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COVID–19
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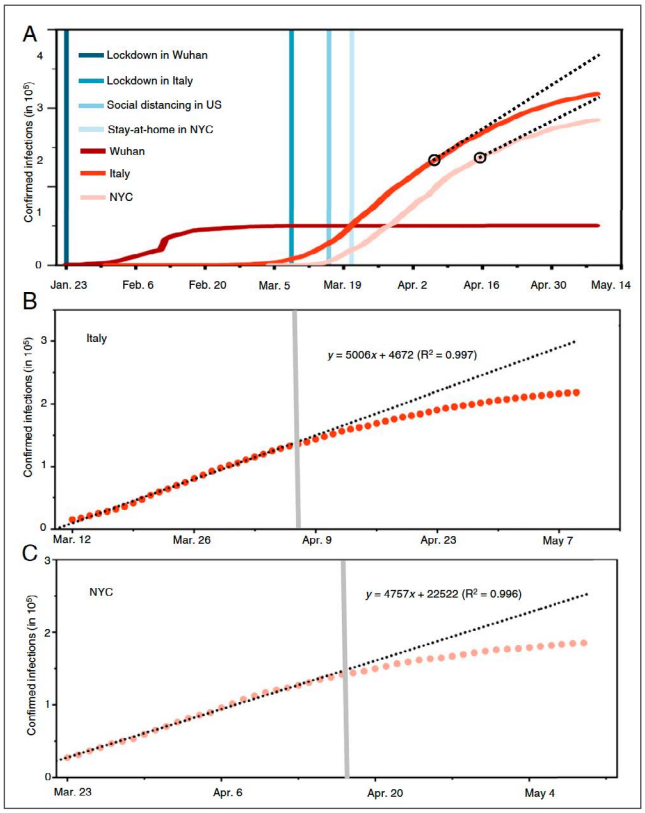
EDUCATIONAL FORUM

Wearing face masks appears to be the most effective population strategy for decreasing COVID-19 transmission

Virus transmission between humans can occur via direct contact (virus deposited on persons), indirect contact (virus deposited on objects), and airborne routes (virus transmitted from droplets and aerosols). Mitigation measures such as social distancing and wearing face covers can help to decrease the spread of a virus, but the effectiveness of a given intervention would depend, in large part, on the mechanism(s) of virus transmission. Investigators recently analyzed how mitigation measures affected SARS-CoV-2 transmission in Wuhan, China, Italy, and New York City.[1] By analyzing when the mitigation strategies were implemented relative to changes in transmission rates the investigators were able to extrapolate which mechanisms of virus transmission are most important.

Since China started several mitigation strategies at the same time, the effects of each individual strategy were difficult to discern. You can see however on the upper panel of the graph below, that this combined effort completely shut down the pandemic in Wuhan. City lockdown and isolation measures began in Italy on March 9, and social distancing — maintaining six feet distance and avoiding group gatherings and crowded places — was implemented in New York City March 22. But transmission rates continued to increase in both locations. Social distancing appears to have had little impact on COVID-19 transmission. In contrast, Italian authorities required the use of face coverings starting April 6. New York mandated face coverings in public on April 17. Extrapolating from prior transmission rates, use of face coverings "reduced the number of infections by over 78,000 in Italy from April 6 to May 9 and by over 66,000 in [New York City] from April 17 to May 9." Linear regression demonstrates that new cases decreased at a rate of 3% per day. The effects of masking in Italy and NYC can be seen in the bottom two panels of the below graph. The authors note that social distancing is beneficial because it prevents direct contact and droplets which typically don't carry more than six feet, but it is insufficient (without face masks) to prevent inhalation of aerosolized virus as aerosols do not obey the six-foot role.



The authors conclude that implementation of face coverings as a mitigation strategy accounted for a more substantial reduction in infections compared to social distancing. Face coverings help to block atomization and inhalation of virus-bearing aerosols. These findings indicate that airborne transmission is the dominant mechanism for COVID-19 infection. Social distancing without a face cover is insufficient to protect the public.

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Facemasks and distancing to manage COVID-19 infection risk[2]

A new modeling study published in The Royal Society showcases the effectiveness of universal masking in preventing spread of COVID-19. The researchers' model showed that universal mask use (masks worn by everybody) can be significantly more effective at preventing spread than selective mask use (masks worn only by those with symptoms), because of the protective effects of masking on the wearer and because of the asymptomatic infectious period. Of note, the model suggests that this policy could push the viral reproduction number below one (R_0), and control epidemic spread even without lock-down measures or perfect compliance by the public. These results are consistent with observations of attenuated viral spread in countries where universal masking has been successfully adopted.

N-95 and surgical mask sterilization possible but not without consequence

Shortages of personal protective equipment (PPE) during the COVID-19 pandemic continue to occur. Sterilization of surgical and N-95 masks has been proposed to allow for extended use. Researchers at the University of Oklahoma compared the filtration efficacy of two types of N-95 masks and a surgical mask before and after sterilization.[3] Masks were sterilized using plasma vapor hydrogen peroxide and chlorine dioxide. The filtration efficacy universally decreased with sterilization. Mask types differed. N-95s maintained filtration efficacy more than surgical masks. All masks performed better using hydrogen peroxide sterilization over chlorine dioxide. Importantly, filtration efficacy after sterilization decreased more for particle size of 300nm (a size consistent with infectious particles). This study suggests that sterilization of masks is possible. However, sterilization methods differentially affect mask types and masks of the same type from different manufacturers. Care must be exercised in reusing sterilized masks as the efficacy may be significantly degraded.

Blood type may contribute to the severity of COVID-19 infection

One of the lesser understood aspects of COVID-19 infection is the wide patient to patient variability in disease severity. This is partially, but not completely accounted for by comorbidities and advancing age. Additionally, male sex remains one of the major contributors to increased mortality with an unknown mechanism to date. A study in the NEJM this week attempted to understand this disease variability and looked at over 1,600 patients admitted to hospitals in Italy and Spain and compared them to matched controls.[4] They examined over eight million single nucleotide polymorphisms (SNP's) and found two gene loci associated with an increased risk of disease severity as defined by the development of respiratory failure. In the first locus, one gene encodes a protein that interacts with angiotensin-converting enzyme 2, the SARS-CoV-2 cell-surface receptor in the lung. Another gene within this locus encodes chemokine receptors which regulate the specific location of lung-resident memory CD8 T cells affecting the immune response to airway pathogens, including influenza viruses. The other locus included the ABO blood type genes. The risk of respiratory failure was examined as a function of blood type. Compared to the other ABO blood types, there was a 45% higher risk of respiratory failure in those of blood group A and a 35% lower risk of respiratory failure among those with blood group O. The mechanism underlying this varying risk as a function of blood type is unknown.

Healthcare workers infections related to contacts at home

Researchers in Belgium offered all staff (clinical, non-clinical and volunteers) working at the Hospital East-Limburg the opportunity to participate in serologic testing. Both IgG and IgM antibodies were assayed.[5] The IgG test utilized had a sensitivity/specificity of 92.2/97%. IgM test performance was poor, and those results were not utilized. 74% of 4,125 staff agreed to participate. Persons with symptoms consistent with current COVID-19 were excluded. Overall 6.4% were positive for IgG. Fever and anosmia were the two symptoms more frequently reported among seropositive individuals. Anosmia occurred in 35% of patients in this report. Fifteen percent of seropositive persons reported no symptoms. In a related study in JAMA Otolaryngology 55% of patients from an Italian cohort noted loss in taste or smell.[6] In this group of health care workers, none of the following work-related COVID risks was associated with seropositivity: working during lockdown (the most intense COVID case volumes), being involved in clinical care, caring for COVID patients, or exposure to a COVID positive coworker. However, and importantly, staff having a contact with a household member with confirmed or suspected COVID had an R_0 of 3.15. These findings were similar to a study of health care workers in Wuhan, where the most common source of infection was household and not hospital related contacts. In this group of health care workers, fever and anosmia stood out as sentinel symptoms. Household contact was a much greater risk factor associated with infection than work with COVID patients.

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Prone positioning improves oxygenation in non-intubated patients

When a high burden of COVID-19 infection in a community strains ICU and ventilator capacity, other solutions to manage the hypoxic respiratory failure of COVID-19 pneumonia can be valuable to control resource utilization. Additionally, the timing of intubation with worsening hypoxemia in these patients is still controversial, as outcomes are not uniformly better with mechanical ventilation. This may be related to the fact that COVID-19 pneumonia has important differences from ARDS in that alveolar inflammation and microthrombosis may be important mediators of impaired gas exchange. Prone ventilation has been shown to improve oxygenation in intubated patients possibly by preventing over inflation and subsequent lung damage in areas of the lung having less disease involvement, and improving V/Q matching. A study in JAMA IM looked at 25 patients consecutively admitted to the Columbia University step down unit who met the criteria of respiratory failure based on a respiratory rate of >30/min or an oxygen saturation <93% while using both maximal nasal cannula and non-rebreather oxygen flow rates.[7] They were treated with maximally tolerated voluntary prone ventilation and the end point was the risk of intubation in those who achieved a saturation over 95% compared to those that did not. Seventy-six percent of patients achieved a saturation over 95% within one hour of prone ventilation and the subsequent risk of intubation was 37% in this group. Of the 24% of patients who did not improve their oxygenation, 83% were intubated. Twenty-five percent of those requiring intubation died, while all patients not requiring intubation survived. As noted in the below graph, the response to prone ventilation is rapid. Importantly, this technique can be used in seriously ill outpatients who have dyspnea with or without hypoxia who otherwise do not meet inpatient criteria.

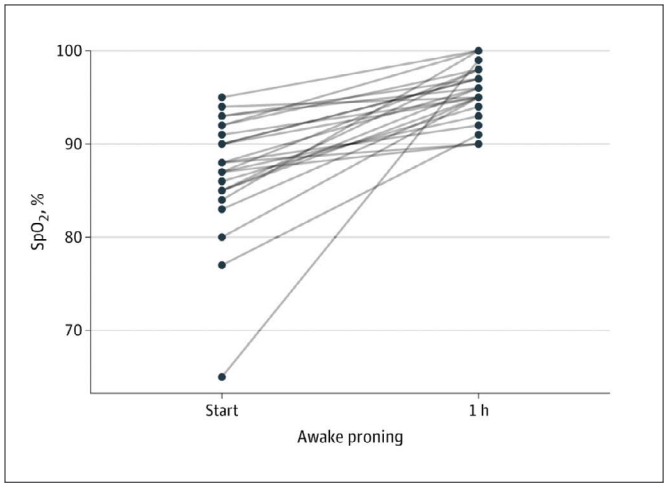

Figure legend: Oxyhemoglobin Saturation (Spo2) 1 hour after initiation of the prone position in awake, nonintubated patients with COVID-19. Spo2 before and 1 hour after initiation of the prone position in awake, nonintubated patients with COVID-19 severe hypoxemic respiratory failure (n = 25).

The RECOVERY Trial[8]

This British multi-arm study is currently the most comprehensive prospective randomized trial of treatments for COVID-19. 11,500 patients have been enrolled into the six arms of the trial. The trial is using a pragmatic design with a single placebo group to compare all the above regimens. The results are anxiously awaited. It received international attention this week when preliminary data were released showing a mortality benefit to low dose dexamethasone treatment in patients hospitalized with severe COVID-19 infection.

The study is not yet available for review however the preliminary results were published on the trial website. A total of 2,104 patients were randomized to receive dexamethasone 6mg once per day for ten days and were compared with 4,321 patients randomized to usual care alone. Among the patients who received usual care alone, 28-day mortality was 41% in those who required ventilation and 25% in those patients who required oxygen only. Dexamethasone reduced deaths by 33% in ventilated patients and by 20% in the other patients receiving oxygen only. There was no benefit among those patients who did not require respiratory support. Based on these results, one death would be prevented by treatment of around eight ventilated patients or around 25 patients requiring oxygen alone.

The other arms of the study include:

- Hydroxychloroquine treatment — this treatment arm was canceled due to the accumulated body of evidence on the harms of treatment with HCQ.
- Tocilizumab — this is a monoclonal antibody to the IL-6 receptor and has shown significant clinical benefit in a small observational study.
- Azithromycin
- Convalescent plasma
- Usual care

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Prospective study of monoclonal antibody therapy for COVID-19 infection[9]

Monoclonal antibodies hold promise as treatments for COVID-19 infection. Broadly, antibodies can be utilized in two different ways. They can be directed at the spike protein of SARS-CoV-2 and thereby prevent or treat infection. They can also be directed at the mediators of the cytokine storm to block production of the mediators or their receptor binding sites. A prior study highlighted in this forum looked at the use of the monoclonal antibody tocilizumab (approved for use in rheumatoid arthritis) which binds to and blocks access to the IL-6 receptor in patients with severe COVID-19 infection. There was rapid clinical improvement in this small observational study. A second study looking at monoclonal antibody use was published this week in The Lancet Rheumatology. The drug is mavrilimumab, an anti-granulocyte macrophage colony-stimulating factor (GM-CSF) receptor monoclonal antibody. It is currently in late phase trials for use in rheumatoid arthritis and giant cell arteritis. Binding to the GM-CSF receptor activates multiple pro-inflammatory pathways in macrophages and neutrophils, and results in increased secretion of proinflammatory cytokines, including tumor necrosis factor, interleukin (IL)-1, IL-6, IL-23, and IL-12. It was studied at a single hospital in Milan and prospectively enrolled 13 patients with evidence of severe COVID-19 pneumonia and serum markers compatible with cytokine storm. They were compared to 26 matched control patients. Patients on mechanical ventilation or in the ICU were excluded. There were no deaths in the treatment group compared to a 27% mortality in the control group. Only one patient in the treatment group progressed to mechanical ventilation compared to 35% of the control group. In the survivors, significant improvement was seen in eight days in the treatment group and 19 days in the control group, allowing for a 50% reduction in hospital length of stay. Treatment was well tolerated with no serious adverse effects. Patients in this study received treatment on average at day eight after symptom onset, a time period known to correlate with the onset of cytokine storm in susceptible patients. We still lack large randomized trials of monoclonal antibody therapy, but importantly the British RECOVERY Trial includes a treatment arm using tocilizumab and hopefully these results will soon be available.

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Kenneth Roy Cohen, MD, FACP | *Chief Medical Officer*

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He has successfully developed and reported numerous clinical quality studies in primary care, including tobacco cessation, osteoporosis, asthma, diabetes, hypertension, and ischemic vascular disease. 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 has served as Chief Medical Officer since 1995. 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 | *Senior Medical Director*

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 | *Senior Clinical Practice Performance Consultant*

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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