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COVID–19
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The COVID-19 vaccine: The reality and what to expect

COVID-19 vaccines are of intense interest to health care and the general public. There is an expectation that a vaccine will allow for a return to social and economic interactions as they existed prior to the COVID-19 pandemic. Expectations have been set that vaccination will stop the pandemic and vaccines will be available in 2020. These expectations need to be modified to correctly reflect a more accurate timeframe for vaccine availability and impact.

Vaccination to generate protective immunity against SARS-CoV-2 is very important but vaccination alone will not result in pandemic control. Multiple COVID-19 vaccinations will become available beginning in late 2020 and extending into 2021 and 2022. However, only a limited number of vaccines and doses will be available initially.

This is important for two reasons:
1) Not all the vaccines will be equally effective or well-tolerated in all patient types.
2) Prioritization of who to vaccinate first will be needed due to the limited number of doses that will be available.

The CDC and the National Academy of Medicine (NAM) have both recently provided suggestions for equitable distribution of a limited supply of COVID-19 vaccines.[1,2] These are based on ethical frameworks for allocation of scarce resources. All recommendations call for a multi-phased approach. Each phase is designed to prioritize a greater number of persons as more vaccine becomes available. In order to achieve acceptance, it is very important to communicate clearly to the public the rationale for the prioritization of the plan. CDC recommends a three phased approach (Table 1). The first phase is divided into two subgroups and is expected to begin late in 2020.

Phase 1-A begins with vaccination of health care workers directly involved in the provision of health care, those unable to work from home, or those exposed to infectious materials.

Phase 1-B would include those persons:
1) Who are at higher risk for complications from COVID-19 infection as a result of comorbidities
2) Who live in long-term care
3) Who are greater than 65 years of age
4) People who play a key role in keeping essential functions of society running and cannot socially distance in the workplace (e.g., health care personnel not included in phase 1-A, emergency and law enforcement personnel not included in phase 1-A, food packaging and distribution workers, teachers/school staff, childcare providers).

Initially, the vaccine will not be available to all persons in the above groups. Therefore, it is suggested that each vaccine distribution "jurisdiction," which most commonly represents a state, develop subgroups within the populations to prioritize vaccination in phase 1. An example of a subgroup of all health care workers would be health care workers who are exposed to COVID-19 more than twice weekly.

(continued on page 2)

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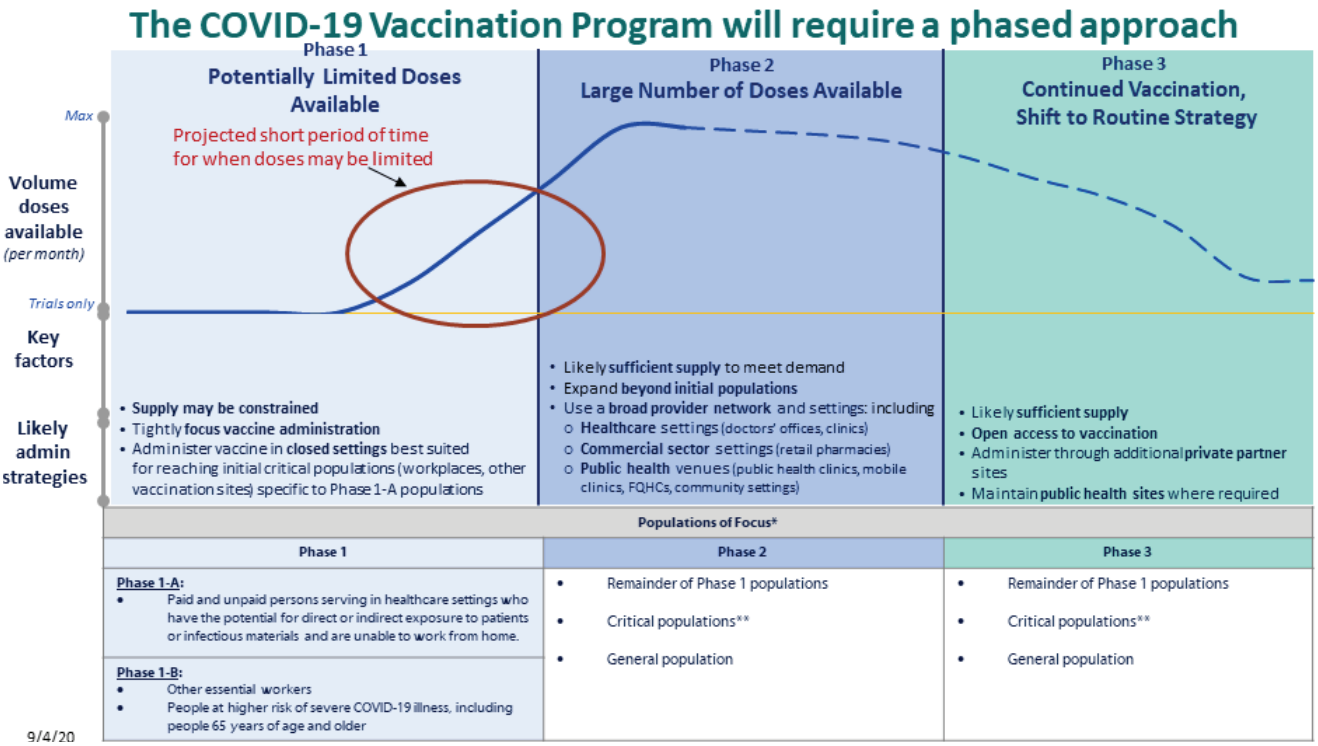
Table 1. CDC recommended COVID-19 vaccination phases



*Planning should consider that there may be initial age restrictions for vaccine products.
**See Section 4: Critical populations for information on phase 1 subset and other critical population groups.

Phase 2 vaccination will occur with the increase in available vaccines (estimated to be in mid-2021). Vaccination in phase 2 will prioritize completion of phase 1 persons, vaccination of other critical populations, and then members of the general population. Critical population definitions may vary by jurisdiction depending on local industries and pandemic stage.

Phase 3 will occur when ample perhaps even excess vaccine supplies are available. All persons desiring vaccination will be encouraged to be vaccinated in phase 3.

Many of Optum's frontline health care workers would be included in phase 1. The second phase would include Optum's clinical workers not part of phase 1, and many or most UnitedHealth Group employees. These vaccination priority groups are not determined with any degree of certainty, are likely subject to local and state public health guidance and may change depending on the status of the pandemic at the time of vaccine availability.

It will be important to understand the number of persons in each of the various populations in the priority plan as this may also play a role in vaccine allocation. Population estimates are indicated in Table 2 for many of the subgroups in phase 1 and 2. These subgroups are distributed as a roughly equal portion of each state's population. It is of note that more than 15 million persons are in phase 1-A alone.

(continued on page 3)

Table 2. Persons in United States in population subgroups

Population subgroup in the U.S.[3,4,5,6,7]	Estimated persons in U.S. (millions of people)	Anticipated vaccination phase
Health care practitioners, technical staff and support staff exposed to COVID-19 more than once/week.	9.8	1-A
Health care workers in skilled nursing facilities	0.43	1-A
Full-time nursing home employees	1.5	1-A
Home health workers	3.2	1-A
Morticians, undertakers, funeral directors	0.025	1-A
EMS personnel	0.262	1-B
Fire fighters	1.1	1-B
Police	.70	1-B
Persons with multiple comorbid conditions (estimate)[8]	20	1-B
Nursing home residents	1.3	1-B
Residential care facility residents	0.8	1-B
Persons older than 65 below the poverty line[9,10]	4.7	2
Food and beverage workers	1.7	1-B
Cashiers / food store workers	0.87	1-B
Pharmacists and pharmacy staff	0.62	2
Public transit workers	0.18	2
Total health care workers in U.S.[11]	15	2
Teachers primary and secondary	8.6	1-B
Childcare providers	0.46	1-B
Persons over 65 years of age	49	2
Persons over 65 without comorbid conditions	13.2	2
Group home residents	0.47	2
Homeless persons	0.57	2
Correctional residents and staff	2.7	2

Several factors are critical to the success of a mass vaccination program for COVID-19.

- The plan must be easy to understand, based on sound priorities and communicated repeatedly to the public.
- The public must understand and have confidence in the science supporting the efficacy and safety of any vaccine or vaccines.
- The health system will need to coordinate with public health to conduct efficient vaccine delivery to the targeted populations.
- The public must understand the benefits and limitations of a COVID-19 vaccine.

There has been a significant erosion of trust in the CDC and FDA as a result of recent missteps. This has increased the percent of the population that may be vaccine adverse. The estimates on what percentage of the population would need vaccination for us to achieve herd immunity remain imprecise, but 70% vaccination is a reasonable first goal. As health care providers, it is our responsibility to educate our population on the critical role vaccination plays in ultimately controlling the pandemic.

With preparation, communication and collaboration between public health, vaccine manufacturers and health care providers, a successful mass vaccination program for COVID-19 can occur over the next 12–18 months.

Novavax phase 1 vaccine trial results[12]

The vaccine trials on which we have reported to date have been either mRNA or viral vector-based vaccines. Neither of these vaccine platforms has yet been used in an approved vaccine for humans in other diseases. The Novavax vaccine is a protein subunit-based vaccine, and results of the first portion of the phase I/II trial were published in the NEJM this month. The trial was funded by the Coalition for Epidemic Preparedness Innovations (CEPI). This vaccine differs from the others that have been reviewed in several important ways. First, the technology uses a synthesized viral-like particle (VLP) to which a recombinant full

(continued on page 4)

SARS-CoV-2 spike protein is affixed, after which an adjuvant is added to increase immunogenicity. Next, it does not rely on the human host to generate spike protein antigen, and therefore the antigen dose is fixed and known. Lastly, the vaccine platform and adjuvant used to build the Novavax vaccine have already been FDA-approved. This platform has been used to build an influenza vaccine that recently completed a successful phase III trial and is awaiting FDA approval.

One hundred and eight participants received two doses of the vaccine and 23 received placebo. With both vaccine doses, local and systemic symptoms were absent or mild in most patients, with a mean duration of two days, and only one patient had mild fever with the second dose. By 35 days post vaccination, neutralizing Ab rose to levels that were at least sixfold higher than those levels seen in convalescent serum from symptomatic outpatients with COVID-19. T-cell studies showed that the vaccine-induced antigen-specific polyfunctional CD4+ T-cell responses that were reflected in IFN-y, IL-2, and TNF-a production on spike protein stimulation. These results suggest that the vaccine will have significant efficacy against SARS-CoV-2. The second portion of the vaccine trial has already enrolled several thousand participants and results are pending. The phase III is expected to launch next month.

Childcare facilities as a significant source of COVID-19 spread[13]

Although transmission of SARS-CoV-2 by children aged ≥ 10 years has been established, transmission from younger children is less well understood. Contact tracing of three COVID-19 outbreaks in three childcare facilities in Salt Lake City clearly establishes transmission by children three years old and younger to both other children and adults. Across these three distinct COVID-19 outbreak events, 31 confirmed cases of COVID-19 were traced back to infection in one of the childcare facilities. Of the 13 pediatric cases, 12 were acquired in the facility. The children subsequently infected 12 additional non-facility contacts (26% of 46 total contacts), most of whom were family members. One of the parents required hospitalization. In two of these transmissions, the index child was entirely asymptomatic. Daily temperature checks and symptom screening were in place at all three facilities; two facilities also required staff masking.

Temperature and symptom checks of participants (students and teachers) are not enough. CDC guidance for childcare programs recommends that staff members and children with symptomatic household members should quarantine and seek testing. None of these facilities followed this policy and it likely would have reduced infections. Individuals in a household with children even with mild symptoms should consider testing, given the high rate of transmission between household contacts, including from children to adults.

Typical protective immunity to seasonal (non-SARS/MERS) coronaviruses is short-lasting[14]

Researchers evaluated stored blood samples collected every 3–6 months from 10 healthy individuals across a 35-year period to study how frequently those individuals were infected with coronaviruses that cause the common cold. They evaluated frequency of infection with four seasonal coronaviruses by detecting temporal elevations in levels of serum antibodies against each distinct coronavirus. Reinfections were detected as early as six months, and many instances of reinfection at 12 months were noted. The mean interval period for reinfection was 30 months.

The genetic and biologic makeup of these four seasonal coronaviruses is quite different but share many commonalities with SARS-CoV-2, so the researchers hypothesize that these findings are generalizable to SARS-CoV-2. If so, we can expect increasing susceptibility to reinfection with SARS-CoV-2 beyond six months and (hopefully) reduced severity of symptoms, based on early reinfection case reports.

MRI demonstrates myocardial inflammation in some collegiate athletes recovering from COVID-19

Previous research has shown that myocardial inflammation can follow recovery from COVID-19 infection, even among asymptomatic and mildly symptomatic patients.[15] Since myocarditis can cause sudden death in athletes, a finding of myocardial inflammation could inform risk and return to play when an athlete recovers from COVID-19. Investigators recently performed cardiac evaluations, including cardiac MRI, in competitive college athletes who tested positive for coronavirus.

Twenty-six athletes recovering from COVID-19 participated. Twelve reported mild COVID-19 symptoms; the remaining individuals were asymptomatic. In all cases, ECG did not show diagnostic ST/T wave changes, serum troponins were normal, and echocardiography demonstrated normal ventricular volumes. Four athletes had MRI findings consistent with myocarditis based on two imaging features: increased T2 signal suggestive of myocardial edema and late gadolinium enhancement consistent with nonischemic myocardial injury. Pericardial effusion was present in two of these individuals. Two reported shortness of breath, while the other two remained asymptomatic.[16]

(continued on page 5)

While these results are important, urgent questions about short- and long-term prognoses remains. Follow-up data that includes subsequent imaging, health evaluations, and post-mortem examinations are needed to adequately interpret and act on these findings for the general population, particularly in young healthy individuals who might be expected to have similar MRI findings, as well as the athlete returning to sport.

Randomized placebo trial of remdesivir for treatment of COVID-19 pneumonia

The data on the efficacy and cost-effectiveness of remdesivir therapy is still lacking. At over $3,000 for a five-day course of therapy, the drug should be expected to show unequivocal efficacy. The first randomized, placebo-controlled trial of remdesivir among patients with COVID-19 conducted in Wuhan, China, did not show a significant benefit in time to recovery or mortality.[17] The target enrollment was not reached, as public health measures markedly reduced the infection rate. Subsequently, in a larger randomized, double-blind placebo-based trial in the United States, patients with severe COVID-19 treated with a 10-day course of remdesivir had a four-day shorter time to recovery than those receiving placebo (11 days vs. 15 days), with no statistical difference in mortality between treatment and placebo.[18] This trial was prematurely halted when an EUA was granted by the FDA and enrollment into the placebo arm was halted.

Added to this body of literature, we now have results from a large trial of 600 patients randomized to a 5- or 10-day course of remdesivir compared to standard of care.[19] This was an international study enrolling patients with moderate pneumonia due to SARS-CoV-2 infection, and importantly, all patients were enrolled within four days of a positive PCR test. The primary endpoint was improvement in clinical status on day 11. There were no significant differences in mortality, need for mechanical ventilation, duration of hospitalization or time to recovery. Looking at only the primary endpoint of clinical improvement on day 11, this was seen in 65% of patients receiving a 10-day remdesivir course, 70% of patients receiving a 5-day course, and 61% of patients receiving the standard of care. This reached statistical significance with a p value of 0.2 and the effect size was deemed by the authors as of uncertain clinical importance. The Institute for Clinical and Economic Review (ICER) has done a cost-effectiveness analysis of remdesivir pricing based on an assumption of a mortality reduction versus no mortality reduction.[20] In the mortality reduction scenario, the derived cost-effective price would be ~$2,650. In the scenario where we currently are, with no evidence of a significant mortality reduction, the ICER-derived cost-effective price would be $310 for a course of treatment.

Glucocorticoids with or without tocilizumab in COVID-19 with impending cytokine storm[21]

Whereas glucocorticoids now have an evidence-based role in the treatment of SARS-CoV-2 pneumonia, we are still awaiting the publication of the large randomized placebo-based tocilizumab arm of the RECOVERY trial.

Researchers in the Netherlands looked at patients with COVID-19 who had impending cytokine storm as evidenced by rapid respiratory deterioration plus elevation of at least two biomarkers (C-reactive protein >100 mg/L; ferritin >900 µg/L; or D-dimer >1500 µg/L). Eighty-six patients received high-dose intravenous methylprednisolone for five consecutive days (250 mg on day one followed by 80 mg on days 2–5). If the respiratory condition had not improved sufficiently within two days, patients then received an 8 mg infusion of the IL-6 receptor blocker, tocilizumab. Forty-three percent of the patients went on to receive tocilizumab. These 86 patients were matched to historical control patients, who also had impending cytokine storm as per the above definition. Approximately 90% of the patients in each group received prophylactic doses of low molecular weight heparin. The primary outcome was ≥ 2 stages of improvement on a seven-item WHO-endorsed scale for trials in patients with severe influenza pneumonia, or discharge from the hospital. Secondary outcomes were hospital mortality and the need for mechanical ventilation. Treated patients were 79% more likely to achieve the primary outcome (64 versus 44 patients). Hospital mortality was 65% lower in the treatment group (14 versus 41 patients) and the need for mechanical ventilation was 71% lower (10 versus 24 patients).

This study adds to the body of observational data suggesting a beneficial role for the IL-6 receptor blocker tocilizumab in patients with severe progressive SARS-CoV-2 infection. It also adds to the evidence base supporting glucocorticoid use as 57% of the patients in the treatment group received only methylprednisolone. Although observational by design, the results were highly statistically significant compared to the historical control group. The results of the RECOVERY arm utilizing tocilizumab are anxiously awaited.

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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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