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COVID–19
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EDUCATIONAL FORUM

Difficulty in achieving herd immunity with SARS-CoV-2[1,2]

Herd immunity describes indirect protection from infection. This protection is not from individual immunity but rather from the inability of a disease to propagate when a significant portion of the population is immune. The percentage of immune individuals required to achieve herd immunity is influenced by disease transmission rates under real-world conditions (the R_0), and can be as low as 50% (influenza) or has high as 95% (measles). Herd immunity works best when immune responses, to either natural infection or vaccine, are durable and prevent forward transmission. The immunity is then spread evenly through a population. On the other hand, partial immunity can reduce or eliminate symptoms in an individual while still allowing viral shedding and propagation of the virus to others.

The R_0 of SARS-CoV-2 is estimated to be between 2–6, suggesting a herd immunity threshold of between 60–85%. As we have seen, social distancing can temporarily reduce the R_0, theoretically allowing temporary achievement of herd immunity at a lower percentage of immunity in the population. Conversely, imperfect durability in immune protection or unevenness in immunity throughout communities will push the required threshold percentage higher. Note that in many communities to date, SARS-CoV-2 infection (and presumed immunity) is heavily concentrated in younger individuals. Because individuals tend to interact with people their own age, we will probably never achieve herd immunity in the elderly population without a vaccine. Durability of the protective immune response is an important unknown that will drive long-term epidemic patterns. Modeling exercises suggest that a protective response of <1 year will lead to annual outbreaks, and a protective response of two years would lead to outbreaks every other year. Historical experience with the influenza vaccine suggests it will be difficult to maintain the herd immunity threshold in the United States over time, and yearly re-vaccination could be the norm. However, the presence of memory T cells in those previously exposed or vaccinated should help reduce the disease severity, even if it does not prevent infection outright as the length of immunity begins to wane. COVID-19 is likely here to stay, probably with less lethality over time.

If we produce a successful vaccine, can we then achieve herd immunity?[3]

The medical community and the broader society alike are holding out hope that a successful vaccine can put an end to the current pandemic. Assuming vaccine success, how likely is the vaccine to end the pandemic? As noted in the Forum dated May 29, eight vaccine candidates have entered or completed phase 1 trials. Although a vaccine will not be available until 2021, as launches of prior mass vaccination programs have demonstrated, careful planning to ensure readiness of both the public and the health community for a COVID-19 vaccine should begin now. Although the range of estimates is broad, as noted above, it is likely we would need to achieve a vaccination rate of >60% and possibly as high as 85% to achieve herd immunity. Even if we are able to scale production for mass vaccination, surveys have suggested that only about 30% of individuals would accept a vaccine early after release, with only about 75% eventually being receptive to vaccination. With average seroprevalence nationwide at under 5%, prior infection alone will not contribute meaningfully to herd immunity. When considering childhood vaccinations, the three broad categories of parents' concerns are the necessity of vaccines, vaccine safety and freedom of choice.

- Whereas one could imagine how necessity might be questioned with a disease such as measles which most adults have never witnessed, hopefully few Americans will question the necessity of a vaccine for COVID-19.
- With respect to vaccine safety, acceptance is highest during a pandemic, particularly since the daily impact of this pandemic has been high for most Americans. Vaccine safety will nonetheless be a significant concern given the rapid development and testing process along with the mistrust of the government's pandemic response. As such, being transparent about the rigorous testing and ongoing monitoring required by the vaccine approval process will be critical, as well as sharing any important adverse effects of the vaccine. Educational campaigns also should include information about the important societal contribution of individual vaccination to herd immunity.
- Arguments based on freedom of choice may reflect mistrust of the medical community. Early reports from cities and states demonstrate the disproportionate burden of COVID-19 disease borne by African American people and other minorities. While various subpopulations have their bases for mistrust, the perspectives of African American individuals, in particular, are critical to consider as a matter of health equity. This needs to be addressed early in the vaccine campaign process.

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Given the need to achieve very high levels of vaccination to combat the intrinsically high R_0 of SARS-Co-V2, public health campaigns need to start now and should:

1. Harness traditional and social media to engage a diverse audience around the importance of a mass vaccination program for COVID-19.
2. Enlist cultural leaders outside of traditional medical and public health communities as vaccination champions, particularly for minority communities.
3. Educate frontline health care workers who will play a central role in encouraging COVID-19 vaccination. Many studies have found that physicians are the most important influencers of vaccine decision-making.

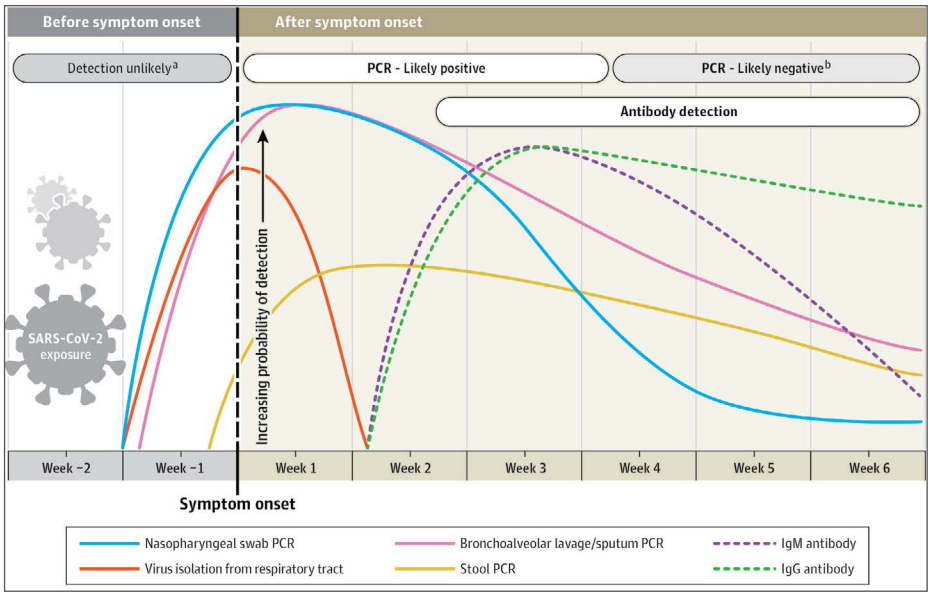
The health care community will likely benefit from early public enthusiasm for a COVID-19 vaccine, and it is critical to build on that momentum to encourage swift, broad vaccine uptake as it becomes available.

Detailed viral analysis of patients infected with COVID-19[4]

Investigators conducted detailed viral analyses of nine individuals with mild COVID disease.[5] This extensive survey looked at viral RNA detection using PCR, direct viral culture, as well as tests for neutralizing antibody, IgG and IgM levels. All measurements were conducted at several time points throughout the illness course for each patient. Several key observations were made confirming previous findings. All patients developed neutralizing antibodies to SARS-CoV-2 but the height of the antibody titer was not closely correlated to clinical course. Peak viral shedding was very high in the first week. Peak viral loads were 1000 times higher than were seen in SARS, likely accounting for the higher R_0 of SARS-CoV-2 infection. Viral shedding did not abruptly decline with seroconversion; but, rather showed slow steady decline. Importantly however, viral shedding did not correlate with the duration of infectivity.

Investigators then studied subgenomic RNA, which is present only in infected cells. Subgenomic RNA was not detected after day 5 in the throat, however it was found in sputum up to day 11. Viral load in sputum tended to be more prolonged in those individuals with more pulmonary involvement. This correlates with the longer duration of RNA detection in hospitalized patients who have COVID-19 pneumonia. However, and importantly, no live virus was cultured after day seven. This is not unexpected as viral loads are decreasing by that time.

Urine was consistently negative for viral RNA, whereas stool samples were positive for RNA but virus could not be cultured from stool. The investigators hypothesize that viral replication does occur independently in the digestive tract, as RNA detection did not correlate with respiratory tract viral load. Additionally, subgenomic RNA was occasionally detected in stool, and in one patient RNA was detected in stool for more than three weeks after complete symptom resolution. Fecal/oral transmission, however, has not been identified in SARS-CoV-2 infection. The combined data confirm that droplet spread is the most likely source for infectious spread. A cutoff for cessation of infectivity is suggested to be a viral load of less than 100,000 viral RNA copies/ml of sputum and being more than 10 days from symptom onset. This is consistent with our current return to work guideline. This important article presents a study of viral RNA, subgenomic RNA, viral culture, and antibody production at multiple time points during clinical disease in a group of nine patients. These data match closely with the graph published last month in JAMA, shown below.



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SARS-CoV-2 infection confers some protective immunity against re-exposure in rhesus macaques[6]

We have still not yet definitively demonstrated that infection with SARS-CoV-2 infection confers immunity. This is a critical issue, as development of a human vaccine for SARS-CoV-2 requires that infection provides clinically meaningful protection against re-challenge with the virus. Knowing if SARS-CoV-2 infection confers protective immunity also has important implications for public health policy during the COVID-19 pandemic.

Using a rhesus macaque model, researchers explored how SARS-CoV-2 infection affected viral loads from subsequent re-challenge. Macaques developed high viral loads and upper and lower respiratory tract infections from initial SARS-CoV-2 intranasal and intratracheal exposure. Viral RNA peaked on day 2 and typically resolved by day 10–14 from bronchoalveolar lavage samples and by day 21–28 from nasal swab samples. This closely mirrors the findings in humans. Cellular immune responses were seen in all animals; multiple antibody responses included binding antibody to the SARS-CoV-2 spike protein and as well as neutralizing antibody. Intracellular cytokine staining assays demonstrated both spike protein-specific CD8+ and CD4+ T cell responses. Thirty-five days from initial infection and following full viral clearance, the macaques were re-challenged with the same viral doses. Compared with the initial challenge, viral loads from both nasal and bronchoalveolar lavage were dramatically lower. The majority of virus represented the actual doses administered for the repeat challenge, suggesting that significant viral replication was not occurring. Following re-challenge the animals exhibited rapid anamnestic immune responses. Most importantly, little or no clinical disease was observed.

SARS-CoV-2 infection provided protective immunity to re-challenge in a non-human primate model. Although important differences exist between SARS-CoV-2 infections in humans and macaques, these results suggest that a similar protective response may be seen in humans.

Cytokine storm and IL-6[7,8]

We now know that the subset of patients who ultimately have a poor prognosis, including the requirement for mechanical ventilation, are those who progress from initial viral infection to secondary cytokine storm. We struggle to identify these patients earlier in the disease course and as a result, our interventions are often occurring well into the established cytokine storm phase, by which time the cascade of organ damage is well underway. Interleukin 6 (IL-6) is one of the major mediators of cytokine storm. Studies to date have shown that rising CRP and D-dimer levels are both predictive of higher mortality. A recent study out of Germany, to be published in the Journal of Allergy and Clinical Immunology, looked at 89 hospitalized patients — an initial cohort followed by a second validation cohort. Baseline clinical and laboratory findings at admission and during the disease progression were identified. Maximal IL-6 levels before intubation showed the strongest association with the need for mechanical ventilation followed by maximal CRP levels. The calculated cutoff for maximal IL-6 was 80 pg/mL, above which the median time to mechanical ventilation was 1.5 days (range 0–4 days). Maximal IL-6 levels predicted respiratory failure with highest accuracy, followed by CRP levels. Moreover, at presentation, IL-6 >35 pg/ml as well as CRP >32.5 mg/l showed high sensitivity to detect patients at risk for respiratory failure (84% and 95%) with moderate specificity (63% for both parameters). Of the 30 patients with values below the IL-6 cutoff, 83% did not require mechanical ventilation, while this was the case for 88% of patients remaining below the CRP cutoff. Immunologically, CRP and IL-6 are closely intertwined. IL-6 is known to induce gene expression and release of CRP from the liver and immune cells. On May 22, the Forum reviewed a preliminary small observational study of Actemra (tocilizumab), a monoclonal antibody which blocks IL-6 receptors which is currently approved for rheumatoid arthritis. With tocilizumab treatment, this study showed that patients had a rapid decline in CRP levels within 1 to 3 days of administration correlating with clinical improvement. Randomized trials are currently underway. Elevated IL-6 levels at presentation might turn out to be an effective screen for the subpopulation of patients who may benefit from therapies directed at reducing cytokine storm, including IL-6 targeted therapies.

Monoclonal antibodies to spike protein hold promise in neutralizing SARS-CoV-2

A team of international researchers reported on whether the neutralizing activity of human monoclonal antibodies to SARS (from 2003) would also have neutralizing effects on the current SARS-CoV-2.[9] The SARS antibodies were active against SARS-CoV-2 spike protein, which is the protein that promotes virus entry into the host cell. The spike protein is currently being targeted by many of the teams working on a vaccine to SARS-CoV-2. SARS and SARS-CoV-2 belong to the same viral subgenus and their spike proteins are similar.

To study this, the research team investigated SARS-CoV-2 neutralizing antibody in the memory cells of an individual who had been infected with SARS in 2003. One of the antibodies, S309, had strong neutralizing activity to SARS-CoV-2. This neutralizing activity was enhanced when combined with other SARS-CoV-2 antibodies from the same patient. Importantly, this combination of antibodies showing efficacy should make it difficult for the SARS-CoV-2 to escape neutralizing antibody through viral mutation. Such antibody combinations could be manufactured and used as prophylaxis after high risk exposure, treatment of active infection, and also aid in vaccine development. Additionally, this is encouraging, as it provides support to the potential effectiveness of vaccines targeted at spike protein. Such vaccines will hopefully produce neutralizing antibodies.

Autopsies demonstrate consistent alveolar damage and frequent thromboembolic events among patients with COVID-19[10,11]

Two studies have been published recently that describe the autopsy findings of patients who died with COVID-19 infections. The first study characterized lung, heart, liver, spleen, kidney, brain, pleural effusion and cerebrospinal fluid specimens from 10 consecutive patients, all with severe acute respiratory distress syndrome. The median duration from admission to death was 7.5 days (range, 1–26 days). Disseminated alveolar damage (the histopathologic correlate of acute respiratory syndrome) was present in all patients, including six who did not receive mechanical ventilation. Consistent histopathologic lung findings included hyaline membrane formation, intra-alveolar edema, and thickened alveolar septa with perivascular lymphocyte-plasmocytic infiltration. Five patients had minor neutrophil infiltration, indicative of secondary infection or aspiration. Liver histology showed minimal periportal lymphoplasmacellular infiltration with signs of fibrosis. Additionally, four patients had mild lymphocytic myocarditis, and two had signs of epicarditis. Thrombus formation or other signs of hypercoagulability were not reported.

The second autopsy study described a high incidence of thromboembolic events among 12 consecutive patients who died from COVID-19. Ten died in the hospital and two as outpatients. Autopsy revealed deep venous thrombosis in seven (58%), four of whom had massive pulmonary embolism as the cause of death. All seven patients had venous thromboses that affected both legs. In six of the nine men in the study, fresh thromboses were found in the prostate venous plexus. This high incidence of venous thromboses underscores the important clinical feature of coagulopathy with COVID-19 infection.

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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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