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COVID–19
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EDUCATIONAL FORUM

Pfizer and Moderna phase III vaccine trial update

The first interim result of efficacy of the Pfizer and Moderna vaccines were reported to the media. They were not accompanied by a peer review publication; therefore, we have very limited data to report. Recall that these are messenger RNA vaccines that will require two doses and will require a cold chain of storage from manufacture to administration at a temperature of -80° Celsius for the Pfizer vaccine and -4° Celsius for Moderna. These trials each enrolled over 40,000 participants and after 95 cases of COVID-19 were confirmed in the trials, the study blind was broken in these patients. Each trial reported results in excess of 90% efficacy. For example, in the Moderna trial, of the 95 COVID-19 cases, five were in the vaccinated group and 90 were in the placebo group. There were no serious infections in the vaccinated group. No serious adverse outcomes have yet to be reported. The earlier phase trials showed that the vaccines have a moderately high rate of transient sore arm, myalgias, fatigue and fever, typically lasting one to three days. If the final analysis confirms the above results, it would appear that the vaccines are highly efficacious. If the cold storage can be effectively managed and patients are willing to be vaccinated and are tolerant of the mild-to-moderate side effects of the vaccines, we may finally be on our way to herd immunity. More than one vaccine will be required, and the phase III trials of the Johnson and Johnson, AstraZeneca, and Novavax vaccines are all well underway. Likely the only benefit of our severe worldwide surge in disease incidence will be the higher number of infected patients in our vaccine trials allowing for earlier documentation of efficacy.[1]

Household transmission of SARS-CoV-2

Few studies have characterized the transmission of SARS-CoV-2 within households. To better understand household transmission, a case-ascertainment study was conducted in Nashville, Tennessee and Marshfield, Wisconsin.[2] When an individual received a positive RT-PCR test for SARS-CoV-2 and that person lived with at least one other person in a household, that "index patient" (n=101) and all household members (n=191) were recruited into the study. Household members tracked and recorded symptoms (if symptoms occurred) and collected nasal swabs with or without saliva samples daily for 14 days. Fifty-three percent (102 of the 191) household contacts became infected. Infection rates for any household member when a child was the index patient were 53% for children less than 12 years of age and 38% for children 12–17 years. Household transmission occurred rapidly with nearly 75% of household infections developing within five days of the index patient's infection.

A contact-tracing study conducted in San Francisco demonstrated that transmission rates were higher among household contacts than non-household contacts.[3] Since the methodologies differed between studies, the transmission rates are not comparable, but 90% of the secondary cases identified from contact tracing in the San Francisco study were household contacts.

Given the high rates of transmission among household members, precautions are recommended whenever an individual becomes infected with SARS-CoV-2 and lives with others. Precautions include self-isolation and wearing masks when in shared spaces in the home.

COVID-19 outbreak aboard a United States naval aircraft carrier

An outbreak of COVID-19 occurred aboard the Theodore Roosevelt from March to May of 2020.[4] This was a naval warship with a crew of 4,779 persons. The median age of the crew was 27 years, 78.3% were male and no crew member was over 65 years of age. There was a notable association between the crew work environment and infection rates. Those crew working in close proximity with one another (i.e. the engine room) had a higher attack rate than those on the flight deck.

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The crew's sleeping and dining arrangements also placed them in close proximity, likely promoting the spread of the SARS-CoV-2 pathogen. Once the outbreak was identified, all crew members were tested. Of the entire crew, 72.1% did not develop COVID-19, 26.6% had confirmed COVID-19 and 1.3% had suspected COVID-19. Of these, 1,331 were confirmed and suspected cases, 43% were without symptoms at any time, 30.5% were pre-symptomatic at testing but then went on to develop symptomatic disease, 22% had symptomatic COVID-19 at the time of testing, and 4.5% had a symptomatic, suspected case of COVID-19.

The most common symptoms reported at any time during the illness were headache (68%) followed by cough (59.5%), nasal congestion (43.8%) and altered taste and smell (42.3%). Symptoms present at presentation were cough (32.8%), headache (31%) and alteration in smell or taste (24.1%). Shortness of breath was noted at some point by 20.3% of the infected individuals. Fever was present in only 13.2 %. Only 23 (1.7%) required hospitalization and one death occurred as a result of COVID-19 related cardiovascular complications.

This outbreak is notable based on its occurrence in a closed population of young, generally healthy persons. They lived, dined and often worked in close quarters. The outbreak demonstrates the ability of SARS-CoV-2 to spread rapidly in such an environment. It also demonstrates that a large percentage of persons remain asymptomatic: 43% in this outbreak. The symptoms were primarily headache and respiratory symptoms with fever present in relative few cases. While not completely analogous, many similarities exist between this population and college students on campus where housing, communal dinning and social gatherings create risk. College campuses have worked to mitigate these risks. Measures to minimize situations where large groups work or eat in close proximity should be high priority. This study also demonstrates that symptom screening, particularly for fever, has relatively low sensitivity and therefore the need to implement public health measures that are known to be effective in reducing the spread of COVID-19.

Utilization of masks and new COVID-19 cases in Kansas

Researchers in Kansas followed patients from March until October of 2020.[5] They compared new COVID-19 cases in counties with mask mandates in place versus those without. It was consistently observed that in those counties with mask mandates, cases decreased with the initiation of the mandate. This decrease occurred, as expected, several weeks after the initiation of the mandate corresponding to the SARS-CoV-2 incubation period. Additionally, the counties with a mask mandate in place were able to demonstrate stabilization of case increases during the July 2020 surge, in contrast to those without a mandate where new cases continued to rise.

Overall, new cases were reduced by 50% in those counties with a mask mandate compared to those without. New cases per 100,000 persons were 14.3 in the nonmask counties and up to 7.3 cases per day less in those requiring masks. This result clearly demonstrates that mask mandates very significantly reduce, but do not prevent new cases. This further emphasizes the need for multiple nonpharmaceutical interventions to achieve pandemic control. No single intervention alone will be enough.

SARS-CoV-2 genetic variants identified among farmed minks in Denmark

Since June 2020, 214 human cases of COVID-19 in Denmark have been identified with SARS-CoV-2 variants.[6] The SARS-CoV-2 isolated from 12 of these patients had mutations that have not been observed previously, referred to as the "cluster 5" variant. Eight of these patients had a direct link with the mink farming industry, and the other four were from the local community where the minks were raised. Based on initial observations, the clinical presentation and disease severity from the cluster 5 variant appears to be similar to other circulating SARS-CoV-2 viruses.

Per the World Health Organization (WHO), minks were infected following exposure from infected humans. Minks can act as a reservoir for the virus, transmitting the disease back to humans. The concern with the high rate of infection in the mink population, which numbers in the tens of millions, is that this large reservoir could further increase the rate of viral mutation which could have the effect of increased transmissibility or increased severity of infection. To date, SARS-CoV-2 has been found among farmed minks in six countries: Denmark, the Netherlands, Spain, Sweden, Italy and the United States. Danish authorities have announced several actions to enhance COVID-related public health, including:

- Culling of all farmed mink
- Enhanced surveillance of the local population
- Expanding viral sequencing for human and mink infections
- Rapid sharing of variant mutations
- Movement restrictions to the northern region (North Jutland) where farming occurs to reduce further transmission.

The WHO advises all countries to "enhance surveillance for COVID-19 at the animal–human interface where susceptible animal reservoirs are identified, including mink farms." They advise against any travel or trade restrictions for Denmark based on the information currently available.

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Persistence of antibodies to SARS-CoV-2

Researchers at Mount Sinai Hospital in New York City sampled 72,401 individuals for antibodies against SARS-CoV-2 beginning in March of 2020.[7] All screened patients had either laboratory-confirmed COVID-19 by PCR, or suspected COVID-19 disease with symptoms or exposure to a known case. Most of the symptomatic persons had mild-to-moderate disease (95%). Of the 72,401 screened patients, 30,082 (41.6%) had antibodies to SARS-CoV-2. Titers of 1:80 and 1:160 were considered low; 1:320 moderate; and 1:960 and higher were considered high. Ninety-three percent of patients had moderate or high antibody responses. Even in those with low titers, neutralizing activity was present in 50% of the patients. In those with the higher titers, 90% with moderate titers and 100% of high titer patients had neutralizing antibodies (Table 1).

Table 1: SARS-CoV-2 antibody responses

Titer	1:80	1:160	1:320	1:960	>>
Relative antibody level	Low		Moderate	High	
# persons (%) with antibody detected	690 (2.3)	1453 (4.8)	6765 (22.5)	9564 (32)	11610 (38.6)
% neutralizing antibody	50		90	100	

A subset of these patients (121 patients) was followed over time to gain an understanding of the persistence of the antibody response, and this is summarized in Table two. These 121 persons underwent two additional antibody measurements at a median of 82 days and 148 days, essentially three and five months after symptom onset. Notably, the geometric mean titer was still in the moderate range (90% neutralizing) at five months. This data is consistent with observations of the time to reinfection with other coronaviruses with a mean reinfection exceeding one year.[7]

Table 2: Antibody persistence

Time period	Elapsed time (post sx onset)	GMT (geometric mean titer) of antibody
First	30 (33-67)	148 (113-186)
Second	82 (52-104)	690
Third	148 (113-186)	404

These results suggest that vaccines may produce lasting immunity and protect from reinfection at least in the short-to-medium term.

Convalescent plasma treatment for COVID-19

Data suggesting a benefit from convalescent plasma have all come from observational trials. Two randomized trials were discontinued prematurely and neither of these showed a mortality benefit. We have learned from the early trial results of the Regeneron and Lilly monoclonal antibodies that these are ineffective when given for severe disease.[8] This is not unsurprising since the assumed mechanism of action is binding to viral particles and preventing cell entry and replication. Therefore, both monoclonal antibodies and convalescent plasma would be expected to be more beneficial in early disease. A study from India looking at convalescent plasma for moderate disease was published in the British Medical Journal. Four hundred sixty-four patients hospitalized at tertiary care centers with moderate COVID-19 pneumonia were randomized to this prospective open label trial of convalescent plasma versus standard of care. Eighty-three percent of the patients already had neutralizing antibody at study enrollment. The primary outcome was progression to severe disease over 28 days and the secondary outcomes were measures of disease improvement over 28 days. Disease progression, mortality, and time to resolution of symptoms were all virtually identical in the treatment and control groups. In a sub-analysis of the patients who did not have detectable neutralizing antibodies at enrollment, the outcomes were no different. This study did not support any benefit of convalescent plasma in moderately severe COVID-19 pneumonia.

Bamlanivimab: monoclonal antibody treatment for outpatients with COVID-19

Bamlanivimab (LY-CoV555) is a monoclonal antibody that was derived from an early survivor of COVID-19. It has been cloned and is being produced by Lilly as a potential treatment for COVID-19. As noted above, it is likely that if monoclonal antibodies directed against the spike protein of SARS-CoV-2 would be effective, it would be early in the disease course. We now have early interim results of a phase II trial of bamlanivimab in 452 outpatients with mild to moderate COVID-19. Seventy percent of the patients were over age 65 or had at least one recognized risk factor for worsened COVID-19 outcome.[9] Patients received one

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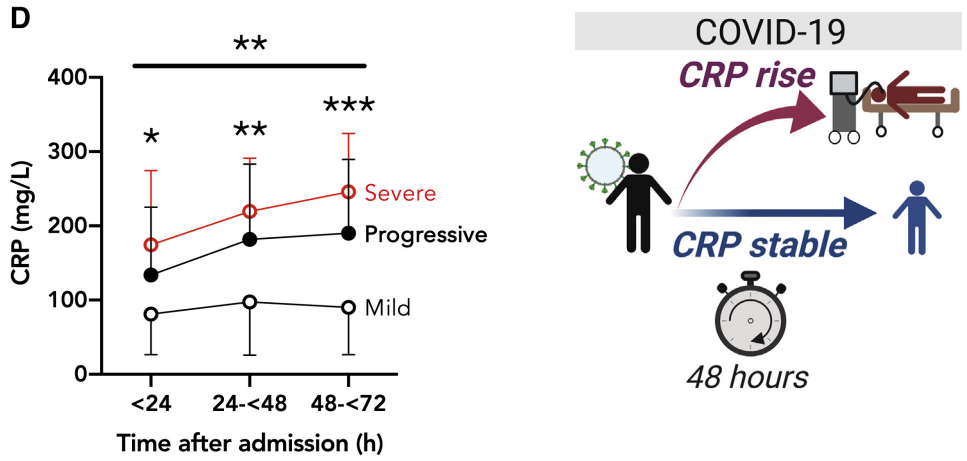
of three doses as a single infusion and the outcomes were both viral clearance and symptom improvement measured at day 11 post infusion. Importantly, the median time from symptom onset to drug infusion was four days. For patients who received the intermediate dose, the difference from placebo was a viral load that was lower by a factor of 3.4, and this was statistically significant at p=0.02. Smaller differences from placebo were observed among the patients who received the lowest and highest doses, and neither of these results reached statistical significance. On days two to six, the patients who received LY-CoV555 had a slightly lower severity of symptoms than those who received placebo. The percentage of patients who had a COVID-19 related hospitalization or visit to an emergency department was 1.6% in the LY-CoV555 group and 6.3% in the placebo group. At day 29, the percentage of patients who were hospitalized with COVID-19 was low in both the treatment and the placebo groups; however there was a difference between the groups in the bamlanivimab group at 1.6% (five of 309 patients), and in the placebo group at 6.3% (nine of 143 patients). The drug was well-tolerated with no severe adverse effects. A total of 2.3% of patients had reactions during the infusion, typically consisting of pruritus, flushing, rash or mild facial swelling. A large phase III trial looking at newly diagnosed patients over age 65 is about to be launched. If the reduction in hospitalization rate is confirmed in that trial, this may be an important therapy for early disease in higher risk individuals. Regeneron has a similar drug, two monoclonal antibodies in this case, in a phase II/III trial and we are awaiting peer-reviewed results of this trial.

Escalating CRP levels predict respiratory deterioration in COVID-19 hospitalized patients

This was a single-center, retrospective cohort analysis of hospitalized COVID-19 patients.[10] The authors looked at the first 100 patients admitted to Brigham and Women's Hospital with non-critical infection, and examined both the initial CRP as well as the rate of rise of the CRP over the first 48 hours of admission. Both predicted more severe disease; however a rapid rise in CRP levels better predicted subsequent respiratory deterioration and intubation. Because the initial CRP level did have prognostic value, it might also be of value when outpatients are seen with more severe disease not requiring hospitalization. If CRP levels are markedly elevated in this subset of patients, more intense follow-up might be indicated. It could also suggest a marker for which outpatients might benefit from a course of dexamethasone; however there are no prospective data looking at treating this subset of patients with dexamethasone.



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Kenneth Roy Cohen, MD, FACP

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of OptumCare. He served as Chief Medical Officer from 1995 to 2020. He now serves as the Executive Director of Clinical Research for UHG R&D and Senior National Medical Director for OptumCare. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

Geoffrey Heyer, MD

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

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