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COVID–19
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Vaccine development — perception versus reality[1,2]

Physician's Weekly recently offered an editorial entitled, "Is evidence-based medicine dead?" It concerned hydroxychloroquine and the broadcasting by the president of anecdotal observations versus the significant body of evidence regarding unfavorable outcomes of treatment using hydroxychloroquine. Another important area where broadcasted predictions have created an expectation that is out-of-step with established scientific evidence is in the area of vaccine development. The good news is that there is early evidence that suggests we may be able to develop an effective vaccine. The disconnect is on how long this will take. Vaccine development is typically a five- to ten-year endeavor. It is hard to imagine in the history of medicine a greater coordinated effort to achieve a goal, than that being applied to the vaccine development effort against SARS-CoV2. What then is the reality of how this will occur?

Vaccine effectiveness

Although the spike protein of SARS-CoV-2 appears to be a good target for vaccine-induced antibody development, the best segment of the protein for targeting has not yet been proven. Coronaviruses mutate and therefore if the targeted antigen is not "conserved" (one that does not mutate), the vaccine may become ineffective before widespread use. Phase 1 trials can confirm that vaccination results in antibody development and demonstrates in the lab that the antibodies produced will neutralize the virus. These trials involve small numbers of volunteers and cannot provide useful information safety and effectiveness. Eight vaccine manufacturers have launched or are about to launch candidate vaccines for phase 1 trials. These trials can be accelerated to be completed in 12 weeks. One vaccine candidate has already reported results on 108 of individuals who have completed the phase 1 trial. However, preclinical experience with vaccine candidates for SARS and MERS raised concerns about these vaccines having the potential to cause harm by directly inducing pulmonary reactions or by causing antibody dependent enhancement (ADE) of lung disease. ADE is a helper T cell mediated immunological reaction which occurs when a vaccinated individual becomes infected. The ADE can then exacerbate the course of the infection. These potential adverse reactions would only appear in larger phase 2 and 3 trials. Vaccine safety, and immunogenicity (which confers protection), can only be demonstrated in large phase 3 clinical trials. Typically, many vaccine candidates drop out as trials move from phase 1 to phase 3. Another issue with vaccine development during a pandemic is the ethics of multiple placebo groups for each of the vaccine trials. One solution would be a single placebo group and simultaneous testing of multiple different vaccines in a single large trial. This has not previously been attempted and would require close cooperation of multiple biotech companies, but is nonetheless feasible.

New vaccine platforms

SARS, MERS and H1N1 influenza have taught us that we need to develop new technologies for rapid vaccine development. As a result, the NIH and the Coalition for Epidemic Preparedness Innovation (CEPI) have invested in platforms that can be "at the ready" to take new viruses and accelerate vaccine development against them. CEPI is funded by eight governments (not the United States) and multiple foundations including the Bill and Melinda Gates Foundation. It is also charged with developing vaccines to five recurrent epidemic pathogens and bringing them through phase 2 trials, such that if needed, they can rapidly complete phase 3 trial and go to market with an approved vaccine. As a result of these investments, there are new DNA- and RNA-based platforms, as well as platforms for developing recombinant subunit vaccines. These new platform infrastructures, for the first time, have created a standard manufacturing process to allow for rapid synthesis of candidate vaccines once the appropriate antigenic target has been identified. These platforms have already been used to develop effective vaccines for other diseases, including influenza. Several of these are already FDA licensed, eliminating an important step in the approval process.

Financial considerations

Because of the high cost of vaccine development and the high dropout rate of candidate vaccines, companies move cautiously through the trial phases, with multiple pauses for data analysis. In the past, when this process was accelerated and the vaccine then not produced, the high cost of early vaccine development was borne by the companies. This occurred with the companies working on the SARS and MERS vaccines when the funding for the vaccine development was reallocated once the epidemics subsided. This is where a new funding method is being used to accelerate the process of

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vaccine development. With guaranteed external sources of funding, a "parallel" process of vaccine manufacturing is being attempted. Using this funding stream, companies can begin to build the infrastructure (i.e. factories) necessary for large-scale vaccine production before the results of the phase 3 trials are available. This places the financial risk on the funding sources (CEPI, NIH, etc.) such that if a vaccine fails phase 2 or 3 trials, the company is not at risk for this cost. On the other hand, when a vaccine has a successful phase 2 trial, large scale manufacturing can begin and if the phase 3 trial is successful, vaccine production will already be underway. This new approach is more expensive as millions of dollars will be deployed to develop a manufacturing process which will not be utilized for ineffective candidate vaccines. However, this should markedly accelerate the large scale production of one or multiple successful vaccines. It is using this approach that has allowed the NIH to postulate that a vaccine could potentially be available as early as mid-2021.

Sero-prevalence of COVID-19: What we know

SARS-CoV-2 arose as a novel new coronavirus late in 2019.[3] We now appreciate it to be a zoonosis; first infecting humans as a result of close animal contact associated with an exotic animal market in central Wuhan, China.[4] There was no specific innate immunity to this particular coronavirus in humans (although as noted below, there may be cross immunity from other coronaviruses). SARS-CoV-2 demonstrated its ability to be highly transmissible with an R_0 estimated to be 2.5 (or greater); significantly more infectious than seasonal influenza.[5] SARS-CoV-2 has an incubation period of 5.2 days and is spread primarily through droplets and aerosols. Viral shedding occurs 1–3 days before symptoms or in the absence of symptoms in 30–50% of individuals.[6] The immune naivety, infectivity, unique combination of disease characteristics and failure of early containment rendered the current pandemic a virtual certainty.

The key to any efforts to control pandemic activity is an accurate understanding of the extent of disease activity and pattern of infection. The United States has seen a wide variance of SARS-CoV-2 infections. As the pandemic progresses, we should expect this pattern of outbreaks to continue. The exact prevalence of COVID-19 in the general population is still a matter of debate. We have estimates of prevalence in the general population ranging from 4.5% in Los Angeles County,[7] 25% in New York City[8] and 31.5% in Boston (Table 1).[9] Disease transmission is likely facilitated by population density; hence, major metro areas worldwide have early prevalence higher than rural areas. French researchers demonstrated this with a prevalence of 9.9% in Paris and 3.0% in the countryside.[10] Additionally, the true incidence is likely 10–100 times higher than the reported case numbers as the result of incomplete testing and extensive asymptomatic infection.[11,12] Currently, the CDC is working to obtain a more accurate estimate of the prevalence in the general population.

In certain populations, as a result of proximity in the workplace or crowded living conditions, rapid dissemination of COVID-19 can occur following introduction of a single case. It is not surprising that in some work environments, nursing homes and homeless shelters disease prevalence can be very high. One study reported that sero-positivity in homeless shelters was as high as 66% in San Francisco.[13] Nursing home prevalence is of particular importance. Not only do residents live in shared space; they are also at very high risk for complications from COVID-19.[14,15] Minnesota recently began screening all nursing home residents. In a community facility in Minnesota with 100 residents 16 were found positive by the second week of weekly testing.[16] Work conditions can also promote disease transmission. Meat processing plants place workers in close proximity often with poor quality air flow with resultant efficient disease transmission. CDC investigators noted prevalence in meat processing plants as high as 18%.[18] These unique high incidence populations are critical to identify and manage as workers can then transmit infection to the general community populations.

Reports vary concerning the prevalence of disease in health care workers. One study suggests health care workers have a prevalence 7% higher than the general population.[19] This study was in an area with high ongoing community transmission. On the other hand, serial testing of healthcare workers and the general population in London showed that health care worker prevalence closely mimics that of the community.[20] It is likely that overall, health care workers have a higher disease prevalence than the general population to the extent that they have additional disease exposure as part of their daily work.

In the general population and in each of these unique populations further study is needed to understand the true disease prevalence. Prevalence data is essential to target pandemic control efforts and predict future pandemic activity.

Table 1. Prevalence: examples

Location	Area A	Area B	Reference
French population	Paris 9.9%	Hauts-de-France 3%	Salje
United States population	Boston 31.5%	Santa Clara 2.5–4%	Vogel
Meat processing facilities	South Dakota 17.3%	Iowa 18.2%	Dyal
Nursing homes	Minnesota 16%	Washington 5%[17]	Personal communication, Roxby
Homeless shelters	San Francisco 66%	Atlanta 4%	Mosites
Health care workers	London 1.5–7.6%	New Jersey 7%	Treibel; Barrett

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Helper T cells active against SARS-CoV-2 may be already present in half the population[21]

A small study yields important results in our understanding of the current pandemic. Researchers at the La Jolla Institute for Immunology tested the blood of 20 non-hospitalized adult COVID-19 survivors (20–35 days post symptom onset) and 11 blood samples from unexposed individuals between the years 2015–2018. They found varying degrees of positive CD4+ T cell activity against SARS-CoV-2 in ~50% of the historical samples, in addition to strong CD4+ and antibody activity in 100% of the COVID-19 survivors. While it is not possible to say whether this T cell activity in the unexposed individuals confers immunity, it does offer a potential explanatory mechanism for observed rates of asymptomatic infections and apparent immunity in some members of the population.

Abbott-ID-NOW test sensitivity in question

Researchers at New York University (NYU) studied the Abbott-ID-NOW rapid diagnostic test for COVID-19.[22] All samples were collected at the NYU Langone Tisch Hospital. NYU labs use two large validated testing platforms, the Cephid Xpert Xpress and the Roche Cobas for PCR SARS-CoV-2 RNA detection. In the NYU laboratory, these two tests have similar limits of detection of 250 and 100–150 copies/ml respectively for SARS-CoV-2 viral RNA. The Abbott-ID-NOW test claims a sensitivity of 125 copies/ml.

The NYU team evaluated the performance of the Abbott system compared to the Cepid Xpert Xpress test platform on both nasopharyngeal swabs (NP) collected in viral transport media (VTM) and dry nasal swabs. The Abbott-ID-NOW test identified 10 of 15 NP swabs obtained from COIVD-19 patients in VTM; five were falsely negative (33%). Detection using a direct dry swab approach without VTM, a method suggested by Abbott to improve test performance, resulted in the Abbott platform correctly finding only 51.6% (16/31) of tests positive by the Cephid Xpert Xpress; a false negative rate of 48%. The Abbott test's viral limit of detection as determined by NYU was 20,000 copies/ml and not the 150 copies/ml Abbott claims. In summary, the NYU team found the Abbott-ID-NOW test for SARS-CoV-2 missed 1/3 of NP swabs in VTM and 48% using dry nasal swabs from patients confirmed to have COVID-19. At another lab, Northwell Health, 7 of 107 NP swabs were falsely negative; a sensitivity of 87.7%. The Cleveland Clinic also reported a lower sensitivity with a false negative rate of 14.8% for the Abbott testing platform.[23]

The sensitivity of the Abbott-ID-NOW test platform seems to range from 52 to 88% in different laboratories. The Abbott test seems to have reduced sensitivity with lower viral loads, and the performance may be worse with dry nasal swabs as opposed to collecting the specimen in VTM.[24]

Remdesivir — NIH ACCT randomized trial[25,26]

Preliminary data on the ACCT trial has just been published. Recall that this was a randomized, double blind, placebo based international trial enrolling 1063 patients. The study population was inpatients with evidence of COVID-19 pneumonia. Median time to randomization was nine days, and 89% of patients had severe disease. This trial represented the best means of establishing whether remdesivir would reduce the mortality of COVID-19 infection. It received attention when the data safety monitoring board released very early results showing a reduction in disease duration of about four days and a non-clinically significant trend towards lower mortality. However, in a very controversial move, the NIH then ended the placebo arm of the study and allowed those individuals still participating to receive remdesivir, further reducing the likelihood that this critical mortality question would be answered. The trial has now been fully enrolled and the NIH has published preliminary data on the full cohort of patients, although 25% of the patients have not yet reached the 30-day endpoint.

The most clinically important study results included:

1. A median recovery time of 11 days in the remdesivir group as compared with 15 days in those who received placebo (P<0.001).
2. There was no improvement in the rate of recovery in patients who were on high flow oxygen or were receiving mechanical ventilation.
3. Although the rate of mortality was once again noted to be numerically lower in the remdesivir group compared to placebo, this did not reach statistical significance. It is unknown whether this will change when the full data set becomes available.
4. Overall toxicity was similar in both groups.

The lack of response in the more severely affected patients once again underscores the need to study anti-viral therapy earlier in the disease course. The only other randomized placebo-based trial looking at remdesivir was conducted in China, enrolled 237 patients, and did not show any benefit to therapy. The issue of whether remdesivir improves mortality is an important one. The Institute for Clinical and Economic Review (ICER), is a nonprofit that estimates the value of a drug based on its performance. ICER has calculated that if the drug is proven to decrease mortality, it could justify a price of around $4,500 for a treatment course. If it doesn't and the drug only shortens hospital stays, that value-based price goes down to $390. This may have wide-ranging importance given that over three million people have already been affected by COVID-19. The drug is manufactured by Gilead and the price has not yet been set.

Large international registry trial of hydroxychloroquine (HCQ) and chloroquine (CQ)[27]

As reviewed in this Forum over the past couple of months, there have been five published trials of HCQ and CQ use. Two of these were randomized trials, the other three were observational trials. All five showed either no effect or an increased mortality with HCQ/CQ use. The Lancet has now published the largest trial, looking at 96,000 individuals worldwide, almost 15,000 of whom received HCQ/CQ either alone, or with azithromycin. This was an observational registry study. Compared to the control group who received neither an antimalarial nor azithromycin, patients treated with these regimens demonstrated the following mortality rates.

Table 2. Results of five published trials comparing mortality rates of hydroxychloroquine (HCQ) or chloroquine (CQ) treatment alone or with azithromycin

Treatment regimen	Mortality
Control group	9.3%
HCQ	18%
CQ	16%
HCQ/azithromycin	24%
CQ/azithromycin	22%

These results are compelling for two reasons. The first is the consistency of the data showing an increased mortality when HCQ/CQ were evaluated both alone and with the addition of azithromycin. The second is the added mortality with the addition of azithromycin in this study. The new onset of ventricular arrhythmias in the HCQ/CQ and azithromycin groups ranged from 6–8%, compared to <1% in the control group. Both HCQ/CQ and azithromycin are known to prolong the QT interval in certain individuals and this effect would be expected to be additive. The increased mortality with combination therapy could therefore be related to this observation. Based upon the results of this study, the NIH has paused enrollment into its randomized, placebo-based HCQ trial and will do an interim analysis of the data prior to enrolling any more subjects. Several other ongoing randomized, placebo based trials are underway.

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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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