Update from the Advisory Committee on Immunization Practices

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Abbreviations: ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; VFC, Vaccine for Children Program; GRADE, Grading of Recommendations Assessment, Development and Evaluation; EtR, Evidence to Recommendations Framework; EUA, Emergency Use Authorization; VAERS, Vaccine Adverse Event Reporting System; VSD, Vaccine Safety Datalink; PCR, polymerase chain reaction; WG, Work Group.

ABSTRACT: The Advisory Committee on Immunization Practices (ACIP), a group of medical and public health experts, normally meets 3 times per year to develop recommendations for vaccine use in the U.S. Because of the SARS-CoV-2 pandemic, there are several SARS-CoV-2 vaccines currently in late stage clinical trials, so the ACIP is now meeting monthly for single day meetings, with plans to continue standard 2-3 day meetings as per usual (February, June, and October). Emergency meetings of ACIP may occur if a vaccine candidate receives an Emergency Use Authorization (EUA) from the FDA. This Update provides a combined summary of the August 26 and September 22, 2020, meetings, both of which focused completely on COVID-19 vaccines. Representatives from the American Academy of Pediatrics (YAM, DWK) and the Pediatric Infectious Diseases Society (STO) are present as liaisons to the ACIP.

Key words: ACIP; CDC; immunization; COVID-19; SARS-CoV-2

Overview of Current ACIP Considerations

The COVID-19 Vaccine Work Group meets weekly. Within the United States, 2 vaccines are in Phase III clinical trials and are actively enrolling, 1 vaccine is in Phase III clinical trials but currently is on hold, and 3 vaccines are in Phase I/II clinical trials and are actively recruiting. The Phase III study of the mRNA-1273 vaccine (Moderna) had enrolled 25,296 participants as of September 16, 2020; 28% of participants enrolled are from "diverse communities." The Phase III study of the BNT162b2 vaccine (Pfizer/BioNtech) had enrolled 31,928 participants as of September 21, 2020; 26% of participants enrolled have "diverse backgrounds." Pfizer has proposed expansion of the study to 44,000 participants. A summary of vaccines being studied in the United States is provided in Table 1.

Table 1. COVID-19 vaccines in human clinical trials in the United States as of September 14, 2020:

Candidate	Manufacturer	Type	Phase	Trial characteristics	Trial #	Recruiting
mRNA-1273	ModernaTX, Inc.	mRNA	III	• 2 doses (0, 28d) • IM administration • 18-55, 56+ years	NCT04470427	Yes
mRNA-BNT162	Pfizer, Inc. /BioNTech	mRNA	II/III	• Single or 2 doses • IM administration • 18-85 years	NCT04368728	Yes
AZD1222	University of Oxford/AstraZeneca consortium	Viral vector (NR)	III	• 2 doses (0, 28d) • IM administration • ≥18 years	NCT04516746	On Hold

Ad26COVS1	Janssen Pharmaceutical Companies	Viral vector (NR)	I/II	• 2 doses (0,56d) • IM administration • 18-55, 65+	NCT04436276	Yes
--	Sanofi/GSK	Protein Subunit	I/II	• Single or 2 doses • 18-49, 50+	NCT04537208	Yes
NVX-CoV2373	Novavax	Protein Subunit	I/II		NCT04368988	Yes
AV-COVID-19	Aivita	AuDendriticcell	I/II		NCT04386252	
INO-4800	Inovio Pharmaceuticals, Inc.	DNA plasmid	I	• 2 doses (0, 4w) • SC administration/ electroporation • ≥18 years	NCT04336410	

The Work Group is reviewing Phase I/II data from manufacturers as they become available, as well as developing the structure for independent data review that will occur once Phase III data are available. Once these Phase III data are available, the ACIP Work Group will conduct independent review of safety and efficacy data utilizing the Evidence to Recommendation (EtR) Framework and GRADE. Based on this data review, the Work Group will present policy options to the full ACIP.

If/when an FDA decision is announced for an Emergency Use Authorization of a specific vaccine candidate, the ACIP will have an "emergency" meeting with a public comment session at which the ACIP will review safety and efficacy data using GRADE/EtR. The ACIP then will vote on recommendations for the vaccine and populations for use. ACIP recommendations could be more targeted or detailed than the FDA "Conditions of Use." After an ACIP vote, the ACIP will submit its

recommendations to the CDC Director. If the recommendations are accepted, they will be published in the MMWR and become official CDC Policy.

The Work Group and full ACIP has reviewed published COVID-19 vaccine prioritization and allocation frameworks, as well as qualitative research on a future COVID-19 vaccine. Clinical development programs for a COVID-19 vaccine, including data from Phase I/II clinical trials and plans for Phase III clinical trials, have been presented, including racial and ethnic disparities in COVID-19 testing, exposure, severity, and clinical disease impact. The association between social vulnerability and risk of becoming a COVID-19 hotspot is a major area of focus. All of these considerations inform considerations for Ethics/Equity Framework for COVID-19 vaccine allocation and further discussions regarding COVID-19 vaccine allocation.

Overview of Safety Considerations for COVID-19 Vaccines

For COVID-19 vaccines, a separate safety group was assembled in June 2020 to support the COVID-19 Vaccine Workgroup and the full ACIP on the safety of COVID-19 vaccines in development and post-authorization or post-licensure. Known as the COVID-19 Vaccine Safety Technical (VaST) Subgroup, it includes 3 ACIP members and several consultants. The VaST group has assessed the following questions:

- *Should safety monitoring for Phase III clinical trials be harmonized?*

  VaST Answer: Yes. By harmonizing, this allows for the combination of data, if appropriate, and maximizes the sample size for any given adverse event of special interest (AESI). It also allows for comparison of safety across different vaccine platforms and trials, if appropriate, and enables dynamic assessment of benefit-

risk balance. Harmonization with international standards (e.g. Brighton Collaboration) is preferred. Trials usually are designed for efficacy, but can also be designed for safety if sufficient follow-up is allowed (e.g. rotavirus vaccine trials). The minimum duration of follow-up needed to assess safety (i.e. benefit-risk balance) depends on the types of adverse events and associated risk intervals.

- *Should safety monitoring for post-authorization or post-licensure safety surveillance systems be harmonized?*

  VaST Answer: Yes. Common protocols, outcome definitions, risk windows, and approaches to severity grading can support rapid evaluation of statistical signals. However, different systems have different capabilities, and may need to align, rather than harmonize. The capability for timely evaluation of statistical signals is crucial for vaccine confidence. Coordination across post-market safety surveillance systems is recommended.

VaST has identified six conditions for success for COVID-19 vaccine safety monitoring:

1. Ability to capture vaccine exposure in vaccine safety surveillance systems;
2. Ability to define background rates in general population and among those with COVID-19 disease;
3. Minimize conflicts of interest among members of the data review group;
4. Shared review and shared learning across all vaccine safety surveillance systems;
5. Ability for data review group to discuss findings independently;
6. Well-developed communication plan on safety issues.

COVID-19 Vaccine Safety Surveillance Among Early Recipients

A challenge with COVID-19 vaccine safety monitoring in early recipients is that during the early phase of a national COVID-19 vaccination program, initial doses may be distributed to specific groups such as healthcare personnel and other essential workers. In this scenario, activities to enhance traditional vaccine safety monitoring systems (e.g., the Vaccine Adverse Event Reporting System [VAERS]) will be necessary. The response to this challenge is to prepare traditional monitoring systems, to conduct active surveillance in early recipients through smartphone-and email-based web surveys, and to obtain vaccination and safety monitoring data from healthcare facility and long-term care facility surveillance. For COVID-19 vaccines, VAERS report processing times for death reports will be 1 day, serious reports will be 3 days, and non-serious reports will be 5 days. The CDC and FDA will receive updated datasets daily. VAERS analysis for COVID-19 reports will include review by FDA scientists of all VAERS reports classified as serious. Attempts are made to follow-up on all serious reports to get medical records and other medical documentation. CDC scientists will review VAERS reports for adverse events of special interest (AESI). The CDC and FDA will coordinate on analysis of VAERS data and both agencies will conduct data mining.

Other enhanced monitoring programs are being designed to meet the challenge of COVID-19. One of these is called vaccine safety assessment for essential workers (V-SAFE). V-SAFE is a smartphone-based text, text-to-web survey, and email-to-web survey active surveillance program for early vaccine recipients. It uses contact information (phone numbers) from the registration process for COVID-19 vaccination of essential workers, which will be up to 20+ million people during the

first few months of a vaccination program. V-SAFE conducts health checks on vaccine recipients via text messages and email daily for first week post-vaccination and weekly thereafter for 6 weeks post-vaccination. Active telephone follow-up will be conducted with a person reporting a clinically important adverse event during any V-SAFE health check. A VAERS report will be taken during telephone follow-up, if appropriate.

COVID-19 Vaccine Implementation Planning

COVID-19 Vaccine Planning has been piloted in 5 jurisdictions: North Dakota, Florida, California, Minnesota, and Philadelphia. The Federal participants included the CDC, the Indian Health Service, Operation Warp Speed, and the Assistant Secretary for Preparedness and Response (ASPR). Common themes among all pilot sites are as follows: 1) COVID-19 vaccination is going to be resource-intensive, likely beyond what most jurisdictions currently have available; 2) social distancing adds significant logistical complexity into the vaccination event planning; 3) clear and transparent communication from CDC to jurisdictions will be critical; 4) information gaps challenge planning; 5) technology concerns are persistent and are significant; 6) public confidence in the vaccine is among the highest concerns for jurisdictions; 7) border communities (along city/state borders) highlight the need for clear guidance from CDC so that neighboring jurisdictions do not differ in their approaches to vaccination; 8) specific, uniform federal guidance on whom to vaccinate in the earliest days of vaccine availability will lead to less complexity and fewer questions at the state/city levels; and 9) vaccine allocation should consider the critical populations jurisdictions expect to vaccinate and not be simply based on population.

Next steps in the vaccine allocation planning process are to work with commercial partners and federal entities who may receive direct allocations to expand access; to collect vaccine provider agreements and onboard providers to be able to receive and administer vaccine, including providers who serve critical populations; to enumerate critical populations who may be prioritized for early vaccine allocation or require special consideration for distribution and access; to begin engaging with community stakeholders to address vaccine hesitancy; and to ensure state data systems have processes to monitor vaccine distribution, uptake, demand and wastage.

Social Vulnerability and Health Disparities in COVID-19 Epidemiology

Racial and ethnic minority groups represent 40% of the total U.S. population, but nearly 60% of COVID-19 cases and 50% of deaths. Disparities in COVID-19 hospitalization rates among racial and ethnic minority groups occur in both young and older age groups. Some of the many inequities in social determinants of health that put racial and ethnic minority groups at increased risk of getting sick and dying from COVID-19 include discrimination; healthcare access and utilization gaps; occupation in higher risk settings, education, income, and wealth gaps; and housing that is crowded or lacks basic services. Additionally, Black persons are more likely to be employed in essential industries and occupations that may have increased exposure to SARS-CoV-2.

The Social Vulnerability Index (SVI) was developed by CDC to identify communities that need support before, during, and after public health emergencies (https://www.atsdr.cdc.gov/placeandhealth/svi/index.html). It is a measure of social determinants of health using U.S. Census data, and ranks each county and census tract on 15 social vulnerability factors and groups them into four related themes: 1) socioeconomics; 2) housing composition and disability; 3) representation of racial and ethnic minority groups; and 4) housing and transportation.

From June 1-25, 2020, the CDC conducted a social vulnerability assessment of the risk of becoming a COVID-19 hotspot. Using data from the Social Vulnerability Index (SVI) and county-level COVID-19 cases, they examined associations between social vulnerability and hotspot detection. Among hotspot counties, they described COVID-19 incidence after hotspot detection by level of social vulnerability. COVID-19 hotspots were defined as counties with rapidly increasing COVID-19 incidence, identified using standard criteria developed by CDC. SVI scores were categorized as quartiles (Q) based on distribution among all U.S. counties, overall and by urbanicity, with Q1 = lowest vulnerability and Q4 = highest vulnerability. Counties with the highest social vulnerability had greater risk of being a COVID-19 hotspot compared to counties with the lowest social vulnerability. The risk of becoming a COVID-19 hotspot is higher among counties with certain social vulnerabilities—especially in less urban areas. Among hotspot counties, areas with the highest social vulnerabilities had markedly higher COVID-19 incidence than those with less vulnerabilities.

Overview of Vaccine Equity and Prioritization Frameworks.

The ACIP has discussed inclusion of ethics and equity principles as part of the process to identify proposed groups for early COVID-19 vaccination. As a first step, the Work Group reviewed frameworks and published literature related to COVID-19 vaccine allocation. The three published frameworks for early COVID-19 vaccine allocation that were selected were the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE); the Johns Hopkins Bloomberg School of Public Health; and the National Academies of Sciences, Engineering, and Medicine. The WHO SAGE has prepared a values framework for the allocation and prioritization of COVID-19 vaccination. Priority groups were not ranked. They include populations with significantly elevated risk of being infected. These were identified as health workers at high risk, employment categories unable to physically distance, social groups unable to physically distance, and groups in dense urban neighborhoods or living in multigenerational housing. Populations with significantly elevated risk of severe disease/death include older adults, groups with comorbidities, and sociodemographic groups at disproportionately higher risk of severe disease and death.

The Johns Hopkins Bloomberg School of Public Health has prepared an interim framework for COVID-19 vaccine allocation and distribution in the United States. The purpose is to identify candidate groups for serious consideration as priority groups, and to demonstrate how ethical principles and objectives can be integrated to produce an ethically defensible list of candidate groups. The authors note the

importance of transparency and a fair process, equity including access to healthcare, and community outreach and engagement.

The National Academies of Medicine (NAM) framework has the overarching goal of maximizing societal benefit by reducing morbidity and mortality caused by transmission of novel coronavirus. Allocation criteria are risk based. Individuals have higher priority to the extent of their risk of acquiring infection, risk of severe morbidity and mortality, risk of negative societal impact, and risk of transmitting disease. The NAM framework has the following vaccine allocation phases:

- Phase 1a: "Jumpstart phase" consisting of high-risk workers in health care facilities and first responders (EMS, police, fire).
- Phase 1b: People of all ages with comorbid/underlying conditions that put them at significantly higher risk, i.e. >2 CDC designated medical conditions, consisting of older adults living in congregate or overcrowded settings, e.g. nursing homes, residential care facilities.
- Phase 2: Critical risk workers in industries essential to functioning of society and at substantially high risk of exposure, consisting of teachers and school staff, people of all ages with comorbid/underlying conditions that put them at moderately higher risk (i.e. 1 CDC designated medical condition), all older adults not in Phase 1, people in homeless shelters or group homes for individuals with physical or mental disabilities or in recovery, and people in prisons, jails, detention centers, and similar facilities as well as staff.

- Phase 3: Young adults (18-30 years), Children (0-19 years), and workers in industries essential to the functioning of society and at increased risk of exposure not included in Phases 1 or 2
- Phase 4: Everyone not previously vaccinated

The Work Group interpretation is that the published frameworks all identify healthcare personnel important for early phase vaccine allocation. Equity is a crosscutting consideration.

The ACIP ethics/equity framework for COVID-19 vaccine allocation assists the ACIP in the identification of early recipients for allocation of COVID-19 vaccine in the setting of a constrained supply. Its goals are to minimize death and serious disease, preserve functioning of society, reduce disproportionate burden on those with existing disparities, and increase equity of opportunity to enjoy health and well-being.

The next steps are to continue the progress in the development of an ACIP ethics/equity framework and receive input from ACIP regarding the 5 proposed ethical principles. Further discussions to apply ethical/ethics framework to "Phase 1" allocation discussions will be held. How ethics and equity can be incorporated into the Evidence to Recommendations (EtR) Framework for COVID-19 vaccines will be considered.

Prioritization Considerations for Early COVID-19 Vaccine Administration.

Administration of COVID-19 vaccine will require a phased approach. The goals of the COVID-19 vaccine program are as follows:

- To ensure safety and effectiveness of COVID-19 vaccines
- To reduce transmission, morbidity, mortality of COVID-19 disease
- To help minimize disruption to society and economy, including maintaining healthcare capacity
- To ensure equity in vaccine allocation and distribution

"Healthcare personnel" are defined as all paid and unpaid persons servicing in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials. They include persons not directly involved in patient care but potentially exposed to infectious agents while working in a healthcare setting. The estimated population size is ~ 17-20M. Examples include hospitals, long term care facilities (assisted living facilities & skilled nursing facilities), outpatient, home health care, pharmacies, EMS, and public health.

"Essential workers (non-healthcare)" are defined as workers who are essential to continue critical infrastructure and maintain the services and functions Americans depend on daily. Workers who cannot perform their duties remotely and must work in close proximity to other should be prioritized. Sub-categories of essential workers may be prioritized differently in different jurisdictions, depending on local needs. The estimated population is ~ 60M. Examples include food and agriculture,

transportation, education, energy, water and wastewater, and law enforcement. There is substantial overlap between essential workers and high-risk medical conditions. Racial and Ethnic minorities are also overrepresented in many industries considered essential, particularly building services, transportation services, grocery stores and wholesalers, child care services, and the US Postal Service.

Obesity, chronic kidney disease, diabetes, and hypertension are associated with hospitalization for COVID-19. Among hospitalized COVID-19 patients, the adjusted rate ratios for underlying medical conditions association with death ranged from 1.19 (diabetes) to 1.39 (immunosuppression). Adults with such medical conditions at higher risk for severe COVID-19 constitute >100M persons. Examples include obesity (31% of the population), diabetes (11% of the population), COPD (7% of the population), heart conditions (7% of the population), and chronic kidney disease (3% of the population). Nearly 90% of hospitalized adults had at least one high risk medical condition, and over 60% had 3 or more.

Adults 65 years and older comprise ~53M people, representing 16% of the U.S. population. People in this age group make up nearly 80% of COVID-19 deaths. Approximately 3M live in long-term care facilities. Adults 65 years and older have the highest cumulative rate of COVID-19 associated hospitalizations. Older age is the strongest independent risk factor for in-hospital death. There is also significant overlap between age ≥ 65 years and high-risk medical conditions.

There are key unknowns in prioritization considerations for COVID-19 vaccines. Individual vaccine characteristics, which are required to understand the magnitude and balance of benefits and potential risks, are presently unknown, as are storage, distribution, and handling cold chain requirements. Vaccine efficacy and immunogenicity in younger and older adults are also unclear at this time. Additionally, the pathway to approval versus Emergency Use Authorization (all adults vs younger adults) has not been determined yet. The number of doses available at time of approval and rate of scale-up also is not known.

The Work Group considerations and next steps are summarized as follows:

1. Continue to build scientific understanding of the epidemiology of the outbreak and risk in Phase 1 groups, modeling the impact of various vaccination strategies and interpretation of clinical trials safety data and plans for post-market safety monitoring.
2. Prepare Evidence to Recommendation Framework (EtR) for vaccines in Phase III clinical trials prepare an equity domain to add to the EtR and gather evidence on value and acceptability of COVID-19 vaccine. Once data are available from Phase III, GRADE safety and efficacy, the Work Group will prepare policy options for ACIP consideration

The September 22 meeting ended with the following questions posed to the full committee:

1. If constrained vaccine supply necessitates sequencing of groups in Phase 1b, what are the most important information gaps we need to fill for ACIP to make sequencing recommendations?
2. What is the correct balance of national guidance and local flexibility?

A lengthy discussion ensued. An ACIP member made the point that the benefit:risk balance for a specific vaccine may influence the populations recommended to receive that vaccine, so the characteristics of the vaccines will determine the populations recommended to receive it. Discussion of local realities on the ground in a given community and how that would influence who receives vaccine was explored. Hotspot analysis was also discussed, but the challenges of the storage and shipping of the leading vaccines make it difficult to see how they could be very helpful in hotspot settings. National guidance with local flexibility could be stated as a theme of the discussion.

There will be a 3-day ACIP meeting in October, with a full day devoted to COVID-19 vaccines. No vote will be held on COVID-19 recommendations, though.