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COVID–19
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Vaccine update

It's been over a month since vaccine development was last reviewed in this Forum and there have been new developments worth highlighting. Many individuals view vaccine deployment as the path to post-pandemic normalcy, and this has created urgency around the development, testing and approval processes. The World Health Organization (WHO) has produced guidance on minimum characteristics for a vaccine, including greater than 50% efficacy, temperature stability, potential for rapid scale-up, and proper evaluation against the other vaccines in development, including safety assessments. This last point is important, as our current vaccine trials are all placebo-based and it does not appear we will have comparative data between candidate vaccines at the time they are approved. Moreover, with each large phase III vaccine trial using its own placebo group, recruitment can be a challenge. Worldwide, there are 36 vaccines in human trials with nine having reached phase III trials, necessitating over a quarter million subjects. Another important factor is the SARS-CoV-2 prevalence in the regions where the vaccines are being tested. Results could come quickly where prevalence is high or take much longer when prevalence is low. Lastly, and perhaps most importantly, there are multiple different vaccine platforms with different mechanisms of action. Some of these platforms are novel and have not yet resulted in any vaccine which is approved for use in the United States. The major vaccine platforms which are moving to late-stage testing are as follows:

- **Messenger RNA and DNA vaccines:** These are promising technologies, however they have not yet been used in an approved vaccine. One type delivers altered viral messenger RNA (mRNA), in this case incorporating genetic material from the spike protein region of SARS-CoV-2. Following vaccination, this mRNA is then transported into the cell cytoplasm and replicated by the human cell, allowing for production of viral spike protein antigen by those human cells. These viral antigens, now being produced in human cells, elicit the immunological response. The mRNA is then degraded. As noted above, one of the WHO vaccine criteria is temperature stability, and the current mRNA vaccines in development need to be stored at minus eighty degrees centigrade. This could complicate distribution and widespread use, as efficacy would degrade if strict temperature controls are not maintained. DNA-based vaccines have a similar mechanism of action and pose the potential of permanently integrating with human DNA, with unknown future consequences. Moderna, Pfizer/BioNTech and CureVac are examples of messenger RNA vaccines currently in phase II and III trials.[1]

- **Viral vector vaccines:** These vaccines use a genetically modified non-replicating adenovirus. The adenovirus then carries DNA-encoding protein antigens from an unrelated organism, in this case the spike protein of SARS-CoV-2, into a host cell for production of spike protein antigen that can be tailored to stimulate a range of immune responses, including both antibody and T-cell mediated immunity. The adenovirus can either be a human strain or a nonhuman primate strain. The potential drawback of the human adenoviruses is that there could be preexisting immunity to the strain that would render the vaccine ineffective in some individuals. With respect to the primate strains, there are no licensed vaccines using these strains, and effectiveness is currently unknown. There are viral vector vaccines approved for animal use, but none are currently approved for human use. CanSinoBIO, University of Oxford/Astra Zeneca, and Johnson and Johnson vaccine candidates are all in phase II or III trials.[1]

- **Protein-based vaccines:** This is a mature technology used in other vaccines and some of these production platforms have been FDA licensed. These vaccines use spike protein or fragments of spike protein attached to a matrix with or without an adjuvant to generate an immunological response. An example of this type of vaccine is from Novavax. It uses a VLP (viral-like particle) and attaches a spike protein antigen to it. Several other protein-based vaccines are in phase I and phase II trials. Interestingly, two of these are using spike protein genetic material inserted into the tobacco plant genome, with spike protein being manufactured by the tobacco plant. Certainly, the first time a tobacco plant may improve population health.[1]

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- **Live attenuated viral vaccines:** This is also a mature and widely used technology. These vaccines use an inactivated version of SARS-CoV-2 to elicit an immunological response. Sinopharm and Sinovac have vaccines in phase III trials, with several others in phase II trials.[1]

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

- Existing evidence from other known coronaviruses showing 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[1]

Vaccine manufacturing will be ongoing 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 for the immediate launch of vaccination programs when safe and effective vaccines are approved, since mass production will already be well underway. If geographies with high case rates are chosen, safety and efficacy could be established within several months; however the reality is that the phase III trials will take longer than this, particularly due to recruitment challenges. 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, although this action risks widespread use of a vaccine before full safety data become available. This is a critically important issue since as much as 30% of the population is vaccine adverse. Recent decisions by the FDA and CDC have eroded confidence in these agencies and could further diminish the acceptance of a SARS-CoV-2 vaccine. Because of these multiple variables, it is not possible to predict the timeline for vaccine availability nor how successful mass vaccination will be. Hopefully vaccine availability could occur by quarter two of 2021.

Has reinfection with SARS-CoV-2 been proven?

The preliminary results of several studies were released last week and have generated significant attention. They detailed a total of four cases of possible recurrent infection with SARS-CoV-2. The studies have not yet been published and therefore cannot be scrutinized in detail; however the attention they have generated suggested the need to share what we know. In one case, a 33-year-old male from Hong Kong experienced mild symptoms consistent with COVID-19 in late March. He was hospitalized as per the protocol in Hong Kong. Nasal PCR testing was positive, and he recovered uneventfully. Follow-up serology did not confirm an IgG seroconversion. In July, the individual was screened on reentry to the country from travel to Spain. It was part of a mass screening program of all reentering travelers and used saliva testing. This test was reported as positive. At no time did the individual experience any symptoms. This was felt to possibly represent reinfection as the genetic footprint of the initial infection was of the Wuhan strain and the follow-up genetic footprint was of the European strain, which is now the dominant strain worldwide. Furthermore, it was reported that the patient developed an immune response to the European strain. It is therefore possible that this does represent a case of reinfection. The fact that the second bout was asymptomatic despite the absence of an IgG response to the initial infection may represent the anticipated T-cell mediated immune response to reexposure. However, it is also possible that the initial PCR test done on this individual was a false positive. This might be suspected given the absence of an IgG response, which is very unusual after initial infection. Subsequently, three cases of reinfection were reported: one out of Nevada and two from Europe. Again, these are unpublished at this time. The Nevada case is well described with both episodes being symptomatic, and the second episode being moderately severe. Here too, these were established to be genetically different strains of SARS-CoV-2. Should these represent the first reports of SARS-CoV-2 reinfections, the current incidence must be rare given that almost 25 million documented cases have occurred worldwide. What is unknown, is whether typical immunity might last only in the six-month range, which may result in increased cases of reinfection to be documented in coming months. If this should occur, it will mean that immunization rates may need to be higher than predicted in order to attain herd immunity as prior infection may not contribute adequately to herd immunity.[2]

Sex-based differences in immune responses with COVID-19 may explain poorer outcomes in men

A growing body of evidence indicates that men have poorer outcomes from COVID-19 than women. To explore why disease susceptibility differs between men and women, a recent study examined sex differences in viral loads, SARS-CoV-2 antibodies, plasma cytokines and blood cell phenotyping.

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Baseline analyses were performed on 17 men and 22 women who were hospitalized with COVID-19, were not in intensive care, and had not received tocilizumab or corticosteroids. Longitudinal analyses included all patients from the baseline cohort plus an additional 59 patients who did not meet inclusion criteria for the baseline analyses. Several key differences were found between men and women during SARS-CoV-2 infections. Male patients had higher plasma levels of innate cytokines, such IL-8 and IL-18 (at baseline) and CCL5 (longitudinally), with greater induction of nonclassical monocytes (at baseline). Higher levels of innate immune cytokines in women were associated with worse disease outcomes. In contrast, women mounted more robust T-cell activation during SARS-CoV-2 infection, a response that was sustained among older-aged women. Activated CD8 T cells were significantly elevated in female patients compared to male patients. In men, older age correlated with poorer T-cell response, and the poor T-cell response was associated with worse disease outcomes. The authors suggest that differences in immune response with COVID-19 may underlie the heightened disease susceptibility for men. Further, vaccines and therapies that target the T-cell immune response might have greater benefit for men, while women may gain greater benefits from vaccines and therapies that dampen the innate immune activation early during infection.[3]

Nursing home testing: Finding the illusive asymptomatic cases

It is well-appreciated that persons in nursing homes and long-term care facilities are at high risk for complications from infection with SARS-CoV-2. The ability of SARS-CoV-2 to spread quickly among residents and staff in these facilities has prompted calls for universal testing. Investigators in Pasadena, California describe the apparent rapid spread and high prevalence in nursing homes and long-term care facilities in that city.[4] The first case in the community was reported in the city in the second week of March of this year. The first facility-based case was identified in an employee on March 31. Widespread testing of facilities with at least one laboratory confirmed case of COVID-19 was completed by the end of April.

In 19 facilities studies, nine had evidence of sustained transmission with at least three linked cases. In those nine facilities, 1,093 persons (608 residents and 485 staff) were eligible for testing and 85.9% were tested for SARS-CoV-2 using PCR. All PCR positive cases were considered to have had infection with SARS-CoV-2. Symptomatic cases included persons with any one of the standard symptoms or low oxygen saturation any time 14 days prior to the test acquisition date. The overall prevalence of SARS-CoV-2 among the staff and residents was 67.3%. The symptomatic and asymptomatic breakdown is noted on the below chart.

	Positive for SARS-CoV-2 RNA by PCR		
Population subset	Total % (#)	Symptomatic % (#)	Asymptomatic % (#)
Residents and staff	67.3 (631/938)	59.3 (374/631)	40.7 (257/631)
Residents	70.1 (408/582)	50.5 (206/408)	49.5 (202/408)

In a related report, investigators with the CDC COVID-19 Response Team reported on facility-wide testing of nursing home residents from seven different states.[5] Tests were conducted in high- and low-prevalence communities and in facilities with and without known previous cases of COVID-19. In low prevalence communities (14-day cumulative incidence, 19 and 38 cases per 100,000 persons), 64% of nursing homes were without any reported cases and in those facilities 0.4% of PCR tests for SARS-CoV-2 were positive. In contrast, when health departments targeted testing in facilities after a reported case, 12% of tests were positive. Overall, previously unknown cases were identified in 79% of facility-wide testing events when triggered by a case in the facility (in either staff or residents). Testing as soon as possible after a new case identifies fewer cases. This facilitates outbreak control by implementing cohorting and other control measures. Community prevalence is a less reliable trigger to prompt facility-wide testing than identification of an index case in a facility.

Bottom line: If a case of COVID-19 is identified in a resident or staff of a long-term care facility, test all residents and staff as soon as possible and unknown cases are likely to be found. Many cases in long-term care facilities are asymptomatic.

Convalescent plasma use in COVID-19

Last week, the Mayo Clinic published results of a large observational database on the use of convalescent plasma in COVID-19 infection. Unfortunately, this was not a randomized, placebo-based trial and therefore little comparative evidence resulted from the paper. Over 35,000 patients were reported, and the population was quite ill with over 50% requiring ICU admission and over 25%

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requiring mechanical ventilation. In those patients who initiated convalescent plasma within less than three days of admission, the mortality rate was 8.7%, compared to 11.9% in those initiating treatment greater than four days following admission. This resulted in an absolute mortality difference of 3.2% with respect to the timing of the infusion. Unfortunately, these data were misinterpreted or misreported by the FDA, which claimed a 30% mortality reduction. It was also observed that the outcomes were better as a function of increasing concentration of convalescent antibody in the individual treatments.[6] Based upon this publication, the FDA granted emergency use authorization for convalescent plasma treatment, despite many experts commenting that these data were inadequate for the EUA designation. Fortunately, the UK RECOVERY trial includes a convalescent plasma arm and will serve as a large, placebo-based trial. This well-done trial has already provided critically important information (which has been reviewed in this Forum) on the use of hydroxychloroquine (negative results) and dexamethasone (positive results). Anxiously awaited in addition to the convalescent plasma arm is the tociliuzimab arm of the trial.

COVID-19 outcomes following in-hospital anticoagulation

COVID-19 commonly causes thromboembolic disease, but little is known about the benefits of anticoagulation. A recent retrospective study compared outcomes and post-mortem findings among patients hospitalized with COVID-19 who did not receive anticoagulation (n=1,530), those who received prophylactic anticoagulation (n=1,959), and those who receive therapeutic anticoagulation (n=900). The median age of patients was 65 years, and 44% were female. Therapeutic anticoagulation was associated with a 47% reduction in the hazard of inhospital mortality compared to no anticoagulation ($p<0.001$) and a 31% reduction in the hazard of intubation ($p=0.02$). Prophylactic dosing was similarly associated with improved mortality and intubation compared with no anticoagulation ($p<0.001$ and $p=0.003$, respectively). Episodes of major bleeding occurred in 3% of the patients who received therapeutic anticoagulation, 1.7% of those on prophylactic dosing, and 1.9% of those who did not receive anticoagulation. A total of 72 autopsies were performed. The first 26 sequential cases were evaluated microscopically with a focus on signs of thromboembolism. Of these, 11 had thromboembolic disease that was not suspected pre-mortem. Three out of the 11 patients had received therapeutic anticoagulation dosing. These retrospective data may inform future anticoagulation clinical trials for patients with COVID-19.[7]

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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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