than the more typical multi-session organization of previous years.

The strict use of non-pharmaceutical interventions, such as face coverings and keeping groups separate, was successful in preventing transmission while at the camp.

Measures implemented by the camps included

- Pre-arrival quarantine
- Pre- and post-arrival testing and daily symptom screening
- Creation of cohorts and prevention of mingling between groups
- Use of face coverings
- Physical distancing
- Enhanced hygiene measures
- Regular cleaning and disinfecting of surfaces
- Maximal outdoor programming

Before arrival, attendees were instructed to quarantine with their family unit for 10 to 14 days. The area of the country attendees came from was not restricted, but arrival by car was recommended, and those taking buses or planes were instructed to use face coverings while traveling. Three of the four camps required a submission of test results before attendees were allowed entry, and delays in receipt of test results caused one camp to isolate 15 campers until negative results were known, which took up to 4 days after camp arrival.

Upon arrival, all attendees received instruction on hygiene measures, and cleaning of hands was mandated before and after all activity periods, meals, and other high-touch interactions. Campers were split into groups, or cohorts, ranging in size from five to 44 attendees based on bunks or age range. If interacting outside the cohort, attendees were required to wear face coverings and maintain a physical distance of at least six feet for the first 14 days at camp. Additionally, meals and bathroom use were staggered by cohort to reduce mixing of groups.

Importantly, staff members did not leave camp during the session for days off.

The adherence to regulations was monitored by staff and was reported to be high, but the specific level of adherence was not specifically measured.

After the sessions began, testing and symptom screening allowed for the quick identification and isolation of those who were potentially ill. There were 1,022 attendees, and 1,010 were tested before arrival. There were four attendees (corresponding to 0.4%) who were asymptomatic but tested positive. They delayed their arrival at the camp and completed ten days of isolation at home. About one week after arrival, 1,006 attendees without a previous positive diagnosis were tested, and three asymptomatic individuals with positive tests were identified. The results of the tests were available approximately two to three days later.

Following isolation of these persons and quarantine of their contacts, no secondary transmission of SARS-CoV-2 occurred.

However, none of the attendees were tested at the end of the session, and some asymptomatic individuals may have returned home after contracting the virus at camp.

The researchers conclude that multilayered prevention and mitigation strategies in an overnight camp setting can identify and prevent SARS-CoV-2 transmission, regardless of the prevalence of SARS-CoV-2 transmission in the communities from which campers and staff members originate.

Other information is emerging from the return of children to school outside of the United States. Reports from Germany following the return to school of most of the nation's children also suggest that appropriate measures can prevent widespread transmission at schools (Morris and Weber-Steinhaus, 2020). Directly after opening, there were a number of cases in 31 clusters, but these cases would have most likely been initiated before the start of school. Transmission within the schools themselves has been low according to local health officials with mainly single cases being reported.

The low transmission rate within school is being maintained even with an increase in the daily number of cases being reported in the German population as a whole.

The head of the infectious-disease department at Dr. von Hauner Children's Hospital in Munich stated that it is important to keep the number of infections in the community low. Even though the number of new cases has started rising in Germany, the amount is still much lower than currently reported in the United States. For example, in Germany on September 9, there were 1,892 new cases while in the United States there were 33,200 new cases reported. The population of the United States is about four times larger than that of Germany, but the number of new cases in the United States is approximately 17 times larger than Germany. Other countries in Europe have also reported low transmission in schools, but reopening schools in Israel led to a second wave of infections that was associated with the return of students. Researchers are studying the situations to determine what characteristics contributed to the disparate outcomes.

The fact that it is possible to have successful operation of children's programming is an important step for moving forward, particularly because evaluation of CDC records suggests that among the 69.74 million adults living with school-aged children, 41.0% had definite risk factors for severe COVID-19 illness, and 54.0% had definite or possible risk factors for severe COVID-19 illness (Gaffney et al., 2020). Additionally, adults living with children in low-income households were more likely to be at risk.

Overall, the researchers estimate that about 40 million adults in the United States who work or live with school-aged children have definite or possible risk factors for severe COVID-19 illness.

This estimate excludes 4.4 million non-teachers who work at schools and 1.6 million daycare workers as they were not specifically included in the data from the CDC.

Additionally, researchers have compiled outcome results for young adults (aged 18 to 34 years) who were hospitalized for COVID-19 to determine the potential risks associated with exposure at schools (Cunningham et al, 2020 and Katz, 2020).

They found that while fewer young adults are hospitalized for treatment of COVID-19, those that require hospitalization have risks that are similar to older adults.

The researchers investigated the clinical outcomes of 3222 individuals aged 18 to 34 years who were admitted to the hospital for treatment of COVID-19 between April 1 and June 30. This included only those who were initially admitted for COVID-19 and not those who were found to be infected after admission for other conditions. Also, only the first hospital admission for COVID-19 was included.

Of the 780,969 adults discharged from the hospital during the study period, 8.1% (or 63,103 individuals) were identified to have COVID-19, and 5% (or 3222 individuals) were in the hospital for treatment of COVID-19 and not in the hospital for reasons associated with pregnancy. While in the hospital, 21% of individuals aged 18 to 34 required care in an intensive care unit, 10% required mechanical ventilation, and 2.7% died. The median length of stay in the hospital was four days with a range between two and seven. Of those who were discharged from the hospital, 3% required further care in a rehabilitation facility.

Men, individuals with morbid obesity, and those with hypertension had a greater risk of death or need for mechanical ventilation. Of the 140 people who required the use of mechanical ventilation or died while in the hospital, 41% were classified as morbidly obese. There was also a higher proportion of people in this age group who were Black or Hispanic (57%) who were admitted to the hospital for COVID-19 compared to the proportion in the total population

Importantly, the researchers found that young adults with multiple risk factors (e.g. morbid obesity, hypertension, and diabetes) have a level of risk for negative outcomes from COVID-19 that is similar to middle-aged adults (age 35-64 years).

Extent of Infection in the United States

Due to shortages of testing at early phases of the pandemic around the world that have sporadically persisted in the United States in areas with increased infections, it has been difficult for public health officials to estimate the extent of the infection in the United States population. Previous estimates mainly relied on infection models that predict transmission using input describing natural disease transmission systems by modeling the population's age and social structure, travel and commuting patterns, and immune dynamics (Wu et al., 2020).

Another type of estimate used by a group of researchers in California uses information from reports of the amount of testing performed rather than transmission characteristics to determine potential bias in the reported numbers of cases from either incomplete testing or imperfect test accuracy.

Use of different methods to estimate the extent of the pandemic allows for a compilation and comparison of additional data to better understand what the true number of cases in the United State might be.

The estimate reported by Wu and colleagues was computed using information up to April 18. From the calculations, the researchers estimate that the total number of SARS-CoV-2 infections in the United States by April 18 was 6,454,951 (corresponding to 19 cases per 1000 people), which is nine times larger than the 721,245 confirmed cases (corresponding to 2 cases per 1000 people) reported during this period.

Based on this estimate, they report that 89% of the cases in the United States were not officially reported.

This is similar to the value calculated by another group of researchers for the number of undocumented cases (86%) that occurred in Wuhan, China during the initial outbreak.

The main cause of the undocumented cases in the United States was found to be from inadequate testing of the exposed population with only a small amount due to poor test accuracy.

Overall, the lack of tests accounts for 84% of the difference while poor accuracy accounts for only 16%.

In another report, the CDC released a seroprevalence study where they tested the extent of infection in frontline healthcare workers in the United States (Self et al., 2020). The researchers tested 3,248 healthcare workers from 13 geographically distant academic centers between April 3 and June 19. Testing of participants' blood was performed using ELISA methods, which are more accurate than point of care tests, and the reported validation of the test was a sensitivity of 96% and a specificity of 99%.

The overall proportion of workers who tested positive for antibodies to SARS-CoV-2 was 6% and ranged between 0.8% and 31.2% for individual institutions.

Of those who were positive for antibodies, 29% reported they had not had symptoms of COVID-19 from the start of the outbreak until the time of the study. Those who reported always wearing a face covering while treating patients were less likely to have antibodies (5.6%) than those who did not (9.0%). Face coverings were defined as a surgical mask, N95 respirator, or powered air purifying respirator (PAPR).

Characteristics of healthcare workers who were positive for SARS-CoV-2 antibodies

- Fewer females (5.3%) than males (7.2%) had antibodies
- Fewer non-Hispanic white participants (4.4%) than participants of other racial/ethnic groups (9.7%) had antibodies
- Symptoms of an illness were reported more often in participants with antibodies (71%) compared to those without antibodies (43%)
- 44% of those positive for antibodies reported that they did not believe they previously had COVID-19
- 69% of those with antibodies had not previously had positive test results for SARS-CoV-2 infection

The authors summarized that among participants who had positive test results for SARS-CoV-2 antibodies, approximately one third did not recall any symptoms consistent with an acute viral illness in the preceding months, nearly one half did not suspect that they previously had COVID-19, and approximately two thirds did not have a previous positive test result demonstrating an acute SARS-CoV-2 infection.

The study suggests that some SARS-CoV-2 infections among frontline healthcare workers are undetected and unrecognized due to minimally symptomatic or subclinical nature of many infections, underreporting of symptoms, or nonsystematic testing of personnel with symptomatic infections.

Use of facial coverings for all clinical encounters was found to be associated with lower risk of infection, and prioritizing access of personal protective equipment for all healthcare workers and emphasizing its regular use was identified by the authors as an important outcome of the study.

COVID-19 and Pregnancy

There have been preliminary reports of SARS-CoV-2 in the breast milk of women diagnosed with COVID-19. However, the results of the earlier studies were unable to rule out contamination of the samples and tested for the presence of viral RNA rather than infectious virus. Researchers reported an evaluation of 18 women with confirmed SARS-CoV-2 infection with infants between the ages of newly born to 19 months (Chambers et al., 2020). Samples of breast milk were available for before and after a positive SARS-CoV-2 test, and a total of 64 samples were evaluated. One sample that was collected on the day of symptom onset tested positive for viral RNA, but samples collected 2 days prior to symptom onset and those collected 12 and 41 days later tested negative for viral RNA. No replicating virus was detectable in any sample, including the sample that tested positive for viral RNA.

Based on the results, the authors conclude that SARS-CoV-2 RNA does not represent replication-competent virus and that breast milk is not likely to be a source of infection for infants.

Additionally, a review of the available studies on pregnant or postpartum women was published in which the authors determined the outcomes in this population as well as the level of data available (Pastick et al., 2020). The researchers found that there were 11,308 cases of COVID-19 during pregnancy that have been described in published reports. It was determined that 21% of the cases reported were classified as severe or critical illness. The survival rates for mothers was calculated to be 98% and 99% for the newborns. Infection of newly born babies was found to be low with only 41 potential cases reported in published studies.

Based on their examination of the published reports, the authors conclude that clinical outcomes appear reassuring during the initial phase of illness, but long-term information is not yet available.

While the outcomes of COVID-19 during pregnancy were reassuring, the authors emphasized that many of the clinical trials investigating treatments for COVID-19 are excluding people of reproductive age who are pregnant. Overall, 65% of the trials investigating treatments excluded pregnant women.

The researchers found a large number of clinical trials exclude pregnant women even when the treatments have previously been determined to be safe during pregnancy, which could lead to fewer approved COVID-19 treatment options available for this population.

Association of Race and Ethnicity on Hospitalizations

An updated assessment of the association between the rate of hospitalization and an individual's race or ethnicity indicates that minority individuals continue to have an increased rate as the pandemic continues (Karaca-Mandic et al., 2020). There are twelve states participating in the COVID-19 Hospitalization Tracking Project that report the race/ethnicity of individuals hospitalized with COVID-19. Evaluation of the information between April 30 and June 24 indicates that there were 48,788 cumulative hospitalizations among a total population of 66,796,666 individuals in the 12 states during the time period of the study.

The percentage of hospitalizations among Black patients exceeded the proportion of the group in the state population in all 12 states while the share of the population hospitalized who were white was substantially smaller than this group's overall share of the population in all of the states.

The largest difference between the cumulative percentage of hospitalizations and the state population of Black individuals was observed in Ohio (31.8% versus 13.0%), Minnesota (24.9% versus 6.8%), Indiana (28.1% versus 9.8%), and Kansas (22.0% versus 6.1%).

Eleven states reported the number of COVID-19 hospitalizations for Hispanic individuals.

Of the 11 states, 10 were found to have a higher percentage of hospitalizations for Hispanic individuals than their representative proportion of the state population.

The largest differences between the rate of hospitalization of Hispanic individuals and the population in the state were observed in Virginia (36.2% versus 9.6%), Utah (35.3% versus 14.2%), and Rhode Island (33.0% versus 15.9%).

The percentage of Asian individuals hospitalized from COVID-19 was lower than their proportion of the population in six of the ten states that reported the information.

The results of this study are consistent with studies published by the CDC during earlier time periods between March 1 and March 30 and those published by a California health system between January 1 and April 8.

Based on the results of the analysis, the authors suggest that additional reporting is needed for the remaining states that do not currently report information on the race or ethnicity of individuals with COVID-19.

Sex Differences with COVID-19 Infection

Information from multiple countries suggests that there is a higher risk of death in men with COVID-19 than in women (Takahashi et al., 2020). This association has been observed with other viral infections and is thought to occur due to differences in the immune systems of men and women. Researchers have evaluated the differences in viral load, the level of SARS-CoV-2 specific antibodies, the type and amount of cytokines and chemokines in circulating blood, and the types of blood cells between men and women with COVID-19.

The following characteristics did NOT differ between men and women

- The amount of viral RNA concentrations from nasal swabs and saliva
- The amount of IgG and IgM antibodies
- The levels of most of the inflammatory cytokines and chemokines
- The number of B cells (cells that produce antibodies)

One characteristic that did differ was that the women in the study were found to have a more robust T-cell response to infection compared to the men in the study. The women were also found to have both a higher number of T cells as well as a larger proportion of live T cells. There was a general association between a poor T-cell response and increased age as well as an increased risk of more negative disease outcome with a poor T-cell response for the men in the study, but not the women.

Women who were observed to have a higher amount of cytokines produced by the innate immune system were more likely to have worse disease progression, but this association was not observed in the men.

Based on their analysis, it was found that a poor T-cell response was associated with poor outcomes in men while an increased production of cytokines by the innate immune system was associated with poor outcomes in women.

The authors suggest that the elucidation of the differences indicate that “vaccines and therapies to elevate T-cell immune response to SARS-CoV-2 might be warranted for male patients, while female patients might benefit from therapies that dampen innate immune activation early in disease progression.”

AstraZeneca Vaccine Trial

AstraZeneca had put their vaccine trial of a potential vaccine for COVID-19 on hold in order to investigate whether a serious medical condition experienced by a participant was related to the vaccine or not (Robbins et al., 2020). The clinical trial is being organized by AstraZeneca and the University of Oxford, where the vaccine candidate was developed. The clinical trial that was put on hold is a Phase 3 trial that has multiple different study sites around the world, including some in the United States that are about to start recruiting participants. The company voluntarily took action after a report of a suspected serious adverse reaction, and they reported that they followed their typical safety protocols that are part of every clinical trial when a potentially unexplained illness occurs.

When a hold on a clinical trial is enacted, there is a pause in recruiting new participants and in administering additional doses to those already enrolled unless participant safety requires continuation of dosing.

The patient who experienced the serious adverse reaction was located in the United Kingdom, and she is expected to recover (Feuerstein, 2020). The details of the reaction were not initially disclosed, but it has since been reported that the woman experienced a spinal inflammatory disorder called transverse myelitis. A previous hold on the clinical trial for the vaccine was put into place in July when a participant also had neurological symptoms, but it was determined that in the earlier case, the participant was newly diagnosed with multiple sclerosis, and the symptoms were not related to the vaccine.

Transverse myelitis is one of the early symptoms of multiple sclerosis, but it can also occur in some people with no clear cause. There have been cases of the syndrome in other, unrelated vaccine trials, but as transverse myelitis can occur spontaneously there has never been any evidence of a link to a vaccine (Johnson, 2020). One expert explained the situation in this way, “A person may have a heart attack the day after taking an aspirin, for example, but it doesn’t mean the medication caused the event.”

Public health experts not involved in the study have stated that holds of this type are not uncommon because Phase 3 trials involve tens of thousands of participants, and some will fall ill during the trial in ways that are unrelated to the vaccine (Feurerstein, 2020). However, it is necessary to investigate serious medical conditions that develop to make certain there is no relation.

As of Saturday, September 12, the trial in the United Kingdom had resumed after review of the case by an independent safety review committee and by the United Kingdom health regulator.

No more information about the specific illness that stopped the trial was reported in the announcement, and it has not been officially confirmed by trial officials due to privacy concerns. However, several other officials, including National Institutes of Health Director Francis S. Collins, who are not directly involved in the trial have stated that the illness was transverse myelitis (Johnson, 2020).

Treatments for COVID-19

Corticosteroid Treatment

The clinical trial performed in the United Kingdom to test potential treatments for COVID-19 previously reported that use of the steroid dexamethasone improved the outcome in critically ill people with COVID-19. Researchers from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group reported the combined results from seven randomized clinical trials that evaluated the efficacy of corticosteroids in 1703 critically ill patients with COVID-19, confirming the previous results (WHO REACT Working Group, 2020). The trials were performed in 12 different countries between February 26 and June 9, and 678 participants received systemic dexamethasone, hydrocortisone, or methylprednisolone while 1025 participants were given either usual care or a placebo.

When statistical analysis was used to combine the data in a process called a meta-analysis, the researchers found that those taking corticosteroids had a lower all-cause mortality rate within 28 days of treatment compared to those taking the placebo. When different groups of participants were evaluated, those who were receiving invasive mechanical ventilation at the start of the trial had an absolute mortality risk of 30% when treated with corticosteroids compared to 38% for usual care or placebo. Participants who were not receiving invasive mechanical ventilation at the start of the trial had an absolute mortality risk of 23% when taking corticosteroids compared to 42% for usual care or placebo.

Comparisons between participants who required medication for maintenance of blood pressure at the start of trial due to the effects of sepsis showed no difference in outcome based on corticosteroid use. However, those who did not require such medication at the start of the trial had a better absolute mortality risk of 24% with the use of corticosteroids compared to 37% in the group receiving usual care or placebo. The effect of corticosteroid treatment was also more pronounced in older participants (those over the age of 60), but the effect did not differ between men and women.

> **The administration of corticosteroids in individuals hospitalized with COVID-19 was associated with lower all-cause mortality at 28 days after the start of treatment with no suggestion of an increased risk of serious of adverse events.**

Optimal dosing could not be determined based on the data from these trials, but there was no evidence suggesting that a higher dose of corticosteroids was associated with greater benefit than a lower dose of corticosteroids. Additionally, the results from the different trials were found to be consistent with each other with the same conclusions reported by the different authors of the individual studies.

Azithromycin

Early laboratory studies identified a possible beneficial effect from the antibiotic azithromycin when used as a treatment for COVID-19. An open-label trial compared the outcome of standard treatment with the use of azithromycin combined with either standard care or hydroxychloroquine in Brazil (Furtado et al., 2020).

The researchers found that use of azithromycin did not improve clinical outcomes.

There was also no difference in the rate of adverse events between the groups in the study.

NSAID Use

Early in the pandemic there was concern that the use of NSAID pain relievers led to an increased risk of severe symptoms from COVID-19. Researchers have evaluated the outcomes of 9,236 individuals with COVID-19 (Lund et al., 2020). Based on the analysis, they found that 2.7% had filled a prescription for NSAIDs, and 5.8% of the total group died within 30 days of the start of the trial.

There was no association between the use of NSAID medications and the mortality rate, risk of hospitalization, intensive care unit admission, mechanical ventilation, or requirement of therapy for kidney failure during the 30 days of the trial.

References

Blaisdell LL, Cohn W, Pavell JR, Rubin DS, Vergales JE. Preventing and Mitigating SARSCoV-2 Transmission — Four Overnight Camps, Maine, June–August 2020. MMWR Morb Mortal Wkly Rep. ePub: 26 August 2020. DOI: http://dx.doi.org/10.15585/mmwr.mm6935e1

Chambers C, Krogstad P, Bertrand K, et al. Evaluation for SARS-CoV-2 in Breast Milk From 18 Infected Women [published online ahead of print, 2020 Aug 19]. JAMA. 2020;e2015580. doi:10.1001/jama.2020.15580

Cunningham JW, Vaduganathan M, Claggett BL, et al. Clinical Outcomes in Young US Adults Hospitalized With COVID-19 [published online ahead of print, 2020 Sep 9]. JAMA Intern Med. 2020;10.1001/jamainternmed.2020.5313. doi:10.1001/jamainternmed.2020.5313

Feuerstein A. Covid-19 vaccine trial participant had serious neurological symptoms, but could be discharged today, AstraZeneca CEO says. STAT News. Published on September 9, 2020. Accessed on September 10, 2020 at https://www.statnews.com/2020/09/09/astrazeneca-covid19-vaccine-trial-hold-patient-report/

Fisher KA, Tenforde MW, Feldstein LR, et al. Community and Close Contact Exposures

Associated with COVID-19 Among Symptomatic Adults ≥18 Years in 11 Outpatient Health Care Facilities — United States, July 2020. MMWR Morb Mortal Wkly Rep 2020;69:1258–1264. DOI: http://dx.doi.org/10.15585/mmwr.mm6936a5

Furtado RHM, Berwanger O, Fonseca HA, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial [published online ahead of print, 2020 Sep 4]. Lancet. 2020;S0140-6736(20)31862-6. doi:10.1016/S0140-6736(20)31862-6

Gaffney AW, Himmelstein D, Woolhandler S. Risk for Severe COVID-19 Illness Among Teachers and Adults Living With School-Aged Children [published online ahead of print, 2020 Aug 21]. Ann Intern Med. 2020;10.7326/M20-5413. doi:10.7326/M20-5413

Johnson CY. Coronavirus vaccine trial resumes in U.K. after weeklong pause. The Washington Post. Published September 12, 2020. Accessed on September 13, 2020 at https://www.washingtonpost.com/health/2020/09/12/coronavirus-vaccine-trial-resumes/?hpid=hp_world1-8-12_vaccinetrial-1150am%3Ahomepage%2Fstory-ans

Karaca-Mandic P, Georgiou A, Sen S. Assessment of COVID-19 Hospitalizations by Race/Ethnicity in 12 States [published online ahead of print, 2020 Aug 17]. JAMA Intern Med. 2020;e203857. doi:10.1001/jamainternmed.2020.3857

Katz MH. Regardless of Age, Obesity and Hypertension Increase Risks With COVID-19 [published online ahead of print, 2020 Sep 9]. JAMA Intern Med. 2020;10.1001/jamainternmed.2020.5415. doi:10.1001/jamainternmed.2020.5415

Link-Gelles R, DellaGrotta AL, Molina C, et al. Limited Secondary Transmission of SARSCoV-2 in Child Care Programs — Rhode Island, June 1–July 31, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1170–1172. DOI: http://dx.doi.org/10.15585/mmwr.mm6934e2

Lund LC, Kristensen KB, Reilev M, et al. Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: A Danish nationwide cohort study. PLoS Med. 2020;17(9):e1003308. Published 2020 Sep 8. doi:10.1371/journal.pmed.1003308

Morris L, Weber-Steinhaus F. German schools, reopened a month ago, have seen no major coronavirus outbreaks. The Washington Post. Published September 11, 2020. Accessed on September 11, 2020 at https://www.washingtonpost.com/world/europe/covid-schools-germany/2020/09/10/309648a4-eedf-11ea-bd08-1b10132b458f_story.html

Pastick KA et al. A Systematic Review of Treatment and Outcomes of Pregnant Women With COVID-19—A Call for Clinical Trials. Infectious Diseases. Published August 13, 2020. Accessed on September 9, 2020 at https://academic.oup.com/ofid/article/7/9/ofaa350/5892324

Robbins R, Feuerstein A, Branswell H. AstraZeneca Covid-19 vaccine study put on hold due to suspected adverse reaction in participant in the U.K. STAT News. Published September 8, 2020. Accessed on September 9, 2020 at https://www.statnews.com/2020/09/08/astrazeneca-covid-19-vaccine-study-put-on-hold-due-to-suspected-adverse-reaction-in-participant-in-the-u-k/

Self WH, Tenforde MW, Stubblefeld WB, et al. Seroprevalence of SARS-CoV-2 Among Frontline Health Care Personnel in a Multistate Hospital Network — 13 Academic Medical Centers, April–June 2020. MMWR Morb Mortal Wkly Rep 2020;69:1221–1226. DOI: http://dx.doi.org/10.15585/mmwr.mm6935e2

Spiegelhalter D. Use of "normal" risk to improve understanding of dangers of covid-19. BMJ. 2020;370:m3259. Published 2020 Sep 9. doi:10.1136/bmj.m3259

Takahashi T, Ellingson MK, Wong P, et al. Sex differences in immune responses that underlie COVID-19 disease outcomes [published online ahead of print, 2020 Aug 26]. Nature. 2020;10.1038/s41586-020-2700-3. doi:10.1038/s41586-020-2700-3

WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis [published online ahead of print, 2020 Sep 2]. JAMA. 2020;10.1001/jama.2020.17023. doi:10.1001/jama.2020.17023

Wu SL, Mertens AN, Crider YS, et al. Substantial underestimation of SARS-CoV-2 infection in the United States. Nat Commun. 2020;11(1):4507. Published 2020 Sep 9. doi:10.1038/s41467-020-18272-4