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COVID–19
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Potential trajectory of the COVID-19 pandemic over the next several months and beyond[1]

The trajectory of the current pandemic is the most critical question facing both health care providers and the government leaders responsible for controlling the current state-by-state isolation orders. Both SARS and MERS spontaneously subsided with no subsequent flares of disease in the affected regions, and no significant spread outside of the centers of the epidemic. As of today, we don't know the trajectory of COVID-19 but an important study was published in Science this week which may help us understand the potential trajectories. **There are four main variables in the model:**

1. Climate/seasonal effect.

It is well known that there is a seasonal variability to coronavirus infections with a suppression of activity in warmer/damper weather. If the current decline in new case rates within our most active U.S. geographies continues to trend towards zero and new hot spots do not arise, the pandemic may spontaneously subside. However, in other regions of the world where these favorable climate characteristics currently exist, the infection is propagating. Unfortunately, the models used in the Science paper show that SARS-CoV-2 can proliferate at any time of year and in any climate, although there may be seasonal variability. Therefore SARS-CoV-2 does not appear to be following the trajectory of the prior two epidemics and we will therefore likely find ourselves in a situation with SARS-CoV-2 as a new endemic infection.

2. Duration of immunity post infection.

With the SARS/MERS epidemics, the duration of immunity to these coronaviruses was in the 6-year range, and therefore these epidemics never flared in subsequent years. Seasonal URI coronaviruses on the other hand, typically confer immunity only for about 40 weeks, which accounts for their regular seasonal wintertime spikes. If the duration of immunity to SARS-CoV-2 is in this shorter range of 40 weeks, then it will likely sit aside influenza and the other coronaviruses as a yearly seasonal infection. With a longer period of immunity, it might circulate every 2–3 years. Long-term immunity similar to that seen with SARS/MERS would be required to permanently suppress the epidemic. This is an area of intense research, however, currently we have no data on either the length or degree of immunity following SARS-CoV-2 infection.

3. Cross-reactivity to milder coronaviruses.

It is unknown whether antibodies to the usual seasonal coronaviruses present in any individual will confer an element of cross immunity to SARS-CoV-2. Although this will not likely be a major factor, cross-reactive neutralizing antibodies from other coronaviruses could help suppress a return of the epidemic and account for the fact that many cases are mild.

4. Social distancing effects.

This is the single greatest variable. We know that social distancing can suppress transmission of infection by up to 78%. However, the greater the degree of suppression of viral transmission, the higher the likelihood of a severe rebound in any given geography as regulations are relaxed. This is because the prevalence of immune individuals in that population will still be very low when regulations are relaxed (low herd immunity). Intermittent social distancing would allow for the control of peak surges which could otherwise overcome the local medical resources to care for these patients. At the same time, it would allow for gradual increase in immunity in the population and therefore move towards the attainment of herd immunity. This would lessen further surges of disease.

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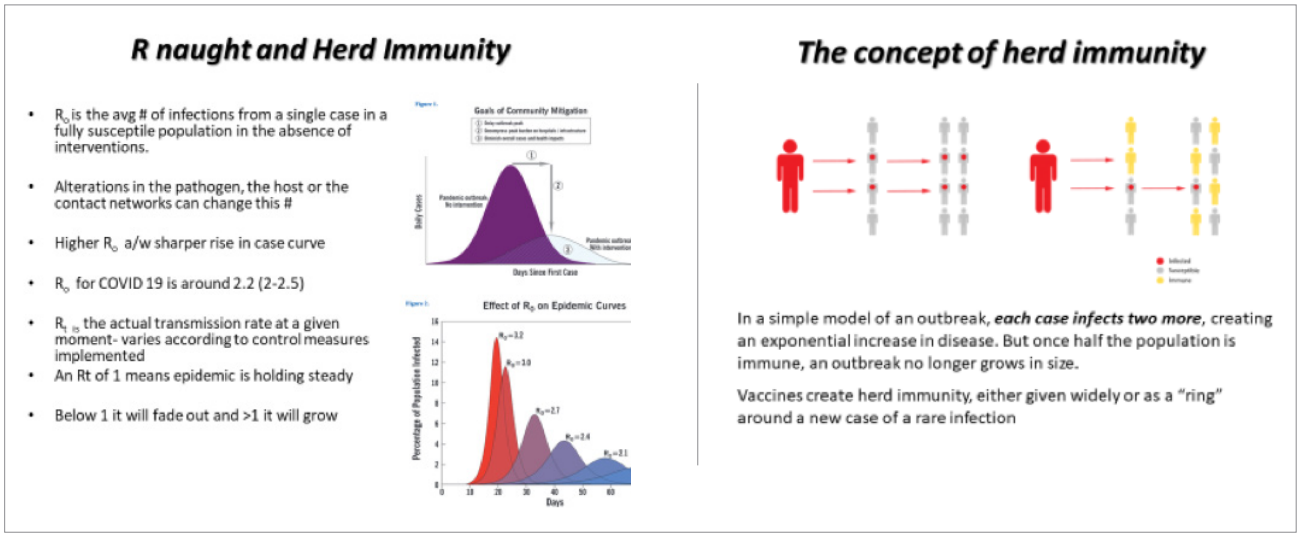
EDUCATIONAL FORUM

Until there is an effective vaccine, the anticipated trajectory of the epidemic will need to dictate our national response. Various social isolation strategies will be the only effective means of disease control and there will likely be waves of the epidemic across the U.S. What's happening now in Seattle and New York will happen in other cities at different times. Each wave will last a couple of months — from valley to peak to valley. If we begin to relax social distancing efforts, which at some point we may need to do, the disease will start to come back. We may therefore find ourselves in a situation of on/off isolation practices dictated by disease activity in any given geography. This is the concept of intermittent social distancing, and this is where the concept of herd immunity plays a role. Once we have achieved significant herd immunity, either through intermittent social distancing or vaccination, transmission chains will be broken and the disease incidence will reach a steady state. How long this will take is unknown as it is contingent upon both the rate of infection with subsequent immunity in any given geography and the eventual ability to vaccinate those who have not become infected. Intermittent social distancing may well be needed until we have an effective vaccine. Surveillance antibody screening will also play a critical role. It will dictate in any given geography, the prevalence of disease immunity, which will then dictate the needed intensity of intermittent social distancing. The two slides below illustrate the basics of herd immunity as it relates to COVID-19 infection.



Non randomized study of hydroxychloroquine in COVID-19 infected patients[2]

Several large randomized trials of hydroxychloroquine (HCQ) use are under way and hopefully results of these trials will be available within the next several months. Until that time we are left with observational trials. A recent French trial, the results of which were published this week, was larger and more accurately conducted than prior trials of HCQ use. They used data collected from routine care of all adults in 4 French hospitals with documented SARS-CoV-2 pneumonia and requiring oxygen ≥2 L/min to emulate a target trial aimed at assessing the effectiveness of HCQ at 600 mg/day. The composite primary endpoint was transfer to intensive care unit (ICU) within 7 days from inclusion and/or death from any cause. Analyses were adjusted for confounding factors by inverse probability of treatment weighting. One hundred eighty-one patients with a median age of 60 were included in the trial. Eighty-four received HCQ within 48 hours of admission and 97 did not. Initial severity was well balanced between the groups. Twenty percent of the patients in the HCQ group were transferred to the ICU or died within 7 days vs 22% in the non-HCQ group. Twenty-four patients in the HCQ group and 23 patients in the non-HCQ group developed acute respiratory distress syndrome within 7 days. Eight patients receiving HCQ (9.5%) experienced electrocardiogram modifications requiring HCQ discontinuation, including 7 with QT prolongation. In conclusion, the study found that HCQ did not significantly reduce admission to ICU or death at day 7 after hospital admission, or ARDS in hospitalized patients with hypoxemic pneumonia due to COVID-19. Although this was not a rigorously performed randomized trial, it represents the largest and most well-done study to date looking at the use of HCQ in severe COVID-19 infection.

Super spreading of COVID-19 infection from a point source outbreak[3]

Contact tracing provides invaluable information about viral spread and transmissibility under real world circumstances. So far, many reports about transmission have reported on transmission occurring among household contacts, health care workers, and within living facilities. In the CDC's April 8th Morbidity and Mortality Weekly Report (MMWR), it shared a detailed analysis of novel coronavirus spread through a cluster of 16 cases in Chicago, IL over three weeks this March. This assessment showcases transmission

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potential from social gatherings and reinforces the need for social distancing and avoiding social congregation.

The index individual studied was an adult male with COVID-19 who experienced respiratory symptoms mild enough that he did not consult a medical professional. While symptomatic, he attended a funeral where he hugged several family members and shared a long face-to-face meal, potluck style, with several others. Three days later, still experiencing symptoms, he attended a birthday party with nine people in attendance of various ages. Three other funeral attendees and seven of the birthday party attendees developed COVID-19 within a week of this contact. Two more cases developed after relatives visited the hospital bed of one of the funeral attendees sickened with COVID-19, and several more presumptive cases resulted from transmission during church services attended by several of the COVID-19 positive birthday party participants, who were by then showing mild symptoms as well. Contact at church was limited to direct, face-to-face conversations, sitting within one row of an infected person, and passing the offering plate.

This contact tracing analysis of 16 cases from a single point of contact reinforces the potential for spread from casual physical contact or simple proximity during social gatherings. Business gatherings can be particularly problematic because travel to and from distant cities is often involved. The now infamous early March Biogen conference, which occurred when the U.S. confirmed case count was only 40, was responsible for 99 confirmed infections in Massachusetts alone, and dozens more in North Carolina, Tennessee and Indiana. We should continue to reinforce local recommendations to avoid social gatherings and comply with stay-at-home orders and remain cautious as business travel restrictions begin to relax.

Positive COVID-19 PCR testing does not necessarily confer infectivity[4]

To help understand the relationship between positive PCR testing and infectivity, researchers in Germany conducted a virologic analysis of serial samples from nine young to middle-aged hospitalized patients with PCR-confirmed SARS-CoV-2 infections. Except for one initially asymptomatic patient, all had mild symptoms, including cough, fever, and diarrhea. Four developed disorders of taste, smell, or both, and one reported dyspnea. All naso- and oropharyngeal swabs obtained during the first 5 symptomatic days were positive. Detection rates dropped to 40% after day 5, with one swab testing positive 28 days after onset. Virus was readily isolated during the first week (17% of swabs and 83% of sputum samples), but no virus was isolated from samples obtained after day 8 despite continued positivity by PCR. Although this was a very small study, it demonstrates a pivotal deficit in our current knowledge. We should not assume that persistent PCR positivity after one week of infection necessarily correlates with ongoing infectivity. This has important implications for return-to-work policies that require serial negative PCR tests. We are close to developing reliable assays of IgG antibody levels. Once these IgG antibodies have been determined to confer immunity, measurement of IgG will likely be a better measure of lack of infectivity than the absence of detectable PCR on nasal swabs.

Severe COVID-19 infections can occur in children, but rarely[5]

Adults with chronic illnesses are at greatest risk of hospitalization and intensive-care interventions with COVID-19 infections. Less is known about COVID-19 infections in children.

Between March 2 and March 16, 2020, investigators characterized screening results and disease severity among pediatric patients at 30 hospitals in Madrid, Spain. Children were screened according to Spanish Public Health recommendations, which included substantial disease with signs or symptoms compatible with COVID-19 infection and likely hospital admission. Forty-one of 365 patients (11.2%) had positive test results, representing only 0.8% of the 4,695 confirmed cases in Madrid.

The median age of children tested was 3 years, and the median age of children with positive results was 1 year. Twenty-five of 41 patients were hospitalized; 4 were admitted to the pediatric intensive care unit; 4 needed respiratory support beyond nasal oxygen. No pediatric patients died. Eleven patients (27%) with positive screening tests and 50 patients (15.4%) with negative screening tests had underlying medical conditions. Although the indications for COVID-19 screening did not differ between children and adults, the infection rate and disease severity appear much lower in children.

Potential hypercoagulable state associated with COVID-19 infection[6,7]

Patients with severe COVID-19 infection can develop a coagulopathy meeting criteria for disseminated intravascular coagulation (DIC), with fulminant activation of coagulation, resulting in widespread microvascular thrombosis and consumption of coagulation factors. These findings have been confirmed pathologically in lung tissue at autopsy. Clinically, this is reflected by thrombocytopenia, prolongation of the PT/INR, PTT, elevation of D-dimer, and decreased fibrinogen levels. Less severe coagulopathy is also seen, meeting criteria for sepsis induced coagulopathy (SIC). A study from Wuhan that correlated parameters of coagulopathy with mortality examined 449 patients with severe COVID-19 infection. Only 13% of patients with SIC survived. D-dimer levels were also directly associated with mortality. Ninety percent of patients with a normal D-dimer level survived compared with only 45% of those with a

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level >8 times the upper normal limit. Ninety-nine of these patients received heparin (predominantly prophylactic doses of low molecular weight heparin) for 7 days or longer. The 28-day mortality of heparin users was lower than nonusers in the subset of patients with an elevated SIC score ≥4 (40.0% vs. 64.2%) or a D-dimer level >6 fold of upper limit of normal (32.8% vs. 52.4%). The current hematology literature has not focused on a primary hypercoagulable state independent of DIC/SIC, and therefore recommends prophylactic doses of LMWH for patients who present with an elevated D-dimer level. There are early data implicating direct viral endothelial damage as a potential cause of increased microvascular clotting. To date, there are no studies suggesting a benefit to therapeutic anticoagulation, although in some critical care settings, this approach is being utilized in the subset of patients with markedly elevated D-dimer levels. Whether there will be a benefit to prophylactic LMWH in ill outpatients is unknown at this time.

Complete loss of smell, a possible COVID-19 symptom

A woman in her 40s developed acute loss of smell without loss of taste (ageusia) in association with dry cough, headache, and muscle soreness.[8] Anterior rhinoscopic exam was normal. A CT scan of the nasal cavity demonstrated bilateral inflammatory obstruction of the olfactory cleft, confirmed by subsequent MRI. Real-time PCR testing for COVID-19 yielded a positive result. Among 214 patients with COVID-19, a retrospective review of neurologic signs and symptoms revealed impaired smell in 11 (5.1%) and impaired taste in 12 (5.6%).[9] Observational data suggests that these rates are much higher. Loss of smell without nasal obstruction or loss of taste should raise suspicions of COVID-19 infection, especially when other common symptoms such as cough or fever are present.

Albuterol shortage during COVID-19 pandemic[10]

Some providers have prescribed short acting beta agonists (SABA) for acute viral bronchitis. There is no evidence base to support this practice and there are now reported shortages of SABAs preventing our patients with asthma and COPD access to these medications. A 2015 Cochrane analysis looked at the 5 large studies that enrolled adults (n=418) with acute bronchitis of presumed viral origin. Overall there were no significant benefits from ß-2 agonists compared with placebo. Daily cough scores, the number of people still coughing after 7 days, and night cough after 7 days did not change with use of ß-2 agonists. Furthermore, the adult patients receiving ß-2 agonists reported increased tremor, shakiness, or nervousness. The only subset of patients in whom there was symptomatic improvement were those with significant wheezing on examination consistent with bronchospasm. In the absence of significant bronchospasm confirmed by wheezing on examination, SABAs should not be prescribed to treat the cough associated with COVID-19 infection in patients who do not have asthma or COPD.

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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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