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Special COVID Edition 15
July 24 | 2020

COVID–19
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COVID-19 vaccine development update

Vaccine development was last reviewed in the May 8 COVID Forum and much has been learned since then. The SARS-CoV-2 seroprevalence around the country varies from 1% to 7% in random sampling[1] and may be as high as the 15%–20% range in intense hot spots such as New York City. Estimates of the seroprevalence needed to achieve herd immunity are in the 65%–75% range. Looking together at these two pieces of data, it becomes clear that an effective vaccine is needed to move us beyond our current trajectory and hopefully suppress the pandemic. It is therefore important to report that multiple candidate vaccines are about to enter phase III trials. In the phase I and II trials of these vaccines, there were no serious adverse events. Side effects, however, were common and often graded as moderate to severe. These included fevers, headache, fatigue, myalgias and injection site pain. The phase III trials will allow assessment of whether the vaccine–induced antibody response confers clinical protection, as well as whether the vaccine proves safe in a larger population of subjects. These vaccines use two different vaccine development technologies.

Messenger RNA vaccines. This is a promising technology, however one that has not yet been used in an approved vaccine. It delivers altered viral messenger RNA (mRNA), in this case incorporating genetic material from the spike protein region. Following vaccination, this mRNA is then transported into the cell cytoplasm and replicated by the human cell, allowing for production of viral antigen by those human cells. These viral antigens, now being produced in human cells, elicits the immunological response. The mRNA is then degraded.

- Moderna vaccine. The phase I trial of this candidate vaccine was published in the NEJM last week[2]. Remarkably, in a process that usually takes many years, the first subjects were vaccinated 66 days after the publication of the genomic sequence of the virus. The phase II trial in 600 adults is already underway. The large phase III efficacy trial should begin this summer.
- BioNTech. This is a collaboration between Pfizer and a German company. The phase I/II trial is awaiting publication and the phase III trial will launch this summer.

Viral vector vaccines. These vaccines use a genetically modified adenovirus and incorporate one or more spike protein antigens. This process is currently used for the hepatitis B vaccine.

- Oxford. This UK vaccine uses a genetically modified chimp adenovirus which incorporates genetic material from the spike protein. Phase I/II trial data have been published and the phase III trial has been launched.
- CanSino. This vaccine is being developed in Wuhan China. It uses a human URI adenovirus which incorporates genetic material from the spike protein. Phase I/II trial data have been published and the phase III trial will launch this summer. The antibody titers have been somewhat lower than the other vaccine candidates, perhaps related to the immunologic familiarity with the human URI virus that is being used.

VLP vaccines. These vaccines use a viral-like particle (VLP) and attaches spike protein antigen to the particle.

- Novavax. Phase I/II trials of this vaccine are underway but have not yet been published, but this vaccine is worth mentioning related to the following. This vaccine technology is already licensed by the FDA and an influenza vaccine successfully completed its phase III trial last year and is awaiting FDA approval. Since the production platform has already been licensed, it is poised to produce a COVID-19 vaccine in large quantities. The Coalition for Epidemic Preparedness Innovations (CEPI) provided a $384 million grant and the United States provided a $1.6 billion grant to accelerate development and manufacture of this vaccine.

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The factors that have coalesced to allow for the accelerated vaccine development include:

- Existing evidence from other coronaviruses that neutralizing antibody against the spike protein is important for immunity.
- The development of novel vaccine platforms that allow both rapid creation of vaccines and rapid manufacture of large quantities of doses.
- Combining phases of clinical trials to reduce to two clinical phases, rather than the historical three.
- Parallel construction of mass manufacturing capabilities for multiple vaccine candidates while trials are still underway. This is being done prior to proving that any given candidate is safe and effective. Although vastly more expensive than waiting for completion and review of phase III trials, this will allow the immediate launch of vaccination programs when safe and effective vaccines are reviewed and approved since mass production will already be well underway.

We will have the above four vaccines in phase III trials by the end of summer, with Novavax soon to follow. If geographies with high case rates are chosen, safety and efficacy could be established within several months. Additionally, there is the possibility that the FDA could issue Emergency Use Authorization or compassionate use guidelines for favorable vaccine candidates while awaiting final FDA approval. Putting all of these factors into play, should we find a safe and effective vaccine, the potential exists for deployment in the first quarter of 2021, but more likely in quarter two.

Wearing face masks protects against the hospital and community spread of COVID-19

The Mass General Brigham (MGB) health care system in Massachusetts comprises 12 hospitals with over 75,000 employees. In March 2020, MGB implemented universal masking of all health care workers and patients. Researchers recently assessed hospital infection rates associated with masking policies, identifying three phases of mask implementation: the preintervention period (March 1 to March 24), the transition to masking period (March 25 to April 5), and the intervention period (April 11 to April 30).[3] Among 9,850 health care professionals who were tested for SARS-CoV-2, 1,271 (12.9%) had positive results. During the preintervention period, the positivity rate increased from 0 to 21.3%, with a weighted increase of 1.2% per day. During the intervention period, the positivity rate dropped from 14.7% to 11.5%, with a weighted decline of 0.5% per day. Accordingly, the implementation of universal masking led to declining infection rates among health care workers. Other policies such as restrictions on elective procedures, social distancing, and increased masking outside of the hospital likely contributed to these results. Despite statewide mitigation strategies, while the positivity rate was dropping in the health care workers, the overall case numbers continued to rise in Massachusetts.

Next is a fascinating study documenting the benefits of masking in the community. We believe that mandating face masks in a controlled environment appears to decrease SARS-CoV-2 transmission. The effects of masks and face covers on the community spread of COVID-19 were recently explored in a tracing study.[4] Two stylists (A and B) working in a hair salon in Missouri sequentially developed respiratory symptoms but continued working for 8 and 7 days post symptom onset, respectively. Both subsequently tested positive for SARS-CoV-2. Both stylists wore double-layered cotton face coverings or disposable surgical masks whenever interacting with clients. Contact tracing was conducted for the 139 clients who had direct contact with at least one of the stylists while they were symptomatic. None of the clients developed signs or symptoms of COVID-19 during 14-day self-quarantine. Testing was offered for all clients; 67 (48.2%) volunteered to be tested. Of those tests that were conducted, none were positive. Although none of the clients were found to have contracted COVID-19, four family members who cohabitated with stylist A when a face covering was not worn developed symptoms and had positive SARS-CoV-2 PCRs. None of stylist B's family contacts became symptomatic.

In summary, face masks and face coverings appear to mitigate COVID-19 transmission in both hospital and community settings. Although observational studies have some limitations, more stringent research methodologies are not ethically feasible. These are the data that should guide policy. The medical community can continue to promote and educate about face masks and other mitigation strategies as a resurgence of COVID-19 cases is reported in many states across the country.

Are COVID-19 mitigation policies effective in decreasing disease rates?[5]

The first three months of the pandemic provides enough evidence to begin empirically studying the impact of policies aimed at slowing virus spread, as opposed to the simulation modeling we have all relied upon until now. Study authors use econometric methods and pre–post study design to evaluate the impact of 1,717 distinct policy intervention actions upon viral growth rate across regions within six countries — China, South Korea, Italy, Iran, France and the United States. The policy interventions studied included travel restrictions, social distancing, quarantines and lockdowns, and additional actions like emergency declarations and expansions of paid sick leave. Without policy interventions, COVID-19 infections grow at roughly 38% per day (doubling every two days). Real-world interventions reduced the infection growth rate to about 8% per day on average, reducing the total infection count by significant

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multiples that depend in large part on how early and how aggressive the interventions were. For example, they find the Chinese interventions (emergency declaration, travel ban, and home isolation) reduced total infection count by 465x, while the US interventions (social distancing, business closures, work from home, and others) reduced total infection count by 17x.

In general, the research finds emergency declarations, social distancing and gathering restrictions, and home isolation to have the largest impact; while school closures, paid sick leave, and religious closures to have the smallest. Importantly, measured impact varies dramatically by country, probably because implementation particulars differ substantially. Additional months of experience will contribute substantially to this work, which we will update as it is published.

Do children transmit SARS-CoV-2 infection at the same rate as adults?[6]

This question assumes paramount importance as the world struggles to understand the risk–benefit ratio of reopening schools for face-to-face learning. Although children have less frequent and milder infections on average, they nonetheless could serve as vectors to transmit disease to the rest of the community, resulting in expansion of the pandemic. To help better understand this, the South Korean CDC studied the country's contact tracing reports from January through March. Over 5,700 index patients were identified as the origin of a COVID-19 infection cluster. Over 59,000 contacts of these index cases were then tested. As prior studies have confirmed, household contact was the greatest risk factor for disease acquisition. About 12% of household contacts acquired infection compared to only 2% of non-household contacts. When these index cases were then stratified by age, households with children aged 10–19 had the highest rate of household transmission with 18.6% of exposed household members becoming infected. Households with children ages 0–9 on the other hand, had transmission rates of only 5.3%. Prospective epidemiological studies can determine the accuracy of the above observations. Pending such studies, the above data can help inform the very difficult question of how best to educate our children during the ongoing pandemic.

Peri-operative COVID-19 infection increases postoperative mortality

A multi-site international study followed 1,128 patients undergoing surgical procedures who were infected with SARS-CoV-2[7] around the time of the surgery. Patients were studied from 24 countries and 235 hospitals. Surgeries were performed between January 1, 2020 and March 31, 2020. Most of the surgeries (74%, 835 of 1,128) were emergent. SARS-CoV-2 infection was diagnosed within 7 days prior to or 30 days after surgery. COVID-19 was confirmed pre-operatively in 26% (294 of 1,128) patients. Pulmonary complications predominated, occurring in 51% (577) of patients. Pulmonary complications were defined as the occurrence of acute respiratory distress syndrome or unexpected postoperative ventilation (use of non-invasive ventilation, invasive ventilation or extracorporeal membrane oxygenation after initial postoperative extubation or a failure to extubate as planned after surgery). This rate of pulmonary complications is at least five times the rate expected.

Overall, 30-day surgical mortality was 23.8%. Mortality was higher in emergent surgeries, major procedures, men, those over 70 years of age and those with an ASA score of 3–5 (Table 1). Patients with pulmonary complications accounted for 83% (219 of 265) of all deaths.

Table 1. Risk factors and mortality rate SARS-CoV-2 infection peri-operatively

Risk factor	Mortality rate (%)	Odds ratio (95% CI)	p value
Age >70 years	25.2	2.30 (1.65–3.22)	<0.0001
ASA score 3–5	32.2	2.36 (1.58–3.53)	<0.0001
Male sex	30.2	1.75 (1.28–2.40)	<0.0001
Emergent procedure	26.7	1.67 (1.06–2.63)	<0.026
Major surgery	27.5	1.52 (1.01–2.31)	<0.047

Infection with SARS-Cov-2 in the perioperative period greatly increases 30-day surgical mortality. Pulmonary complications are greatly increased in these patients and are the primary contributor to increased mortality. This increased risk must be considered in contemplating surgical procedures during the COVID-19 pandemic.

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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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