DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Advisory Committee on Immunization Practices (ACIP)

Summary Report
July 29, 2020
Atlanta, Georgia

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Agenda

FINAL - July 29, 2020

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)
Centers for Disease Control and Prevention
Atlanta, Georgia 30329
July 29, 2020

	AGENDA ITEM	PRESIDER/PRESENTER(s)
Wednesday, July 29		
10:00	**Welcome & Introductions**	Dr. José Romero (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary, CDC)
10:25	**Agency Updates** CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, OIDP	
10:55 (65)	**Coronavirus Disease 2019 (COVID-19) Vaccines**	
	Introduction	Dr. Beth Bell (ACIP, WG Chair)
	Overview of COVID-19 vaccine clinical trials	Dr. Julie Ledgerwood (NIAID)
	COVID-19 vaccine safety considerations	Dr. Kathryn Edwards (Vanderbilt University)
12:00	***Lunch***	
12:30 (50)	Considerations for FDA licensure vs. Emergency Use Authorization of COVID-19 vaccines	Dr. Doran Fink (FDA)
	Considerations for vaccine implementation	Dr. Nancy Messonnier (CDC/NCIRD)
1:20	***Break***	
1:30 (80)	Epidemiology of COVID-19 in essential workers, including healthcare personnel	Dr. Sara Oliver (CDC/NCIRD)
	COVID-19 vaccine prioritization: work group considerations	Dr. Sarah Mbaeyi (CDC/NCIRD)
	Evidence to Recommendations framework and Work Group next steps	Dr. Kathleen Dooling (CDC/NCIRD)
2:50	***Break***	
3:00	**Public Comment**	
4:00	**Adjourn**	

Acronyms

CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
COVID-19	Coronavirus disease 2019
DoD	Department of Defense
DVA	Department of Veterans Affairs
EtR	Evidence to Recommendations Framework
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
NCHHSTP	National Center for HIV, Hepatitis, STD and TB Prevention [of CDC/OID]
NCIRD	National Center for Immunization & Respiratory Diseases [of CDC/OID]
NCEZID	National Center for Emerging and Zoonotic Diseases [of CDC/OID]
NIAID	National Institute of Allergy and Infectious Diseases
OIDP	Office of Infectious Disease and HIV/AIDS Policy
SAGE	Strategic Advisory Group of Experts
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WG	Work Group
WHO	World Health Organization
VE	Vaccine Effectiveness

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
Action Plan	National Viral Hepatitis Action Plan
AE	Adverse Event
AFM	Acute Flaccid Myelitis
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
ANA	American Nurses Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
ASTHO	Association of State and Territorial Health Officers
ATS	American Thoracic Society
BARDA	Biomedical Advanced Research and Development Authority
BLA	Biologics License Application
BLS	Bureau of Labor Statistics
CARES Act	Coronavirus Aid, Relief, and Economic Security Act
CCN	Community Care Network
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CICP	Countermeasures Injury Compensation Program
CISA	Clinical Immunization Safety Assessment
CKD	Chronic Kidney Disease
CMS	Center for Medicare and Medicaid Services
COI	Conflict of Interest
CONUS	Continental United States
COPD	Chronic Obstructive Pulmonary Disease
COU	Clinical Operations Unit
COVID-19	Coronavirus Disease 2019
CoVPN	COVID-19 Prevention Network
CRO	Contract Research Organization
CSTE	Council of State and Territorial Epidemiologists
DFO	Designated Federal Official
DHA	Defense Health Agency
DHS	Department of Homeland Security
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs

ED	Emergency Department
EIS	Epidemic Intelligence Service
ELISA	Enzyme-Linked Immunosorbent Assay
EMT	Emergency Medical Technicians
ET	Eastern Time
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FRN	Federal Register Notice
FY	Fiscal Year
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HCoVs	Human Coronaviruses
HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers
HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
ICU	Intensive Care Unit
ID	Intradermal
IDSA	Infectious Disease Society of America
Ig	Immunoglobulin
IHS	Indian Health Service
IIS	Immunization Information Systems
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
ISO	Immunization Safety Office
IT	Information Technology
JCVI	Joint Committee on Vaccination and Immunisation
LAIV	Live Attenuated Influenza Vaccine
LTCF	Long-Term Care Facilities
ME	Medical Examiner
MenACWY	Meningococcal Conjugate Vaccine
MHD	Milwaukee Health Department
MERS	Middle East Respiratory Syndrome
MIS-C	Multisystem Inflammatory Syndrome in Children
MMWR	*Morbidity and Mortality Weekly Report*
mRNA-1273	Messenger Ribonucleic Acid-1273
NAAT	Nucleic Acid Amplification Test
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAIP	National Adult Immunization Plan
NAM	National Academy of Medicine
NAP	National Action Plan
NAPNAP	National Association of Pediatric Nurse Practitioners

NAS	National Academy of Sciences
NASEM or the National Academies	National Academies of Sciences, Engineering, and Medicine
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
NEJM	*New England Journal of Medicine*
NFID	National Foundation for Infectious Diseases
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIP	National Immunization Program
NMA	National Medical Association
NPI	Non-Pharmaceutical Intervention
NPRM	Notice of Proposed Rulemaking
NVSN	New Vaccine Surveillance Network
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
NYC	New York City
OID	Office of Infectious Disease
OIDP	Office of Infectious Disease Policy and HIV/AIDS
OWS	Operation Warp Speed
PAIVED	Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD
PCP	Primary Care Practitioner
PCR	Polymerase Chain Reaction
PHAC	Public Health Agency Canada
PHEIC	Public Health Emergency of International Concern
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PI	Principal Investigator
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PPE	Personal Protective Equipment
PRNT	Plaque Reduction Neutralization Test
Project COVERED	Evaluation of Risk in Emergency Departments
RCT	Randomized Controlled Trial
RN	Registered Nurse
RNA	Ribonucleic Acid
ROA	Route of Administration
RR	Relative Risk
rRT-PCR	Real-Time Reverse Transcription Polymerase Chain Reaction
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization
SAHM	Society for Adolescent Health and Medicine

SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SCR	Seroconversion Rate
SHEA	Society for Healthcare Epidemiology of America
SIRVA	Shoulder Injury Related to Vaccine Administration
SME	Subject Matter Expert
STI Plan	National Strategic Plan for Sexually Transmitted Infections
TA	Technical Assistance
UK	United Kingdom
US	United States
USG	US Government
USPHS	US Public Health Service
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFC	Vaccines For Children
VICP	Vaccine Injury Compensation Program
VRBPAC	Vaccines and Related Biological Products Advisory Committee Meeting
VSD	Vaccine Safety Datalink
WG	Work Group
WHO	World Health Organization

Call To Order, Welcome, Overview, Announcements, & Introductions

Call To Order, Welcome, Overview, Announcements, & Introductions

José Romero, MD, FAAP
ACIP Chair

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Romero called to order the July 29, 2020 virtual Advisory Committee on Immunization Practices (ACIP) meeting. He thanked everyone for taking time out of their busy schedules to participate and for working with the Centers for Disease Control and Prevention (CDC) and ACIP on this virtual meeting.

Dr. Cohn extended her welcome to those present, reminding everyone that this was an emergency meeting called to discuss only the issue of Coronavirus Disease 2019 (COVID-19) vaccines that, in addition to being virtual, did not coincide with ACIP's regular schedule. She noted that the slides to be presented during this meeting were made available through a ShareFile link for ACIP voting, liaison, and *ex-officio* members and for members of the public on the ACIP website at the following URL, which would be taken down at 5:00 PM following the end of the meeting and eventually would be replaced with a 508-compliant version:

https://www.cdc.gov/vaccines/acip/meetings/slides-2020-07.html

The 508-compliant slides presented during this meeting will be posted on the ACIP website approximately 4 weeks after the meeting. The live webcast videos also will be posted in about 4 weeks following the meeting, and the meeting minutes are posted to the ACIP website generally within about 120 days following the meeting.

In terms of meeting logistics, participants were instructed to raise their hands virtually when Dr. Romero opened the floor for discussion and to keep their video off to reduce problems with the Zoom format. Dr. Cohn explained that during the discussion period, the order in which Dr. Romero would take questions would be first from ACIP Voting Members, second from *Ex Officio* and Liaison member representatives, and then from the audience. The plan was to stay on schedule with the meeting agenda even if they were running early.

The next regularly scheduled ACIP meeting will be convened at CDC or virtually on October 28-29, 2020. Additionally, two virtual meetings have been added to the ACIP calendar that are tentatively scheduled for August 26, 2020 and September 22, 2020. These will likely be scheduled for 10:00 AM to 4:00 PM Eastern Time (ET). Registration for these meetings is not required as they are virtual meetings. The link to the live virtual meeting can be found on the website the day of the meeting.

Dr. Cohn emphasized that ACIP is, at its heart, a public body. Engagement with the public and transparency in ACIP's processes is vital to the Committee's work. As part of ACIP's commitment to continuous improvement, ACIP has strengthened its oral and written public comment process to accommodate increased public interest in ACIP's work, maximize opportunities for comment, and make public comment more transparent and efficient. She announced that for this meeting, one oral public comment period would be held during the first afternoon at approximately 3:00 PM. Because there are typically more people wishing to make public comments than there is time during meetings, people interested in making an oral comment were asked to submit a request online in advance of the meeting via the ACIP website. If more people request to speak than can be accommodated, a blind lottery is conducted to determine who will be the speakers. Speakers selected for this meeting were notified in advance of the meeting. Written public comments may be made via regulations.gov using the docket number ID CDC-2020-0081. Information on the written public comment process, including information about how to make a public comment, can be found on the ACIP website.

As noted in the ACIP Policies and Procedures manual, members of the ACIP agree to forgo participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise while serving on the committee, CDC has issued limited conflict of interest (COI) waivers. Members who conduct vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to these vaccines, but are prohibited from participating in committee votes on issues related to these vaccines. Regarding other vaccines of the concerned company, a member may participate in discussions with the provision that he/she abstains on all votes. Dr. Cohn indicated that for this meeting, no particular vaccine products would be discussed. However, ACIP members were requested to indicate any COIs related to a company that has a vaccine under development for COVID-19. Given that specific products would not be discussed, no members were to be excluded from the discussion.

Dr. Romero conducted a roll call of ACIP members, during which the following COIs were declared:

- Dr. Robert Atmar is serving as the Co-Director of the Clinical Operations Unit (COU) of the National Institutes of Health (NIH)-funded Infectious Diseases Clinical Research Consortium (IDCRC) that is working within the COVID-19 Prevention Network (CoVPN) to evaluate Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) vaccine candidates in Phase 3 clinical trials, including those produced by Moderna and Astra Zeneca.

- Dr. Sharon Frey will be conducting multiple vaccine trials through the NIH CoVPN. The two trials that she is currently aware of are for Moderna and Janssen products.

- Dr. Paul Hunter owns a small amount of stock in Pfizer and has received a small amount of funding for a Pfizer-funded quality improvement project.

- Dr. Pablo Sánchez receives funding from Merck for research focused on global antibiotic use.

Dr. Romero requested that the Liaison and *Ex Officio* members introduce themselves. A list of Members, *Ex Officio* Members, and Liaison Representatives is included in the appendixes at the end of the full minutes for the July 2020 ACIP meeting.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Messonnier presented the CDC agency update. To follow-up from discussions during the last ACIP meeting regarding routine vaccination, there continue to be signs of improvement in pediatric vaccine ordering and uptake. This is not consistent across the whole country and there are still several states that seem to be lagging behind, but month-by-month families are beginning to return to their pediatricians for well-child check-ups and routine vaccinations. That is encouraging news and hopefully everyone will continue working together to keep up that momentum. Regarding influenza, the agency is busily preparing for influenza season. While they certainly hope that social distancing will lead to a mild influenza season, everyone needs to be prepared for a potentially severe influenza season. Influenza on top of COVID-19 certainly would be devastating this Fall. CDC hopes that everyone will continue to work with them to strongly advocate for all patients to get their influenza vaccines. The agency is working on a number of expanded efforts this year with a variety of partners, including health departments, to broaden their reach and to specifically target activities toward those at higher risk for COVID-19 and those with traditionally lower influenza vaccination coverage such as long-term care facility (LTCF) residents, LTCF staff, and communities of color. While COVID-19 is obviously in the front of everyone's minds, it also is important to be aware that the time is nearing when acute flaccid myelitis (AFM) cases normally would be seen. There has been an every-other-year cycle, so 2020 has been anticipated to be a year in which a lot of cases would be seen. The impact that social distancing may have is unknown, but hopefully it will result in less cases. Early recognition of AFM is key. CDC and its partners will launch a variety of activities, including a *Vital*signs™ in the *Morbidity and Mortality Weekly Report* (*MMWR*) to get the word out to frontline clinicians and parents about what symptoms to look for so that cases can be rapidly identified and reported to health department and clinical networks so that children identified to have AFM receive the best care possible.

Department of Defense (DoD)

Dr. Deussing conveyed the DoD's appreciation to ACIP and CDC for continued inclusion of the DoD in this meeting and the ACIP working groups. As mentioned during the February 2020 ACIP meeting, the DoD is interested in the use of Food and Drug Administration (FDA)-approved Southern Hemisphere influenza vaccine. This program began in May 2020 and this vaccine is now required for all Active Duty, Select Reserve Component, and National Guard members and is recommended for all of their beneficiaries who are permanently or temporarily assigned to an areas designated as a Southern Hemisphere influenza zone by the World Health Organization (WHO). Their assignment must be in this zone for at least 14 contiguous days during the period of 1 April through 30 September. The Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED) is beginning its third research year for the 2020-2021 influenza season. The DoD also is working toward approval of an evaluation of the Bavarian Nordic smallpox and monkeypox vaccine for cardiac safety, interaction with other

common readiness vaccines, and optimum booster interval. With respect to COVID-19, the DoD plans to participate in Investigational New Drug (IND) studies of SARS-CoV-2 vaccine candidates with a start date pending. As a result of the COVID-19 pandemic, there has been a noted decrease in children beneficiaries receiving scheduled immunizations on time. This is similar to what has been described in the broader civilian population as Dr. Messonnier mentioned earlier. In response, the DoD developed resources on providing immunization during the COVID-19 pandemic, as well as options to provide immunizations outside of military treatment facilities.

Department of Veterans Affairs (DVA)

Ms. Lori Hoffman-Hogg reported that the DVA developed and released a new national decision support tool, or clinical reminder, for influenza immunization on July 20, 2020. Use of this national immunization reminder is required for all Defense Health Agency (DHA) sites in order to ensure uniform documentation and data capture across the enterprise. In addition, VA updated the national clinical reminder for meningococcal B vaccine to align with the ACIP recommendations for booster doses. VA is preparing for the 2020-2021 seasonal influenza campaign. These preparations include the development of a national toolkit to support VA facilities in standing up drive-through influenza clinics and promotion of Community Care Network (CCN) sites where veterans can obtain no-cost influenza vaccine at retail pharmacies and urgent care centers. VA ordered more than 2.8 million doses of influenza vaccine for the 2020-2021 season, which is an 8% increase over last season, with 50% of the initial supply arriving at VA facilities by September 15, 2020. This report is submitted on behalf of Dr. Jane Kim, Chief Consultant for Preventive Medicine in the DHA National Center for Health Promotion and Disease Prevention, United States (US) DVA.

Food and Drug Administration (FDA)

Dr. Fink reported that FDA continues to work around the clock seemingly at times to review and facilitate development programs for numerous vaccine candidates intended for prevention of COVID-19 and/or SARS-CoV-2 infection. These include candidates such as those that are still in pre-clinical development to several that have recently entered into Phase 3 studies in the US. There are no licensure actions to report since the last ACIP meeting in June 2020. At the end of June 2020, FDA released new guidance for industry titled, "Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry." This guidance provides information on the data in terms of manufacturing, non-clinical information, and clinical information that would be needed to support the development of COVID-19 vaccine candidates at various phases of development; post-licensure safety; diagnostic and serological assays; and additional considerations related to licensure and other mechanisms to make the vaccine available such as Emergency Use Authorization (EUA). Dr. Fink indicated that he would say more about licensure and EUA during his presentation later in the day.

Health Resources and Services Administration (HRSA)

Dr. Rubin reported that as of July 1, 2020 in this fiscal year (FY), petitioners have filed 843 claims with the National Vaccine Injury Compensation Program (VICP) and $180 million was awarded to petitioners and attorneys for fees and costs. As of July 20, 2020, HRSA had a backlog of 922 claims alleging vaccine injury that are awaiting review. More data about the program can be obtained on the HRSA website. On July 20, 2020, the Notice of Proposed

Rulemaking (NPRM) proposing to remove Shoulder Injury Related to Vaccine Administration (SIRVA) and syncope from the Vaccine Injury Table was published in the Federal Register. As a result of the publication of this NPRM, the public is able to submit comments on or before January 12, 2021. Also, a public hearing will be held to allow the public to present comments. Information about this public hearing will be forthcoming and will be announced in the Federal Register. As of July 1, 2020, the Countermeasures Injury Compensation Program (CICP) has compensated 40 claims totaling $5.7 million.

Indian Health Service (IHS)

Dr. Weiser reported that the Incident Command System/Emergency Operations Center ICS/EOC remain activated at all levels of the agency. IHS and CDC are finalizing an agreement for IHS for COVID-19 vaccine adverse event (AE) monitoring. IHS appreciates CDC reaching out to make this happen. Members of Operation Warp Speed (OWS) have recently reached out to IHS to ensure appropriate inclusion of American Indian/Alaska Native (AI/AN) populations in vaccine distribution planning, and those discussions are ongoing. A preliminary review of national immunization coverage reported to the IHS National Immunization Reporting System demonstrates fairly stable coverage for 2-year-olds who are up-to-date overall in most areas. Receipt of measles-containing vaccines for 2-year-olds also has been preserved. The battle against COVID-19 continues with over 30,000 positive tests so far in IHS. The largest number of cases to date have been reported in the Southwest and Oklahoma areas. To data, IHS has conducted almost a half a million tests. IHS continues to coordinate with states, CDC, Federal Emergency Management Agency (FEMA), and other partners in responding to the pandemic.

National Institutes of Health (NIH)

Dr. Beigel reported that on Monday, July 27, 2020, the National Institute of Allergy and Infectious Diseases (NIAID) announced the Phase 3 clinical trail for the vaccine against SARS-CoV-2. The vaccine is called Messenger Ribonucleic Acid-1273 (mRNA-1273) and it is a combination of a lot of work even before COVID-19 started plus rapid implementation of the Phase 1, Phase 2, and now the Phase 3 studies. Phase 3 involves multiple US government agencies and the company, Moderna, to get this 30,000 participant study implemented. He indicated that more updates would be provided in the afternoon and that the remainder of NIH's updates would be submitted in written format.

Office of Infectious Disease Policy and HIV/AIDS (OIDP)

Dr. Kim indicated that the National Vaccine Advisory Committee (NVAC) met on June 9, 2020 with an agenda that centered on the COVID-19 pandemic. The discussion included vaccine development, insurance coverage under the Coronavirus Aid, Relief, and Economic Security (CARES) Act, and efforts to promote routine childhood immunization during the pandemic. The work on recommendations for vaccine confidence and immunization equity continues for NVAC. The subcommittees will submit their reports by February 2021. The next NVAC meeting is scheduled for September 23-24, 2020. Work is in progress on the National Vaccine Plan (NVP) for 2020-2025. Although some of the work was disrupted by the COVID-19 pandemic, the intent is to release the NVP in December 2020. Updates were provided during the February 2020 ACIP meeting on the National Strategic Plan for Sexually Transmitted Infections (STI Plan) and the National Viral Hepatitis Action Plan (Action Plan). The intent is to develop strategies for Hepatitis A and B and human papillomavirus (HPV) vaccination and to integrated issues such

as stigma, disparities, and social inequities. These plans are scheduled for release in late Fall 2020.

Update: Presentation to the National Academy of Medicine (NAM)

José Romero, MD, FAAP
ACIP Chair
Chief Medical Officer
Arkansas Department of Health

Dr. Romero provided an update on comments he was requested to present during the Open Session of the July 24, 2020 meeting of the National Academies of Sciences, Engineering, and Medicine (NASEM or the National Academies) Committee on Equitable Allocation of Vaccines for the Novel Coronavirus. He presented a brief history of the ACIP, the mechanism by which ACIP arrives at its recommendations, the structure of the ACIP, the topics ACIP has covered with regard to COVID-19 vaccines, and previous and future meeting dates. There was a brief discussion afterwards, during which there was certainly a sense of collegiality and cooperation between the two groups. Dr. Art Reingold suggested that perhaps members of the ACIP and the Committee on Equitable Allocation of Vaccines for the Novel Coronavirus could appoint members to sit on each other's committees. While it is not known whether this will go forward, it was clearly a meeting of cooperative interaction.

Coronavirus Disease 2019 (COVID-19) Vaccines

Introduction

Beth Bell, MD, MPH
ACIP, COVID-19 Vaccine WG Chair
Clinical Professor, Department of Global Health
School of Public Health, University of Washington

Dr. Bell indicated that there are over 200 COVID-19 vaccines currently under development, including three in clinical trials in the US. The ACIP is responding to this ongoing pandemic and accelerated vaccine development through scheduling of monthly emergency ACIP meetings. As a reminder, during the June 24, 2020 meeting, ACIP reviewed the following:

- ❑ An overview of the COVID-19 Vaccine Workgroup (WG) and Terms of Reference
- ❑ SARS-CoV-2 disease, immunology, and epidemiology
- ❑ COVID-19 vaccine development and the vaccine landscape
- ❑ Considerations pertaining to COVID-19 vaccine prioritization

The COVID-19 Vaccine WG is now meeting weekly. During the July 2020 meeting, the COVID-19 Vaccine WG:

- ❑ Reviewed published Phase I clinical trial results
- ❑ Considered safety issues regarding COVID-19 vaccines (the COVID-19 Vaccine WG has a Technical Subgroup that is Chaired by Dr. Grace Lee, which is specifically focused on safety issues)
- ❑ Reviewed regulatory mechanisms for the deployment of COVID-19 vaccines with the help of the FDA liaison
- ❑ Received epidemiology updates, including focusing on COVID-19 in healthcare personnel (HCP)
- ❑ Continued consideration of COVID-19 vaccine prioritization
- ❑ Continued to work to fill in the Evidence to Recommendations (EtR) framework to guide COVID-19 vaccine policy

The agenda for the July 29, 2020 ACIP meeting included presentations on the following topic areas:

- ❑ Overview of COVID-19 Vaccine Clinical Trials
- ❑ COVID-19 Vaccine Safety Considerations
- ❑ Considerations for FDA Licensure vs. Emergency Use Authorization (EUA) of COVID-19 Vaccines
- ❑ Considerations for Vaccine Implementation
- ❑ Epidemiology of COVID-19 in Essential Workers, Including HCP
- ❑ COVID-19 Vaccine Prioritization: WG Considerations
- ❑ EtR Recommendations Framework and WG Next Steps

The WG is reviewing considerations for vaccine prioritization in specific groups using a phased approach, and spent quite a lot of time in July assessing essential workers and HCP. Plans are currently underway to review persons at increased risk for severe COVID-19 disease (e.g., older adults, persons with underlying conditions, racial/ethnic minority groups). There is a collection of specific background and evidence that will be examined for this group. The WG will focus on the general population thereafter. As mentioned earlier, the focus of this session would be on essential workers, including HCP. Prioritization considerations for other groups will be reviewed at upcoming ACIP meetings.

They just heard a little from Dr. Romero about NASEM's Committee on Equitable Allocation of Vaccine for the Novel Coronavirus, which is co-sponsored by the NIH and CDC and meant to inform the decisions of health authorities, including the ACIP by developing an overarching framework to assist policymakers in the US and global health communities in planning for equitable allocation of vaccines against COVID-19. The Committee is charged with addressing the following questions, which essentially focus on equity:

- ❑ What criteria should be used in setting priorities for equitable allocation of vaccine?
- ❑ How should the criteria be applied in determining the first tier of vaccine recipients?
- ❑ How can countries ensure equity in allocation of COVID-19 vaccines?
- ❑ For the US, how can communities of color be assured access to vaccination?
- ❑ What steps should be taken to mitigate vaccine hesitancy, especially among high-priority populations?

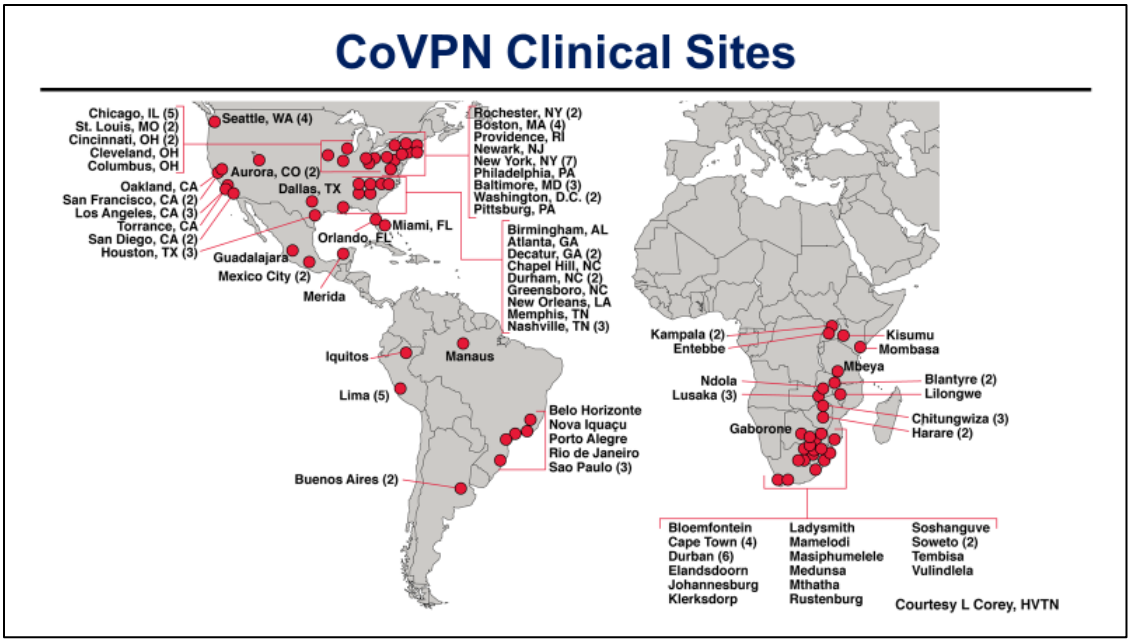
Operation Warp Speed (OWS): Overview of COVID-19 Vaccine Clinical Trials

Julie Ledgerwood, DO
Deputy Director & Chief Medical Officer
Vaccine Research Center
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Dr. Ledgerwood noted that she was presenting during this session as part of the OWS Team, indicated that she would provide an update on the efficacy of trial efforts, and expressed appreciation for the invitation. In May 2020, Drs. Corey, Mascola, Fauci, and Collins published a plan, or vision really, of the public-private partnership to accelerate the evaluation of primarily Department of Health and Human Services (HHS)-funded vaccine candidates, with an end goal of accelerating licensure and, therefore, availability of the vaccines. This plan has served as the blueprint for the ongoing and upcoming OWS trials.

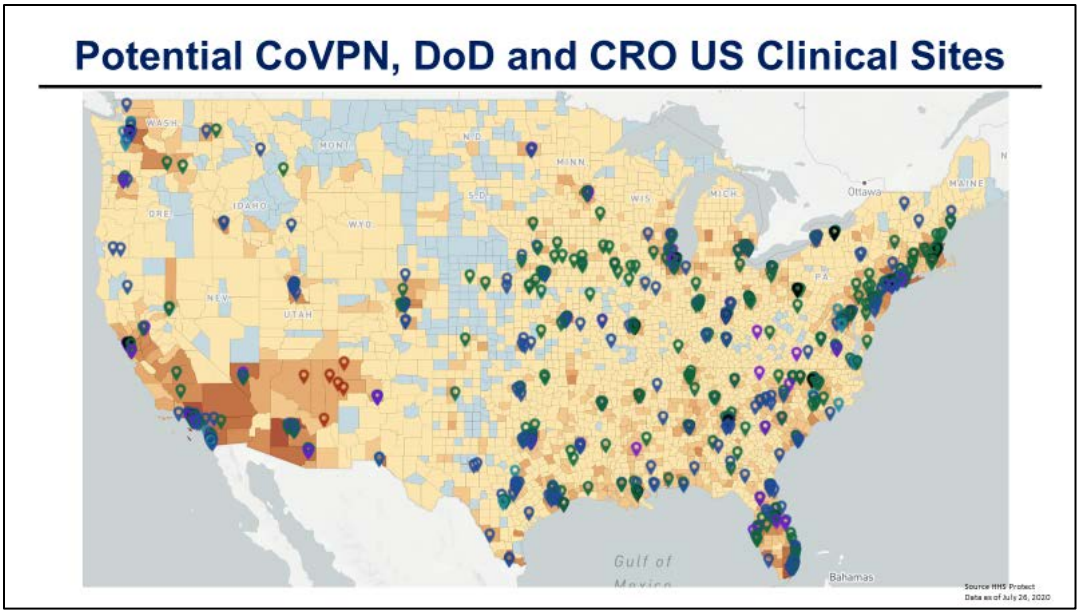
Among the entities launched by the US Government (USG) to combat COVID-19, OWS was established in May 2020. OWS is a multi-agency, or all of government, USG effort being conducted in collaboration with the private sector to provide COVID-19 vaccine, therapeutic, and diagnostic development. The effort is led by Dr. Moncef Slaoui and General Gustave F. Perna. Vaccine leadership includes Drs. Anthony Fauci, Francis Collins, and John Mascola from the NIH and Dr. Matt Hepburn (Maj Gen, USAF Ret) from the DoD. Many hundreds of team members are involved as well.

Within OWS, the Vaccine Development Team supports pre-clinical testing, clinical development, safety monitoring, manufacturing, immune assays, and distribution and access. The funding of these trials is largely through the Biomedical Advanced Research and Development Authority (BARDA) and NIH funding. NIH established the public-private partnership for coordinating the COVID-19 response known as Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV). The idea for ACTIV came primarily from Dr. Collins and was established early in the outbreak to bring together top scientists, manufacturers, and others to coordinate the medical countermeasures. The COVID-19 Prevention Network (CoVPN) was formed by the NIAID at NIH to respond to the global pandemic by using the infectious disease expertise of almost all of the existing NIH research networks that had experience conducting this type of research throughout the country and the world. These groups under the CoVPN are now charged with helping to plan and execute large-scale USG-funded trials The vaccine efforts within the CoVPN are led by Drs. Larry Corey and Kathy Neuzil and their teams. A snapshot of the CoVPN clinical sites throughout the world is shown here:



Multiple networks emerged to implement these trials and these have been supplemented with groups from the DoD, including the VA, from academia, and from private or contract research organization (CRO)-managed sites. That combination has led to an expansive network of site options where many trials with large numbers of subjects are being launched this year. For example, the CoVPN now includes about 117 US sites, which is an increase from about 50 sites just a little over a month ago. The sites are also accommodating the growing needs of these upcoming trials. Many have increased their floor space, members of staff, and added mobile or temporary units to accommodate the trial or adhere to any social distancing requirements in place or necessary where they are. Importantly, as these trials are seeking to enroll volunteers from diverse populations, including minority populations at higher risk of COVID-19, the OWS, NIH, DoD, and the CoVPN teams; the vaccine developers; and the sites are implementing impressive recruitment and community outreach efforts to reach these populations. Internationally, the CoVPN has about 189 sites to offer to the OWS efficacy trial efforts. Many of those are shown on the above map. Some of the trials will occur in the Continental US (CONUS) and some will occur in the CONUS with additional international site involvement.

For any given trial, the CoVPN sites are being heavily augmented by private or contracted CRO sites. The team broadly has identified almost 900 potential sites that could be activated using a variety of contracting mechanisms through various companies to enroll large multi-site efficacy trials. Potential sites as of July 26, 2020 shown here:



Sites continue to be added to this list, with a particular focus on counties in the country that are being hardest hit by the outbreak to ensure that those area are especially engaged in these efficacy trial efforts for multiple reasons.

To address the basis of these efforts to serve the US population and enable rapid vaccine development, a series of underlying principles was formulated. These are derived largely from the publication in May 2020, but have been expanded over the last months. These are referred to as “Semi-Independent Harmonized Trials.” Multiple vaccine candidates are being tested in this way. Specifically, what that means is that the FDA regulatory or Investigational New Drug (IND) sponsorship is with the vaccine developer or company. Because of this tremendous responsibility, the OWS leadership has been designating teams of experts within the USG to assist each of the public partners or vaccine developers in the planning and execution of the trials. Part of that is largely from the CoVPN.

Enshrined in that principle the common elements applied to all trials are use of common endpoints; use of collaborating networks, such as CoVPN; use of common, validated immune assays among collaborating laboratories to ensure consistency and high-quality virologic and immunologic readouts among the trials; use of a common DSMB stood up by NIAID for all OWS vaccine trials, which have the charge to oversee with a strict eye for safety and efficacy; and a between-trial immune and statistical analysis of correlates of protection to enable critical understanding about vaccine responses and protection incurred from a vaccine or multiple vaccines. Of note, a DSMB is a body of experts integrated to oversee the study. They already have been involved ahead of trial launches and during trial design. They will have access to unblinded safety and efficacy data throughout the trial, and will evaluate the interim data for safety and efficacy at multiple timepoints during the study.

The FDA played a large role in the effort to harmonize trial design. In June 2020, the FDA published, "Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry." In that publication is very clear guidance for trial design and implementation that is being adhered to by the OWS vaccine teams and developers. This has offered a great deal of insight into the FDA's requirements. All of this is in an effort to advance development of vaccines more rapidly for the public.

Six of the OWS Phase 3 efficacy trial principles that are being used to design the efficacy trials in a consistent manner include the following:

- ❑ The trials are randomized and placebo-controlled with efficacy endpoints
- ❑ While the sample size of each trial varies, it is approximately 30,000 volunteers for testing one vaccine
- ❑ Study populations at this time are set to be adults ≥18 years of age, targeting a subset of individuals who are at high-risk of both disease and severe disease and making an effort to enroll diverse populations
- ❑ The primary endpoint is prevention of symptomatic COVID-19 disease, which is virologically confirmed by polymerase chain reaction (PCR)
- ❑ The primary efficacy endpoint point-estimate is at least 50% as defined by the FDA guidance document
- ❑ The statistical success criterion should be the lower bound of the confidence interval (CI) >30%
- ❑ The use of harmonized OWS-directed immunogenicity assays and correlates analysis plan
- ❑ Use of a common DSMB that is NIAID-managed and will work with all of these trials as an independent body to oversee safety and efficacy

Although BARDA supports multiple groups in the development of COVID-19 medical countermeasure development, among those groups there are 4 products for which OWS is working toward launching efficacy trials this year. The first is the Moderna mRNA vaccine. That trial was launched on July 27, 2020. Moderna will enroll that trial of about 30,000 participants at 89 sites in the US. Additionally, AstraZeneca is developing product with OWS based on an adenoviral (Ad) vector. While that trial will occur in 2020, the projected start date has not yet been identified. The Janssen Ad vector vaccine trial also will start this year, ideally in September. Novavax has a recombinant protein with adjuvant vaccine, which OWS is protecting to begin in October 2020.

About 4 months after the Phase 1 trial launch, Moderna launched their efficacy trial on July 27, 2020. As mentioned earlier, this trial aims to enroll 30,000 subjects at approximately 89 US sites. This trial is now fully activated and more details are available on clinicaltrials.gov. Dr. Ledgerwood encouraged everyone to seek accurate information about trials from that site. As each trial is approved and launched, that information will be presented there as well.

With multiple large efficacy trials to occur and launch within a timeframe of just a few months, OWS knew that a lot of public engagement would be required. The CoVPN and NIAID established a website that was recently stood up to describe some of these efforts and to engage the public with basic information in a way that a large group of people could understand what is occurring. This site is: coronavirusprevention network.org. Within that website, an opportunity has been embedded for people who are interested in trials to link to an Institutional Review Board (IRB)-approved, volunteer, click to consent registry where people can indicate

their interest in a vaccine trial in general. They provide their information and assess their risk using a series of questions that were pre-determined to have some validity in assessing risk. In just the first 20 days of the website launch, there were over 4 million views of the website as of July 28, 2020. Over 200,000 potential participants have registered their personal information, information about their risks, and their willingness to be contacted by a site for potential enrollment into a clinical trial. This has been augmented with nationwide broad and local community outreach engagement activities by OWS, DoD, NIH, and the individual vaccine developers and their CROs and sites. The key to success will be the recruitment of volunteers who have risk of disease among very diverse populations. The outbreak has hit many minority populations in hard ways, so it is important to engage them to be fully active in these trials as they proceed. This trial site map shows broad US coverage:

A concerted effort was made to have sites represent multiple areas of the country. Some areas are obvious in that they are metropolitan and known to have active outbreaks or be in the view of experts of being at risk of having outbreaks. Others are in more rural areas but have the potential to have outbreaks for various reasons. Sites have been established broadly in an effort to find a large, diverse population at risk for disease.

Discussion Points

Dr. Romero asked whether there are data on the ethnicity and race of the individuals who have demonstrated interest in participating in vaccine trials through the registry portal, and whether information is available in the registry portal in languages other than English.

Dr. Ledgerwood indicated that the site was initially launched with a soft launch ahead of most of the community engagement efforts. A large group of the people who have registered are not minorities, but there has been a fairly robust minority response. The data are still being calculated for the week. Parameters are being established with the registry host, Oracle, to be able to look at the demographic data, population information, and risk level in a more robust way in the coming weeks. Therefore, it is somewhat early to be able to indicate the specifics on that. The ongoing community engagement efforts over the next 2 weeks are anticipated to have a major impact on the diversity of the registry population. An impressive effort is being undertaken. The registry site is fairly general at this point, because it was launched ahead of any trial openings. The site is actively being translated into Spanish. In the coming days and as

specific trials become active, information about those will be highlighted in the registry website as well.

Dr. Kimberlin (AAP Red Book) said that he and others have heard about the possibility of challenge studies for testing vaccines, though not recently. He asked Dr. Ledgerwood to comment whether that is under consideration.

Dr. Ledgerwood indicated that there was a lot of discussion about that and there were some publications regarding those deliberations. OWS's efforts are targeted at traditional efficacy trials, though others in the group could comment on disposition of the challenge studies.

Dr. Lee asked whether there would be ongoing information posted on the website about who is registered so that they can continue to assess risk and the diversity of the populations enrolled, with location as a proxy, to get an understanding of where disease activity might be highest. Also, it would be great to hear more about the nationwide community engagement efforts already being undertaken, and whether there are opportunities to sustain that as vaccine is being distributed in order to continue to understand and learn how to optimally work with communities in ways that get vaccine where it is needed.

Dr. Ledgerwood indicated that she would take the question about posting demographics back to the team. She did not think there was a plan to post that information publicly, but they are certainly tracking it. As of now, the 200,000 registrants are from all over the country. Obviously, the metropolitan areas have large numbers associated with them. However, there is no part of the country where there are no registrants seeking information about the trials. The efforts for community engagement are led by Dr. Nelson Michael from DoD, Dr. Jim Kublin from the CoVPN, and Dr. Hilary Marston from NIAID have taken a great deal of responsibility in the area of community engagement. It is a great idea to try to link what they are doing with eventual success in distribution of vaccination. She asked whether ACIP would like to talk to one of them in the coming month or two about what they are doing.

Dr. Messonnier indicated that CDC is already linked into that effort, and she agreed completely with Dr. Lee's thoughts. Several CDC staff are on those WGs looking at community engagement and specifically looking to make sure that community engagement seamlessly transitions into the future phases of vaccination. CDC can certainly provide an update about that, but as a general principle, she would say that CDC is well-linked.

Dr. Bell asked what information Dr. Ledgerwood could provide to ACIP about at least the other BARDA-sponsored vaccine development programs that are not under the umbrella of OWS in terms of their plans for clinical trials, use of the same sites, sense of their general strategies, whether they are using similar study designs even though they are not under the umbrella of the harmonized vaccine trial design, et cetera.

Dr. Ledgerwood said they recognize that there are many other groups being funded under BARDA for various components of their work. She noted that because she is completely locked in essentially fulltime on this effort with these 4 companies, she is probably not the best source of information about other efforts. The FDA guidance on trial design is pretty clear and OWS is following it to the letter. Most, if not all companies in the US, would be doing that.

COVID-19 Vaccine Safety Considerations

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Dr. Edwards indicated that she is the Principal Investigator (PI) of the CDC-funded Clinical Immunization Safety Assessment (CISA) Project, and that the findings and conclusions in this presentation are hers and do not represent the official position of CDC. During this presentation, she discussed COVID-19 vaccine safety considerations in terms of previous vaccine enhanced disease to explain what is known and what they want to prevent; animal vaccines for SARS; animal models for SARS-2 (e.g., challenge/rechallenge studies and chimp, adenovirus vaccine); and vaccine studies in humans (chimp adenovirus vaccine and 2 mRNA vaccines).

Respiratory syncytial virus (RSV) was isolated in the late 1950s. At that time, it was felt that perhaps an RSV vaccine could be made in the same way that influenza vaccine had been made by formalin inactivation of the whole virus. In the 1960s, there was a large clinical trial that administered RSV formalin inactivated whole virus vaccine to infants. In this study, infants were given 3 injections and antibody responses were measured by both complement fixation (CF) and neutralizing antibody (NA). Dr. Edwards focused on NA because only a small percentage of the infants who received the 3 injections actually developed NA.

The mean fold rise of that NA titer compared with natural infection after recovery from the virus was much lower. Those children were followed very closely for the next 2 years. When the RS lot 100 (formalin inactivated RSV vaccine) was compared to Para 1 lot 23 (formalin inactivate parainfluenza vaccine), the number of hospitalizations of the children who were vaccinated was actually larger than those who received Para 1 lot 23 and more importantly, 80% of those children who were vaccinated were hospitalized and 2 children died [Hyun Wha Kim, Jose G. Canchola, Carl D. Brandt, et al, Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine, *American Journal of Epidemiology*, Volume 89, Issue 4, April 1969, Pages 422–434, https://doi.org/10.1093/oxfordjournals.aje.a120955].

In terms of the autopsy findings of the 2 children who died compared to the controlled, a deposition of antibody and complement was seen in the actual airways. This suggests that there was an immune-mediated problem that was not seen in the control individuals. In addition, eosinophils were noted in the lung tissue quite prominently in Patients 1 and 2 [The *Journal of Experimental* Medicine; Volume 196, Number 6, September 16, 2002 859–865].

Over the intervening 3 decades, a lot of information has been acquired to understand what happened in the immune-mediated pathologic reaction that occurred. As depicted in the following illustration in the upper left corner, crystallography shows that the virus has binding sites that are very important for neutralization of the virus. The red and orange are at the tip of the virus that the individual would see when infected with the virus:

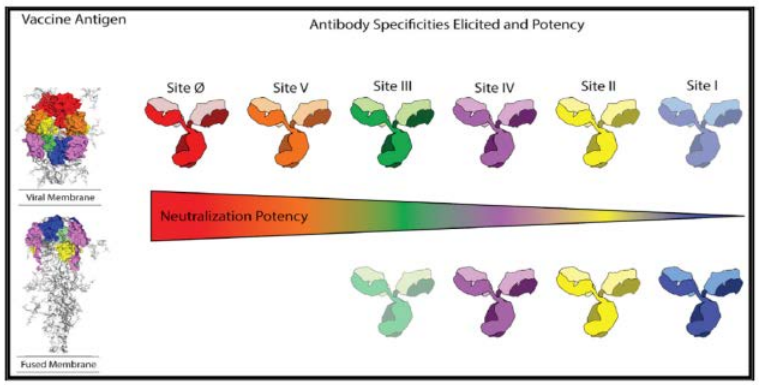

Figure 3. Antigenic Site-Specific Antibodies Elicited by Pre-F or Post-F Antigens
Pre-F elicits antibodies to all the antigenic sites that have been identified on the F protein. While post-F elicits antibodies to antigenic sites I, II, III, and IV, which can sometimes recognize shared surfaces on the pre-F structure, it does not display sites Ø and V, which have been shown to elicit antibodies with high neutralizing activity. Antibodies targeting site I show preference for post-F and tend to have low neutralizing activity, while those that target site III show preference for pre-F and have relatively potent neutralizing activity.

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In contrast, the crystal structure of the fused membrane on the lower left is what occurs when there is formalin inactivation of the virus such that the epitopes shown in red and orange are really gone and now there are purple and blue. The function of the neutralization of the purple and the blue is much less, suggesting that it is necessary to understand the structure of the virus and not destroy it when the vaccine is made.

Another adverse event (AE) with vaccines was shown several years ago with the dengue vaccine. In a trial by Sridhar et al in 2018, the actual serostatus of the vaccine was examined in terms of the efficacy of the vaccine. In terms of the risk of hospitalization for virologically confirmed dengue (VCD) and of severe VCD in children 2 to 4 years of age, children who were seropositive from natural virus before they were immunized were boosted and protected against disease. In contrast, the dengue vaccine was not as functional in neutralizing the virus in children who were seronegative prior to vaccination and those children had worse outcomes than those who were not vaccinated. That is, the control children did better than the vaccination seronegative children in terms of dengue disease [Sridhar et al, Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy, *N Engl J Med* 2018; 379:327-340; DOI: 10.1056/NEJMoa1800820, July 26, 2018].

In terms of how to put these findings into context, in an article titled “Rapid COVID-19 Vaccine Development: Finding the fastest pathway to vaccine availability includes the avoidance of safety pitfalls,” that appeared in 2020 in *Science* by Dr. Graham does a nice job of explaining this. Regarding enhanced disease that is antibody-mediated, through dengue it has been shown that antibody-dependent enhancement (ADE) increases the amount of virus into the cells if antibody is not directed to the neutralizing epitope. As with RSV, vaccine-induced respiratory disease also can occur as a function of antibody and also T-cells. The mechanisms are Fc-mediated increase in viral entry that is seen with dengue or immune complex formation with complement deposition as seen with RSV. The T-cell response in those situations with enhanced respiratory disease is T_H2-biased immune response. The effectors are macrophage activation inflammatory cytokines and complement activation inflammatory cytokines. The mitigation or prevention of those vaccine-enhanced diseases would be administering vaccines that are conformationally correct and the generation of high-quality neutralizing antibody. The T-

cell responses to mitigate against these AEs are T_H1-biasing immunization with strong CD8+ T-cell responses.

Turning to what is known about vaccines and coronavirus, a consensus meeting was convened in mid-March that was sponsored by the Coalition for Epidemic Preparedness Initiative (CEPI) and the Brighton Collaboration (BC). This meeting included two 5-hour sessions during which the experts who had conducted vaccines studies with coronaviruses presented information and discussed the actual data that were available. They assessed the models of enhanced disease in vaccine studies after SARS-CoV-1 vaccines, all of which were animal models. Most were Murine and a couple were non-human primates (NHP). A number of the studies included Alum adjuvants, which often primes for a T_H2 response, and all of them were associated with immunopathology. One of the studies assessed was by Dr. Ralph S. Baric, who is a leader in coronavirus research. Baric et al inactivated a whole SARS-CoV-1 virus, administered it to mice, and then challenged the mice with SARS-CoV-1. This study found that the lung titer of the immunized was clearly less than it was in the control. In addition, eosinophils were seen in the slides of the tissue. This is reminiscent of the RSV-enhanced disease. Again, this documented that the antibody did have a functional activity in decreasing viruses, but immunopathology was noted.

The CEPI/Brighton Collaboration Consensus Meeting had a number of conclusions. One is that they considered that demonstration of some immune enhancement with any vaccine candidate after a viral challenge in animal models should not necessarily represent a no-go signal for deciding whether to progress in clinical development. But continuous monitoring of this risk during clinical trials in an epidemic context will be needed, and that each observed effect should be discussed by the developers with their regulators who will ultimately define the actual requirements for clinical studies. They wholeheartedly endorsed the mitigation strategy of functional neutralizing antibody and a T^H1 response [[1]Lambert, et al (2020). Consensus summary report for CEPI/BC March 12–13, 2020 meeting: Assessment of risk of disease enhancement with COVID-19 vaccines. Vaccine. 38. 10.1016/j.vaccine.2020.05.064].
Shortly after the identification of the SARS-CoV-2 virus, a number of NHP studies were conducted. One of the first that appeared in *Science* by Rockx et al (May 2020) showed that if the SARS-CoV-2 virus is given to NHP, there is an infection. The infection in old primates is greater than in young primates, which may be somewhat reflective of what is observed in humans. A lot of virus is present in the lung, suggesting that this is a really nice model to assess vaccines and vaccine challenges to see whether there might be enhanced pathology. In terms of pathologic findings in the lung after the NHP challenge, pneumonia was demonstrated, there was edema in the lungs, and there was virus in the lung tissue and the ciliated epithelial cells. This again confirms that this was a really good model showing that pulmonary pathology could be assessed.

Several studies followed that examined whether this actual SARS infection protected against re-challenge in NHP. Group 1 got 10^6 of virus, Group 2 got 10^5, and Group 3 got 10^4. Neutralizing antibody and T_H1 responses were seen after the initial infection, which suggests and reassures that the type of antibody and T-cell responses desired were present with natural infection. In the actual challenge of the NHP who were infected, by and large, no virus at all was detected in the bronchoalveolar lavage (BAL) on re-challenge. Some virus was detected initially in the nose as in the nasal swab, suggesting again that in this natural infection, when the animals were re-challenged, they were protected from lung disease and increased virus in the nose. Pathologic

findings in these animals did not indicate any kind of eosinophilic infiltrate, which might be seen if there was a pathologic response.

In a study in which vaccines being used in humans now were studied in non-human primates, the chimp adenovirus produced by Oxford (ChAdOx1 nCoV-19 or the AstraZeneca vaccine) was used to vaccinate rhesus macaques. The enzyme-linked immunosorbent assay (ELISA) antibody titers after the inoculation were robust with the chimp adenovirus vaccine. The neutralizing titer, functional antibody, was very good. The ability to generate the T_H1 response in the chimp adenovirus recipients also was robust. This was a 1-dose vaccine that showed that both humoral and cellular immune responses were generated. When the animals were challenged, some clinical symptoms were seen. However, they were markedly less and in terms of the BAL fluids, there were few copies of the virus in the lungs. There was some virus in the lungs and nose in the ChAdOx1 nCoV-19 group, but that rapidly decreased and was largely gone by 5 to 7 days.

On July 28, 2020, a beautiful paper was published in the *New England Journal of Medicine* (*NEJM*) that discussed the immunization with the Moderna mRNA vaccine and the challenge with natural disease. This study showed very much the same kind of information, which is reassuring in terms of the ability of the vaccine to prevent pulmonary disease and a neutralizing T_H1 immune response. The histologic pictures of the control animals who were not given vaccine compared to the immunized animals show again that there was no infiltrate, no immune deposition, and no eosinophilia noted in these animals. This provides additional reassurance that the immune response is appropriate.

Moving to vaccine studies in humans, there have been reports of 3 Phase 1 vaccine trials in the past 2 weeks that are very reassuring. In terms of the safety of the vaccine, the chimp adenovirus study that appeared in *The Lancet* showed that with the single dose that was given in this study, there was some pain and tenderness in the local injection sites and a number of these individuals needed to take paracetamol for those symptoms. This suggests that there was local reaction. It was also apparent that there was generation of a good antibody response. This vaccine study had a control, the meningococcal conjugate vaccine (MenACWY). No antibody was generated to SARS-2 with the MenACWY vaccine. Within 14 days after vaccination, recipients of the single dose had a very good immune response. Among the recipients, 10 individuals got a boost of the vaccine and again showed that that ELISA antibody was very good and was comparable to what was seen in individuals who were convalescent from natural COVID-19 infections. The study also showed that immune responses were generated. There were Interferon-γ ELISpot responses, which is consistent with the T_H1 response being seen in both the prime recipients as early as 14 days and in the 10 prime boost individuals who received 2 doses of vaccine. This again suggests that this vaccine, as in the NHP, generated a functional antibody response and a T_H1 T-cell response [Folegatti et al, Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial; Open Access Published:July 20, 2020; DOI: https://doi.org/10.1016/S0140-6736(20)31604-4].

A study by Jackson et al published in the *NEJM* enrolled a total of 45 participants, with 15 participants in each of the following dosing groups: 25µg, 100µg, or 250µg. The participants who participated in the study were largely Caucasian (40/45; 89%) with a mean age of 30 to 35 years. As seen with the chimp adenovirus, mild and moderate local and systemic responses were seen after the first dose. After the second dose, more severe local and systemic responses were seen in only those individuals who received the highest dose. Again, this suggests that there are some local and mild responses such as fever, headache, et cetera. However, there were no symptoms or complaints of any kind of respiratory issues that might been seen if there was enhanced disease. In a functional neutralizing assay in which the sera of the individuals were actually taken into the laboratory and neutralized with wild-type coronavirus, the neutralizing titers were very high in the lower and higher dose. This suggests again that the vaccine was generating neutralizing and T_H1 types of responses [Jackson, et al; *N Engl J Med*; An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. 2020 Jul 14;NEJMoa2022483. doi: 10.1056/NEJMoa2022483. Online ahead of print].

A Phase 1/2 Pfizer study of a COVID-19 RNA vaccine candidate (BNT162b1) included a total of 45 individuals, comprised of 12 individuals in each dosing group and 9 in the placebo group (10µg, 30µg, or 100µg). The local reactions after Dose 1 and Dose 2 are reminiscent of those seen in the earlier studies. The systemic reactions of pain, headache, and others also were consistent with what was seen before. However, there were no Grade 4 reactions. Immune responses were assessed in receptor binding domain (RBD) assays. Interestingly, almost all of the doses at 10µg, 30µg, and 100µg gave really robust binding functional antibody compared with human convalescent sera. This suggests that robust functional neutralizing antibody was present [Mulligan et al; Phase 1/2 Study to Describe the Safety and Immunogenicity of a COVID-19 RNA Vaccine Candidate (BNT162b1) in Adults 18 to 55 Years of Age: Interim Report; medRxiv preprint doi: https://doi.org/10.1101/2020.06.30.20142570].

In order to attenuate or alleviate risks, Dr. Edwards emphasized the importance of thinking about the correct antigens, high-quality neutralizing antibody, and T_H1-biasing immunization and CD8+ T-cells. It is also important to ensure that there are standardized, comprehensive safety assessments of local and systemic reactions. There has been a concerted effort to standardize those, certainly in the NIH-funded studies. There is a commonality in the other studies as well. Biomarkers of vaccine-enhanced disease must be measured, including: ratios of neutralizing versus non-neutralizing antibodies (shown to be so important in RSV disease), antibody isotypes and affinities, proinflammatory cytokine levels, and polarity of T-cell responses.

Dr. Edwards conclusions are that an effective vaccine likely will be achieved with at least one of the vaccine approaches. The data available from the 3 initial Phase 1 studies are very encouraging for all 3 vaccines. Vaccine safety will be meticulously assessed in terms of examining the mechanisms. At each level of study, the DSMBs are meticulously evaluating all of the reactions that are seen. If enhanced disease or an indication of that occurs, it will be carefully assessed and the immune mechanisms that might be involved will be investigated. A safe and effective vaccine that is widely available likely would induce herd immunity, and herd immunity to SARS 2 would allow normal activities to resume.

Discussion Points

Dr. Atmar asked whether Dr. Edwards could speculate on the differences that have been seen between what she showed with the SARS-1 coronavirus vaccine efforts in animal models and the data that are available for the constructs that have been reported for SARS-CoV-2. He observed that all of the trials she discussed showed some immunopathology with the SARS-1 vaccines in various formats, but that has not been seen or reported to his knowledge with the SARS-CoV-2 candidates yet.

Dr. Edwards confirmed that this was correct and that it is important to note a couple of things. One is that a number of the studies were in mice. One of the discussion points that was made was that indeed these mouse models can be somewhat difficult and sometimes there can be the development of emerging components to parts of media and some of the other issues in terms of that. Also, the experts in coronavirus felt that in general there was gradation, but certainly the adverse responses in animal models were seen more commonly with SARS-1 than with Middle East Respiratory Syndrome (MERS). Whether that was a function of advances in terms of the animal studies is hard to know. Those kinds of AEs have not been seen in the animal models of SARS-2. Another thing that probably is important to note is that there are some other SARS-1 studies that were conducted in humans, such as a couple of DNA studies that did not induce any kind of adverse human response. Obviously, the numbers were small. There also have been some MERS vaccine candidates, including an mRNA MERS vaccine candidate that has been examined in animals. That does not appear to be associated with the signal. Whether it is a function of the time the studies were conducted or their methodology was not quite as rigid, and whether it was a function of mice being studied and not humans is unclear. This certainly cannot be dismissed, but Dr. Edwards emphasized that what she would like people to hear is that this is not being dismissed. Investigators, such as those in the consortium, are digging down to try to determine what all of this information reveals.

Dr. Bell asked Dr. Edwards to reflect on the issue of detection of these AEs, expected timing of AEs, potential difficulties in identify AEs—understanding that there have been some efforts to standardize case definitions, and what her feelings are about detecting a serious adverse event (SAE) if it were to occur.

Dr. Edwards acknowledged that these are hard questions, but there is work underway in the Brighton Collaboration to identify and characterize AEs. That will include appropriate experts to help determine what might be expected. There also will be an active effort by the DSMBs that will be examining each AE as Phase 2 and Phase 3 studies are rolled out. Each AE will be carefully considered by the DSMBs that are independent of the investigators and manufacturers, and that there will be a clear understanding of what the background rate for these AEs is in the population. For instance, if the background rate in the population is 1 in 1000 but is 1 in 10 in the study population, that certainly would be a concern that will be characterized. There also will need to be a characterization of the severity of diseases seen. The NIH has spent a fair amount of time in their studies thinking about how to characterize disease after it occurs. If there are individuals among vaccine recipients who acquire COVID-19 who have severe disease, it is important to understand why. There will be an ability in those individuals to assess cytokines and immune mechanisms, which will be very important. Certainly, the Immunization Safety Office (ISO) at CDC is thinking about how to respond to questions once a vaccine is licensed. The FDA also has been thinking carefully about how they are going to look at large databases for symptoms. Everyone is working hard and with great

care to ensure that if there is a signal, it will be investigated meticulously pre- and post-licensure.

Dr. Sanchez emphasized that the inflammatory changes seen with re-challenge are of major concern. He asked whether any of the individuals enrolled in the 3 vaccine trials thus far have developed severe disease requiring hospitalization, and whether any have been infected naturally. He also noted that the highest risk groups are among the elderly and wondered what the age groups would be for the planned Phase 3 trials, pointing out that it is known that individuals above 55 to 60 years of age may not respond immunologically to other vaccines. Also, an adolescent study in Korea showed that there is was potential for being vectors among children 10 years of age and older.

Dr. Edwards indicated that to her knowledge, no cases have been reported in these recipients or any SAEs requiring hospitalization. If there is an SAE, the studies likely would be halted. Each of the studies has specific halting criteria. In terms of older adults, each of the Phase 3 trials recruited older individuals. However, the timeframe to report the younger group was very tight so those were reported. Most of the studies indicate that they are interim reports. Older individuals were included in the Phase 1 trials for all of the vaccine candidates. She has not seen the published data about immune responses in the various ages. Immune responses to natural disease are fascinating in that it seems like the oldest individuals have antibody responses that are higher than in the youngest individuals. Protocols are being designed for the use of vaccines in children and pregnant women through the NIH and probably from the other companies.

Dr. Fink (FDA) added that as outlined in the FDA guidance released at the end of June, FDA's expectation is that in order to advance clinical development to include individuals at greater risk of more severe COVID-19 and to advance clinical trials to very large numbers of subjects with medical comorbidities to Phase 3 trials, safety and immunogenicity data will be required that is specific for age subgroups, including elderly subgroups to support the potential for vaccine effectiveness and vaccine-associated disease.

Dr. Bernstein asked whether there are any theoretical safety concerns for individuals who receive a COVID-19 vaccine subsequent to having received an influenza vaccine.

Dr. Edwards does not believe there are any theoretical concerns that there would be interference. However, the individuals participating in the Phase 3 trials with all of the companies will not be permitted to get the influenza vaccine simultaneously with the experimental vaccine. With all trials, receipt of the experimental vaccine and influenza vaccine would have to be separated by 14 days for inactivated influenza vaccine (IIV) or 1 month for live attenuated influenza vaccine (LAIV). She does believe everyone will be encouraged to get their influenza vaccine, but these will not be given concurrently. Dr. Edwards applauded FDA's wonderful guidance document, which will be helpful for everyone moving forward.

Dr. O'Leary said it was his understanding the seronegative individuals are being enrolled in these trials, and he wondered what Dr. Edwards' thoughts were on the implications for that once the vaccines are rolled out into the larger population in terms of whether people will need an antibody test before being vaccinated. Somewhat related, he asked for her thoughts on the potential for a vaccine in children to trigger or not multisystem inflammatory syndrome in children (MIS-C), given the level of uncertainty pertaining to that condition. His concern with MIS-C is that the immune trigger is unknown, which could be the vaccine.

Dr. Edwards responded that there is no serological screening in the studies and there will be no screening in the Phase 3 trials. This would be too difficult with 30,000 people. There are blood draws before and after the vaccine is given. Since the vaccines are primarily spike protein-related, there are other parts of the virus that could be used to serologically prove whether people are infected. It also would be possible before vaccine receipt to look at antibody responses. She has not heard that any of the participants enrolled already were seropositive, but perhaps some were. It would be interesting to see how the vaccine performs in someone who was seropositive before receipt. If it is like the challenge boost seen in the chimp adenovirus, there probably would be a big boost. There is no evidence to suggest that there would be an enhanced problem with that. Obviously, the pediatric studies will be done in a very careful way. The start time for those will be a function of the findings in the Phase 3 adult studies when there is a larger safety database. It also will be important to assess the burden of disease in each population. The risk/benefit of a pediatric vaccine may be greater for teenagers than children 2 to 5 years of age. If enhanced disease is seen, she would hope they would be able to dissect what is occurring with that. She also hopes that the understanding of MIS-C can be greatly enhanced. The fact that a lot of the COVID-19 disease looks somewhat immunologically mediated is also a concern, so she thinks they have to proceed very carefully. Obviously, more research is needed with MIS-C to understand what kind of response is triggered.

Dr. Sanchez asked how Dr. Edwards envisions the vaccine being utilized among immunocompromised patients, if consideration should be given to monoclonal antibodies, and what the plans are for these groups.

Dr. Edwards agreed that this is an important question. There has been discussion about human immunodeficiency virus (HIV)-infected people and whether they can participate in Phase 3 trials if their viral loads are controlled, but she did not know whether that had been determined yet. It may be that certain vaccines work better for certain individuals, and there may need to be an adjuvant for individuals whose immune responses are not sufficient. There is a lot of excitement about and effort going into monoclonal antibodies. At this point, monoclonal antibodies will be studied in terms of people who have been exposed or in nursing home recipients. This seems to be a great group of people who are immunocompromised to participate in some of those studies as well.

Considerations for FDA Licensure vs. EUA of COVID-19 Vaccines

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Dr. Fink noted that to make sure everybody is on the same page in terms of expectations for licensure of COVID-19 preventive vaccines, the applicable statutes and regulations that FDA has to follow require a demonstration of vaccine safety, effectiveness, and controlled and consistent manufacturing to ensure continued safety and effectiveness of the licensed vaccine.

At this time, given the epidemiology of COVID-19 and its trajectory, the FDA expects that at least the first COVID-19 vaccines to be licensed if successful will be licensed under the FDA's "Traditional" approval pathway. Under this pathway, the FDA expects that substantial evidence of effectiveness required to support licensure would be demonstrated in clinical disease endpoint efficacy trials that directly show that the vaccine prevents either COVID-19 disease and/or SARS-CoV-2 infection.

There are other FDA licensure pathways that are applicable in certain situations. These are the "Accelerated" and "Animal Rule" licensure pathways. However, at this time, these alternative licensure pathways would not apply to COVID-19 vaccines, given sufficient COVID-19 incidence to allow for clinical disease endpoint efficacy trials and the limited and evolving understanding of SARS-CoV-2 immunology and immune response biomarkers that might predict protection against COVID-19. Because of these two current conditions, the criteria for these alternative licensure pathways would not be satisfied at this time.

The FDA has received a lot of questions and has heard a lot in the press about what level of vaccine efficacy will be necessary to support licensure of a COVID-19 preventive vaccine. Certainly, demonstrating efficacy is necessary and critical, but in and of itself is not sufficient to support the licensure application. One reason is that a large efficacy trial conducted in areas of high disease activity, such as have been initiated in the US, could rapidly accrue enough cases to achieve the specified efficacy success criterion before additional data that are important to inform benefit risk considerations for review of the licensure application are available. These data could include, among other things, longer term safety data as well as data to support the manufacturing processes, facilities, product characterization, and demonstration of lot-to-lot consistency. Related to the licensure requirement, there needs to be controlled and consistent manufacturing to ensure that vaccine produced in the future will continue to be as safe and as effective as the vaccine that was studied in the trials to provide data to support licensure.

Additionally, the licensure review process takes some time. This is because it must address a number of statutory and regulatory requirements for approval. The licensure review process involves review of complex clinical, non-clinical, and manufacturing data. Review of the data does not involve just review of clinical study reports and the applicant's assessments of the data. It also involves review of the datasets themselves to ensure that there are no issues with data integrity, and to ensure that FDA scientists and statisticians can replicate the results of the key analyses that the applicant has submitted to support licensure. As part of this review process, the FDA often engages in back and forth exchanges with the applicant that include

information requests and meetings to resolve issues and questions that come up. There are inspections of facilities and clinical trial sites to ensure adherence to good clinical trial and manufacturing practices. There is often a safety update with longer term safety data. Sometimes, all of the safety data that are submitted to a licensure application are available at the time the application is submitted. But sometimes, there are additional safety data coming in during the review. Almost certainly that would be the case with COVID-19 vaccines. The review process also includes negotiations with the applicant for a pharmacovigilance plan to continue evaluating vaccine safety after licensure. Additionally, the FDA and applicant need to agree on plans to satisfy pediatric study requirements. The ongoing studies for COVID-19 vaccines that have reached later stage development do not yet include pediatrics subjects. The FDA must have a clear idea of when pediatric subjects will undergo participation in vaccine studies and which age groups will be appropriate to study.

Finally, and certainly not least important for new vaccines, the FDA often convenes an external scientific advisory committee called the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to get their input on the data available to support licensure. This process is critical to ensure transparency in FDA decision-making processes. Certainly, there is a need for transparency for regulatory decisions related to COVID-19 vaccines. The downside of convening this committee is that it requires a lot of work, both on the part of the FDA and the applicant. These are the same staff and personnel who are participating in the review. Looking at all of these activities in aggregate, the usual timeframe for licensure review is on the order of 12 months for a standard review or 8 months for a priority review or expedited review. Certainly, there are things that can be done to be flexible within this review process to have information submitted ahead of a licensure application to pre-position the review team to conduct a more expedited review that can be done to cut down on this review clock time. Even with maximal adjustments to speed up a review, it would be very difficult to imagine a licensure application review process that lasts only a few weeks or even a month. Dr. Fink emphasized that they must be realistic in their expectations of how long the license review process will take.

There are other regulatory mechanisms for making vaccines available that do not involve licensure. One of these, the one that is perhaps most pertinent to addressing the COVID-19 pandemic in the US, is the FDA's authority to grant an EUA. EUAs are authorized under a set of qualifying criteria that are outlined in the FDA guidance document and also reflected in the FDA regulations and general law. The qualifying criteria are first of all a declaration by the HHS Secretary of an emergency situation leading to serious or life-threatening disease or condition. That certainly is happening now. But, there has to be evidence of effectiveness for the product intended to address the emergency. As noted earlier, the standard for licensure is substantial evidence of effectiveness. The EUA standard is worded differently. For EUA, it has to be determined that a product "may be effective." The FDA has flexibility in interpreting that standard and it relates to FDA determining whether the known and potential benefits of the product outweigh the known and potential risks of the product; and the intended use of the product, including the number of individuals to be treated under the EUA and uncertainties in the risks and benefits.

For instance, in the case of a drug being authorized to treat individuals with severe COVID-19 disease that has a very well-characterized safety profile based on extensive experience either pre-licensure or post-licensure for a different indication, the effective standard could be lower than the standard required to support licensure. However, in the case of a vaccine that is intended to be used in tens to hundreds of millions of individuals who are not infected at the

time they are vaccinated, limited safety data are available for that vaccine, and there are additional uncertainties and risks, the effective standard would be much closer to the type of evidence that the FDA would require to support our licensure of the vaccine. The final criterion to quality for an EUA is that there has to be no adequate, approved, and available alternative. All of those three words (adequate, approved, and available) are important. Certainly, if there is no licensed COVID-19 preventive vaccine, then that standard is met. If there is a vaccine that has been being used under an EUA that is not approved, the availability of the vaccine does not count against that criterion. Similarly, if there is a licensed vaccine but there is not a sufficient supply of that vaccine to address the emergency situation, that also is not counted against the qualifying criteria.

In terms of how an EUA works, it is requested by an entity outside of FDA. Typically, it is from a government stakeholders (e.g., CDC, BARDA, DoD) or manufacturer. The EUA submission to FDA must include a number of items, such as the specific details of the requested product use under EUA (e.g., population, dose, regimen); supportive safety, effectiveness, and manufacturing information on which the FDA will make its recommendation; and fact sheets to inform patients and fact sheets to inform healthcare providers (HCP) of the conditions of the EUA and the potential risks and benefits of use under the EUA. This list is certainly not exhaustive. All of the requested product use under the EUA must include the specific population, dose, and regimen. Many of the elements that would be reviewed under a license application also will be revised under an EUA request, but the regulations and law allow for a more rapid review of EUA requests as compared to a licensure application. If the FDA does agree to authorize emergency use, this authorization comes with certain conditions. While this is not an exhaustive list, some of the key considerations include monitoring and reporting of adverse events “to the extent practicable;” specification of the duration of the authorization, which can be renewed as necessary or terminated early if the criteria for EUA are no longer met; and other conditions as applicable (e.g., distribution or advertising conditions).

The FDA’s “FDA Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19” released in June 2020 discusses additional considerations. One concern is that issuance of an EUA based on very preliminary safety and efficacy data from randomized controlled trials (RCTs) could reduce the ability to demonstrate effectiveness and assess benefits versus risks of the vaccine to support licensure. There have been questions about whether an EUA could be authorized based on just immunogenicity data or if it could be based on a very early signal of efficacy that just meets statistical significance criteria. The FDA thinking on those questions is that it could not be. More definitive data are needed that are closer to what the FDA would expect to support licensure. One situation in which the FDA thinks that an EUA could be considered is for a vaccine for which there is adequate manufacturing information. In this case, issuance of an EUA may be appropriate once studies have demonstrated the safety and effectiveness of the vaccine but before the manufacturer has submitted and/or FDA has completed its formal review of the Biologics License Application (BLA). Finally, the considerations for EUA authorization are going to be data-driven regardless of the vaccine. Any assessment regarding an EUA would be made on a case-by-case basis considering the target population, characteristics of the product, preclinical and human clinical study data, and the totality of available relevant scientific evidence.

Additional resources include the FDA’s “Guidance for Industry and Other Stakeholders: Emergency Use Authorization of Medical Products and Related Authorities” and the FDA EUA Website.

Discussion Points

Dr. Frey requested more specifics on how OWS and the EUA have affected the rapidity and timing of the review of the Phase 1 and 2 trial data for this very first vaccine for which the Phase 3 study was initiated this week in terms of what specific data was reviewed and how much data there were.

Dr. Fink responded that he did not think that the EUA considerations really play a role in the FDA's review of data to support initiation of Phase 1, Phase 2, or even Phase 3 trials. Those are all geared toward advancing clinical development with the ultimate goal of supporting licensure of COVID-19 vaccines. Based on his understanding, OWS is working to facilitate and de-risk vaccine development by providing funding, and helping to harmonize amongst different vaccine manufacturers. He left it to others involved in OWS to address any more detailed information about their involvement. Needless to say, the FDA's role is entirely independent from OWS. The FDA has been conducting its usual data-driven review process for FDA oversight of clinical development of these vaccine candidates. The standards that the FDA has been using are really not very different from its usual standards for clinical development of preventive vaccines in general. It is just that things have been progressing much more quickly, with seamless and adaptive clinical trial design and review scientists and other staff at FDA working much harder to review much more information in much shorter periods of time. The FDA guidance documents provide more detailed information about the types of non-clinical and clinical data that the FDA expect to see at each stage of development to support advancement to the next stage. The guidance is reflective of and consistent with the types of data that the FDA routinely requires to support development of preventive vaccines.

Dr. Szilagyi inquired about the extent to which the EUA differs in terms of the level of evidence for efficacy and safety for specific age groups. In other words, if the trials shows a significant amount of efficacy and high safety for a broader age group, he wondered to what extent the guidance differs under the EUA for certain major groups such as age, underlying conditions, pregnancy, et cetera.

Dr. Fink said he does not think there is a meaningful difference in terms of age groups or other demographic or medical factors by which the populations might be classified. The difference lies in the standard where the licensure standard is safe and effective, with "effective" meaning substantial evidence of effectiveness. For EUA, the standard is "may be effective" and known and potential benefits outweigh the known and potential risks. He emphasized that for preventive vaccines, the EUA standards in practice are going to be closer to the licensure standard than for some other drug products that have been or would be considered under EUA. For both licensure and EUA, the FDA does consider subpopulations independently. That does not mean that studies have to be adequately powered to meet statistical success criteria for specific subpopulations, but there does need to be sufficient evidence of effectiveness to support use under EUA for all of the populations included.

Dr. Bell expressed gratitude for a very useful, helpful, and informative presentation and for the FDA's guidance and responsiveness to the difficulties ACIP faces. In terms of some of the concerns that already have been raised in general about public confidence, she asked what incentives exist for manufacturers to continue to speed the process of licensure once an EUA a is issued. Her understanding is that, at least theoretically, an EUA could be continued for the extent of an emergency. That is not to say that the manufacturers want to have an EUA

indefinitely, but there are variations in speed of submission and responsiveness to FDA's request and such.

Dr. Fink said that by the time an EUA would be seriously considered for a COVID-19 vaccine, that vaccine likely would be at a place that is very close to being ready for a licensure application in terms of the outstanding data that are still in the clinical development process.

Dr. Atmar said that he was very pleased to see that the FDA has considered what the potential impact on conducting and completing clinical trials could be by issuing an EUA. It was his understanding that for the Phase 3 efficacy studies, the planned follow-up period is a couple of years and at least part of that would be to address some of the concerns that Dr. Edwards spoke about in the morning from a safety standpoint (e.g., dengue vaccine). It could be that later this year or early next year, there may be substantial evidence of effectiveness of one or more of the vaccines being investigated that would occur well before the planned safety follow-up has been completed. Though it may be an unanswerable question, he wondered how one weighs the potential short-term efficacy that is demonstrated versus the unanswered and unknown safety questions that would be answered by a longer follow-up.

Dr. Fink indicated that the FDA has thought about and struggled with that excellent question quite a bit, and that the best answer he could give at this point would be that they will really have to consider the totality of the evidence available at the time that they are considering a licensure action or decision. The totality of evidence will include clinical trial data from Phase 1, Phase 2, and Phase 3 trials; the extent of longer term follow-up data for safety and efficacy that are available from those subjects; the non-clinical data that are available that will help to inform the potential risk of enhanced disease; and immune response biomarkers and animal models, which might include challenge models with longer intervals between vaccinations and challenge to help inform what happens when the antibody titers wane. Decisions will be made for an EUA or licensure based on all of the available data. Certainly, waiting a full year or two years before taking a regulatory action to make a vaccine widely available would really be counterproductive to addressing the current situation.

Dr. Foster (APhA) asked whether ACIP would be permitted to make a recommendation for a vaccine under an EUA that will have implications on people who operate under standing orders.

Dr. Cohn indicated that under the ACIP's Charter, there is a provision that in an emergency situation, the ACIP can issue recommendations under an EUA or other type of approval that is not for licensure.

Consideration for Vaccine Implementation

Nancy Messonnier, MD
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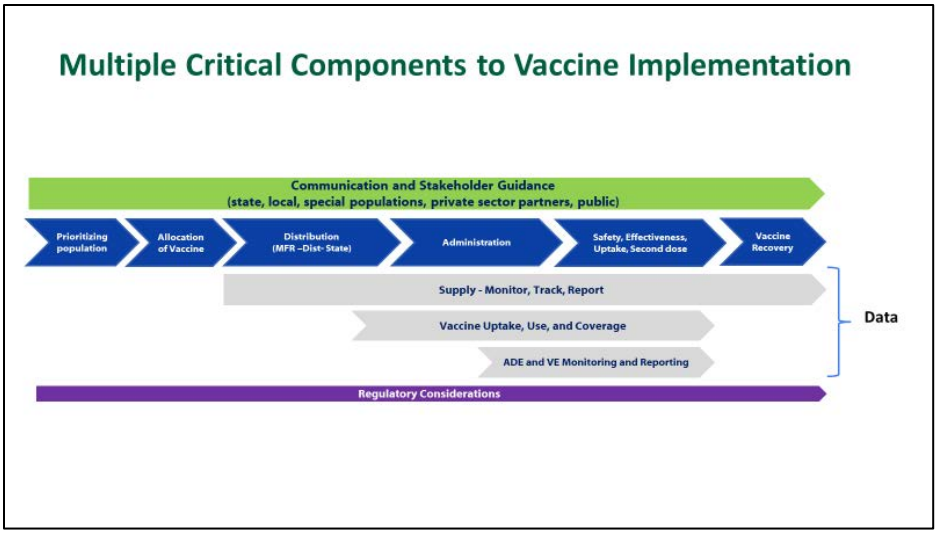
Dr. Messonnier presented considerations for COVID-19 vaccine implementation. She emphasized that the success of this endeavor requires not only safe and effective vaccines, but also a safe and effective vaccine program. As a starting place, an effective vaccine program needs to ensure access and high coverage in all segments of the population. This begins by

appreciating that there are racial and ethnic disparities in current routine immunization coverage, especially in adults. Influenza vaccination coverage in adults ≥18 years of age by race and ethnicity is consistently lower in Blacks and Hispanics. This disparity has existed for a long time, and the current social situation likely exacerbates the issues that surround those lower vaccine coverages. In planning for immunization with COVID-19 vaccine, it is necessary to be more mindful of this as a starting place and to take seriously that novel and more robust strategies are needed to increase uptake of COVID-19 vaccine once it becomes available [Vaccination Coverage among Adults in the United States, National Health Interview Survey, CDC, 2017].

The COVID-19 vaccine landscape is complex and evolving, and all of the answers needed in order to start planning are not going to be available. Even along the way, the landscape is likely to change. Some of these complexities follow:

- There are multiple products, some of which are 1-dose and some of which are 2-dose, and the products are not interchangeable.
- The vaccines have varying presentations.
- Vaccine efficacy and adverse event profiles are different in different populations.
- The cold-chain requirements are different.
- The initial studies are not being done in children and pregnant women. It always has been one of ACIP's principles to want early studies in children and pregnant women and they are not going to have the benefit of that for this vaccine.
- Implementation plans needs to account for socially distanced vaccine practices, adding yet another complexity to program planning.
- Communication and education are always key parts of any of CDC's programs, but for this vaccine in this situation, they understand that that need is greater than ever. Even now, the rumors and misinformation about COVID-19 vaccine are circulating. Certainly, the need to move quickly may lead folks to have incorrect assumptions about cutting corners, which they certainly are not doing.
- Again, the issues around communities of color and the current social situation also will exacerbate these problems. Some high-risk groups for COVID-19 vaccine may distrust public health as a starting point. This has been seen already in some of CDC's early focus groups being conducted to understand attitudes about COVID-19 vaccine.

CDC is aware that they are asking for planning in an incredibly complex environment, yet it is critical to start planning. In fact, many feel that planning is already late and that there is a need to move forward quickly—even given the current environment. This graphic attempts to show all of the different aspects of vaccine implementation and a vaccine program:



While these appear to be in sequence, it clearly does not work that way. Starting in the middle in the blue on the left, CDC greatly appreciates ACIP's work in helping to prioritize populations and the assistance of the National Academies. But it is important to understand that this is going to be an iterative process. As more is understood about the vaccines, it will impact prioritization. That will then impact every other aspect of planning. After prioritization, vaccine will need to be allocated. This involves distributing it from the manufacturer, to a distributor, to a state to administer it. CDC appreciates the importance of gathering additional data on safety and effectiveness, as well as uptake and the need for a second dose. They also understand the importance of planning for vaccine recovery. In gray at the bottom of the graphic are the data requirements.

While the importance of data in any vaccine endeavor are understood, especially for this vaccine CDC believes it is very important to have end-to-end vaccine tracking and dose level accountability. Those data are crucial to allow for flexibility in targeting, allocation, ordering, and vaccine management. Data pertaining to AEs and VE post-licensure are always important, but this is going to be of increased importance for this vaccine, especially as rapidly as it needs to be rolled out. In terms of regulatory considerations, CDC appreciates the FDA's partnership and understands the need to consider how the regulatory requirements impact all of the other components of vaccine implementation. The green bar at the top of the graphic depicts the importance of communication and stakeholder guidance at every level. This is always important in part of everything that CDC handles, but this is of increased importance for this vaccine in the current situation.

One of the unknowns is what quantities of which vaccine with which characteristics is going to be available and when. While having more discrete data would be beneficial, as anybody who is involved in vaccine development knows, there are a lot of uncertainties. CDC is generally planning for the eventuality, that there will be a constrained supply. That may be because there are limited doses or because, although there is more vaccine available, the doses that are released are somewhat constrained. When there is constrained supply, administration will need to be focused on some target populations. In general, ACIP, multiple other countries, and WHO have said that there needs to be some focus on populations where high coverage will be essential to public health. CDC looks forward to continuing dialogue with ACIP about how to

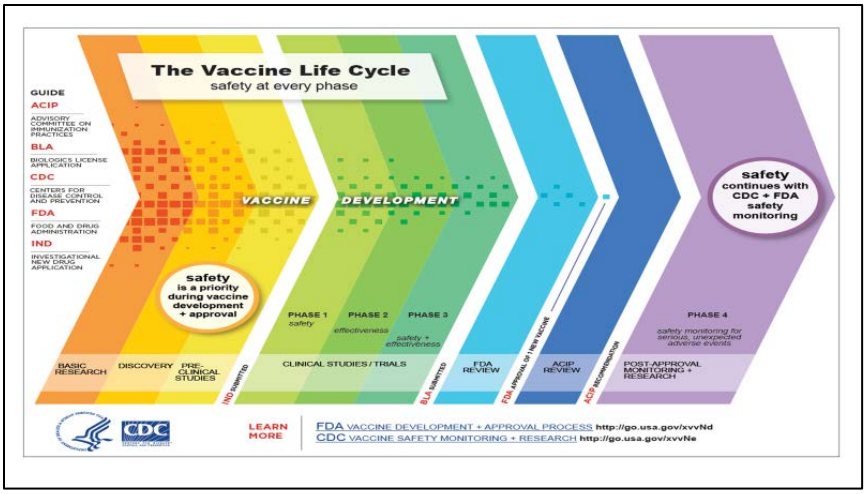
approach this issue. But even when there is maximum vaccine supply available, it will still be necessary to target immunization program efforts. The USG and state and local health departments will need to focus their efforts on the places where, from a public health perspective, they think it is most important. CDC also looks forward to ACIP's guidance about how, when there is greater supply, they would propose that the agency focus its efforts. At the same time, CDC will work to ensure physical and financial access for everybody to this vaccine.

CDC is planning for centralized distribution because they believe that it is the best way to allow full visibility and control, and to be able to shift assets based on the available data to drive vaccine allocation. The agency understands the importance of making sure that ancillary supplies are available. Vaccine will be allocated to jurisdictions as per the normal programs, but in addition, everyone recognizes that this is an unprecedented situation. As a community, they are being asked to do something that they have never done before, which is get vaccine out to the entire population in a very compressed timeline. This will require thinking outside of traditional boxes.

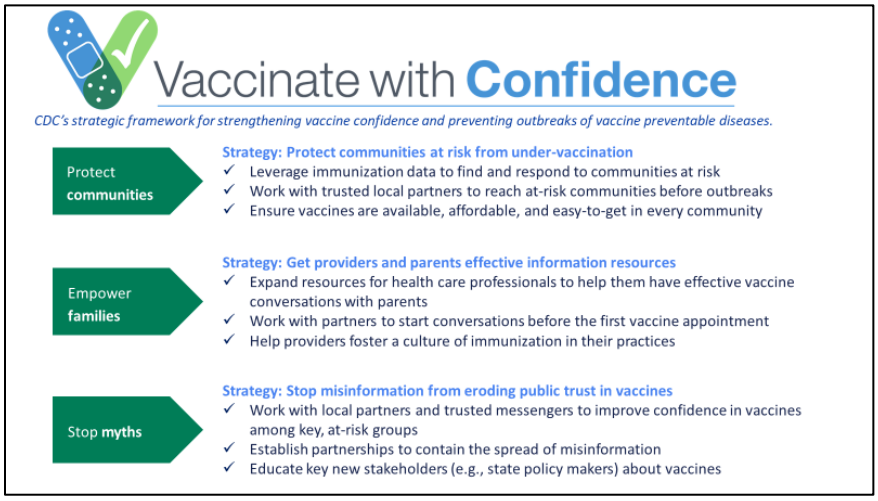
While it will be necessary to rely on routine systems, it also will be necessary to go beyond them. For example, CDC will be planning for allocation to some private partners in order to expand access. Similarly, they will be planning for administration sites in traditional sectors but also believe that they need to be planning for innovative sectors to reach certain target populations. While relying on traditional systems is crucial, it also is important to learn from what has gone right and not right in the past, consider every possible way to make sure that systems are as robust as possible, and be open to many partners that all want to queue up to help CDC figure out how to do an unprecedented thing.

Dr. Messonnier asked that everyone be open to the possibilities of thinking beyond the normal traditional approaches. To distribute and administer COVID vaccines, they must leverage many partners. There are public health experts and assets across all of the federal, state, and local USG that are part of the normal public health infrastructure, but there also are a variety of private partners. CDC works every day with private partners in its routine work. Now they need to expand those partnerships across distribution, administration, and guidance and best practices. CDC will be working with a variety of traditional and new partners in new ways that should result in a more robust COVID-19 vaccination program. Ultimately, this also may result in identification of ways to enhance and expand routine systems.

A key part of all of CDC's programs is always going to be monitoring the safety of vaccines. A key part of what CDC relies upon ACIP to do is continue to review the safety data pre- and post-licensure. The agency recognizes the importance of a highly robust system to monitor safety post-licensure and is working with all of its USG and multiple other partners to build out a plan for how to monitor safety. CDC, FDA, Indian Health Service (IHS), Veteran's Administration (VA), and DoD are just some of the inside government groups. However, CDC also is relying on many of its private partners that are already working with the agency in this space. They recognize the need to build out these systems now in order to be ready when vaccine is licensed, ready, and starts to be used routinely. It is necessary to be able to reassure the American public that they have their eyes on this and will continue to have robust evaluation all along the way. This graphic showcases the different stages of vaccine safety evaluation:



CDC launched a program last year known as Vaccine with Confidence, which is a strategic framework to strengthen vaccine confidence and prevent outbreaks of vaccine-preventable diseases in the US. The idea is that this has to be a "whole of community" enterprise as illustrated here:



The concerns people are voicing about COVID-19 vaccination can be addressed by some of these same principles. The approach needs to be holistic—that it is not just about COVID-19 vaccination. It also is about the public's trust in overall vaccine programs and the people who recommended vaccines. A broad approach is needed to stakeholder engagement in order to ensure that the right information gets to the people who need to know at the time that they need it, and barriers to access to vaccines must be decreased in every community—especially those who already are known to have resistance to vaccination. It is imperative to start now in order to make sure those individuals are ready to accept the vaccine when it becomes available.

There is a long road between now and when the vaccine becomes available. It is going to take all of CDC's partners working together to make sure that they are ready. CDC is highly optimistic about the early data on these vaccines and wants to ensure that the delivery systems are equally ready when the vaccines become available. They do not want there to be any gaps

from the time that the vaccines are recommended by ACIP. Instead, CDC wants to be able to start these programs the next day, which is why they are talking about scaling up now.

Discussion Points

Dr. Hunter said that he is looking at influenza vaccine events this fall as practice for COVID-19 vaccine events later. Traditional mass clinics by local health departments that take place indoors and without social distancing are not necessarily the best model for any mass clinics for influenza or COVID-19 vaccination during the COVID pandemic. Traditionally, these kinds of mass clinics take place at venues away from facilities that have established vaccines or refrigerators, such as in schools rather than next door to pharmacies or clinics. He is part of a community-wide effort in Milwaukee in his role as a medical consultant for the City of Milwaukee Health Department (MHD). And as part of that effort, he is encouraging folks who are starting on pilots already to expand the idea of walk-through or drive-through events that occur outside and adjacent to pharmacies and clinics.

Dr. Messonnier said that one of the concepts CDC has been talking about is the concept of microplanning, which is something that is typically not discussed in the US. Globally, microplanning is utilized when a country is planning for a vaccination campaign, such as for polio or measles. This is much more detailed planning than has traditionally been done in the US—even with influenza vaccines. The agency thinks this is what needs to be done in the COVID-19 situation. There must be much more concrete microplanning with each state and local health department so that they can take into account their local factors to develop creative solutions. CDC is trying to work on some information technology (IT) solutions that would help for example in terms of scheduling clinics, and working with a variety of partners across OWS in terms of creative solutions to how mobile or mass pop-up clinics might be conducted. There are a variety of private partners who have some innovative approaches to this. It is those in the field who are going to have to operationalize this, which is why CDC wants to get past where they are now quickly in order to start that level of planning with every locale. This is a huge challenge and it is going to require a lot of lot of advanced planning and a lot of “boots on the ground.”

Dr. Lee found the graphic depicting the ramp-up to be extremely helpful, intuitive, and useful for ACIP because while they understand that recommendations will drive implementation, they also are cognizant of the fact that implementation is in the EtR framework. Some of those implementation considerations might impact recommendations in different phases. With that in mind, she wondered what the feasibility is of implementation during the ramp-up phase of traditional versus innovative strategies in terms of thinking about the efforts that will be required to distribute vaccines efficiently to as many people as possible.

Dr. Messonnier emphasized that the graphic makes it look like it is simple, but they all know that it will not be like this. There are any number of iterations that one could imagine and plan for. It reminds her of the language that “all models are wrong and some models are useful.” The intent was to show a paradigm to start thinking about it since they cannot know all of the possibilities. In terms of traditional versus innovative, in some ways traditional vaccination in her mind is people going to a doctor’s office to get vaccinated. Some innovative approaches would be, for example, if ACIP recommends a focus on essential workers, partnering with pharmacies to be able to deliver vaccine to essential workers in a way that decreases barriers to access. Many hospitals already do vaccination, but a lot of them probably administer mass vaccinations in mass vaccination availabilities. CDC is working on some IT solutions that would allow folks to

sign up in advance to identify their eligibility and then to schedule a time to get vaccinated. That was perhaps what she was thinking of in terms of innovation. She does not expect that this will be a black-white, either/or approach. For example, there are many complexities with vaccinating people in LTCFs, one of which is the need to go to these facilities. There will be issues related to informed consent or assent to vaccination and complexities in terms of underlying medical conditions that will complicate matters. Some private groups already have the ability to vaccinate in LTCFs, so CDC is considering those groups. Again, many of these private groups are very interested in and willing to do their part. Consideration is being given to how to activate all private and less traditional providers who could be part of the solution.

As a state program planner, Dr. Finley (AIM) acknowledged that many states are actively planning and coordinating with preparedness and their state emergency operation committees to build upon the active structure in place. They are making use of what is available because they already are in an emergency action to develop IT, communications, and other pieces.

Dr. Messonnier said she appreciated that some states and locales are farther ahead. She has had some conversations with state Health Officers who, like sometimes at CDC, are always dealing with the "crisis of the day." Those crises are huge and it is hard sometimes for folks to wall off a team to think about something that in some ways folks feel like is 6 months away. Part of the messaging to local health departments is going to be the importance of starting this planning now. Some states already have embraced that and are actively working on it, which is great. However, plans are needed in every state and locale. The goal always should be to be prepared before the vaccine becomes available.

Dr. Maldonado (AAP) requested additional information about who CDC is engaging with now in terms of focus groups and who the key stakeholders are, particularly in communities of color. It is important to think about other partner organizations and how to engage with them and their constituents to build trust.

Dr. Messonnier said that CDC has its traditional immunization partners. Especially with respect to communities of color, she believes they need to think way "outside the box" in terms of trusted stakeholders. For her, one of the lessons from some of the work that CDC has been doing recently and in thinking about the measles outbreaks about a year ago is that much of this is local. She thinks they need to get past the national, traditional organizations and be much more cognizant of who they need to engage. There must be much broader and deeper stakeholder engagement than already exists. While she feels that they already are behind, this is where we are today and this is the agency's call to action for everyone. It is critical to get moving on stakeholder engagement. Organizing across such a broad and deep set of stakeholders and partners is going to be complicated, and CDC definitely will be looking for advice, input, and help from the traditional partners in immunization.

Dr. Fryhofer (AMA) said that speaking as a private practicing general internist and primary care physician, she appreciates the thinking "outside of the box" about non-traditional ways to distribute and administer vaccination. However, she implored CDC not to leave off the traditional methods of delivery. It is important to remember that physician recommendation is a major motivator of vaccination, especially with this vaccine. The warp speed in which these vaccines are being developed has raised concerns of possible cost-cutting. Right now, especially with this vaccine, physician recommendation is so important in getting patients vaccinated. Therefore, it is imperative for primary care physicians to have access to the vaccine.

Dr. Messonnier wholeheartedly agreed, acknowledging that private physicians are a key part of the routine immunization infrastructure and are key partners in in talking to their patients about immunization. She clarified that when she is talking about some of these non-traditional methods, she did not intend to imply that she meant separated from private providers. Optimally, private providers will be part of some of the innovations. The hope is that local public health will engage private providers in thinking through what the options are such that private providers become major visible stakeholders in implementing some of the non-traditional approaches.

Ms. McNally expressed specific interest in understanding whether, if a vaccine becomes available through traditional FDA approval or an EUA, whether CDC anticipates any changes to the current mechanisms that are in place for safety monitoring.

Dr. Messonnier said that she would not say “changes” but would say “enhancements.” CDC certainly will rely on some of the tried and true systems that the agency uses for monitoring AE, but needs to enhance them in terms of speed, robustness, and penetration of all of the populations who may be getting access to vaccine. Part of the planning for CDC is imagining what groups might get vaccinated first and making sure that especially in those populations, AE monitoring has been built out. Certainly, AEs in those populations could derail the whole effort. Incorrect AEs have derailed immunization efforts. There will be more presentations to ACIP about this. CDC relies on ACIP to review its safety monitoring plans and point out any holes that they see, because they want to make sure that ACIP, CDC partners, and the American public are confident in the agency’s plans.

Dr. Duchin (NACCHO) said that he was somewhat surprised to hear the discussion about detailed implementation planning given all the unknowns, and asked whether guidance has been issued to state and local health departments to guide them on what is appropriate to do at this stage given the unknowns and limited resources. In addition, he wondered whether additional funding would be allocated to support local immunization program implementation.

Dr. Messonnier said that even in the setting of so many unknowns, planning must begin. CDC believes that the moment is now to plan and that planning needs to be flexible to accommodate the range of possibilities in a parsimonious way in terms of which vaccine with which characteristics and how many doses are available. She wished she could say that if they waited another month, there would be absolute clarity about those things. However, knowing that they will not, they believe they need to get started in planning. CDC has not yet put out detailed guidance, which is the launch of the next phase. The agency will be developing more detailed guidance, but equally important is that they will be providing technical assistance (TA) to state and local health departments as they develop their plans and are working very closely with the variety of partners, including our colleagues in the DoD who have tremendous expertise in logistics and planning and asks CDC lots of hard, great questions to ensure that there is nothing that they are missing. CDC will be moving into the next phase of more detailed planning, working with state and local health department, providing technical expertise, and engendering more of a community of practice (CoP) in which CDC can apply lessons from states that already have started their planning to help states that are less far along. This planning is not going to be easy. They need to rely on the things that are planned for already. Given that the context of COVID-19 is very different, more flexibility will be required—even up until the moment when those vaccines become available, because there are still many things that may look different on

that day. While it is not going to be easy, CDC is going to count on all of its partners to work with them.

Epidemiology of COVID-19 in Essential Workers, Including Healthcare Personnel

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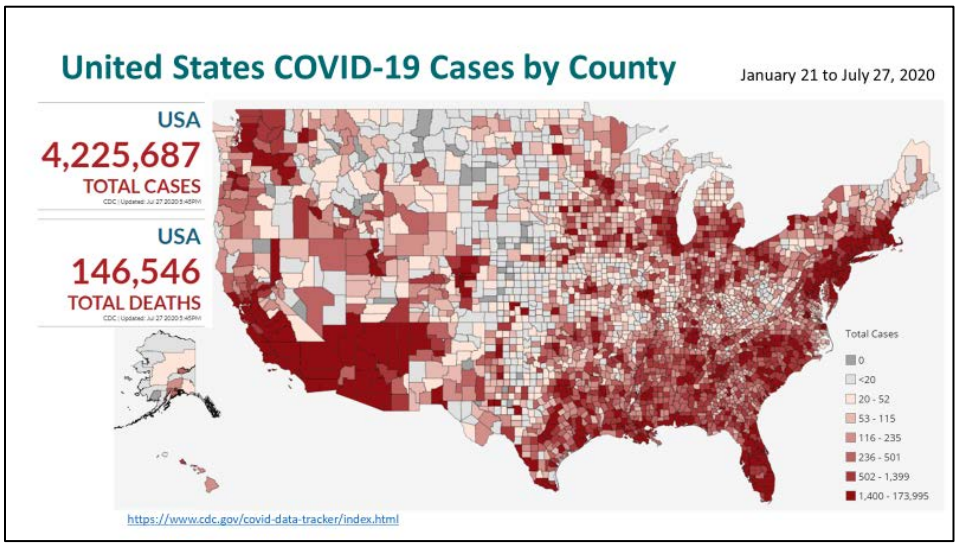
Dr. Oliver presented a brief update on overall US COVID-19 epidemiology and the epidemiology among some essential workers, including healthcare personnel (HCP) and workers at LTCFs, workers in food processing and agriculture, workers in correctional facilities, and military personnel. As of July 27, 2020, a total of 4.2 million cases have been reported to CDC, with 146,00 deaths. This map shows the cumulative case counts by county, with the darker red representing larger numbers of cases:



In terms of trends in the number of COVID-19 cases reported per day in the US, there has been a clear increase in cases reported per day since mid-June [https://www.cdc.gov/covid-data-tracker/index.html#trends].

Regarding the number of specimens tested for SARS-CoV-2, using a molecular assay and reported to CDC by public health laboratories, the overall percent positive at public health laboratories was 8% during the past week. The percentage of specimens testing positive has been increasing since June. The percentage positive is higher in children and younger adults 18-49 years of age compared to older adults. The percentage of specimens testing positive in commercial laboratories also has been increasing since June, with a peak in early July at 10.4%. This past week the percent positive was 9.1%. The National Center for Health Statistics (NCHS) collects death certificate data from vital statistics offices for all US deaths. Through the week ending July 18th, 9.1% of all deaths were due to pneumonia, influenza, or COVID-19. The percentage remains above the epidemic threshold and will likely change as more death certificates are processed [https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html].

With regard to the results from several sero-surveys looking at antibody to SARS-CoV-2 in various populations, data recently were published evaluating the seroprevalence of SARS-CoV-2 antibodies from a cross-sectional study with a convenience sample of residual sera from over 16,000 persons. Samples were collected from March 23 to May 12. Estimates were standardized to site populations by age and sex. The estimates ranged from 1.0% to 6.9%, with the highest seroprevalence in the New York City (NYC) metro area. These data estimate that greater than 10 times the number of SARS-CoV-2 infections occurred than the number of reported cases, ranging from 6 to 24 times the number of reported cases per site [Havers FP, et al. JAMA IM 2020].

In addition, a large scale serologic study was conducted in healthcare workers (HCW) and first responders at two locations. Specimens were collected from mid-May through June in Detroit and through July in NYC. In Detroit, the overall seroprevalence among HCW and first responders was 6.9%, but varied by county. Overall, the seroprevalence among HCP and first responders in NYC is 22.5%. It was highest among staff at correctional facilities and fire departments. Hospitals and police department staff had a seroprevalence around 20%, with medical examiners (MEs) at 11%.

Another seroprevalence survey among HCW was conducted in 13 hospitals in April and May, with a focus on individuals providing care in COVID-19 clinical areas. Serum will be collected at baseline and 60 days after enrollment. The objective is to: 1) estimate the seroprevalence of SARS-CoV-2 infection among HCW (e.g., MDs, RN, respiratory therapists, phlebotomists) working in COVID-19 care areas; and 2) explore risk factors for infection and immune response. The design is a convenience sample of ~3250 HCWs across ~13 hospitals (250 per site). The assay is the CDC Pan-Ig ELISA against spike protein. Within the baseline data collected, seroprevalence ranged from 0.8% to 31%, with the highest seroprevalence again in NYC with the other locations at 10% or less.

Turning to COVID-19 epidemiology among HCP, for background, CDC's definition of HCP is as follows:

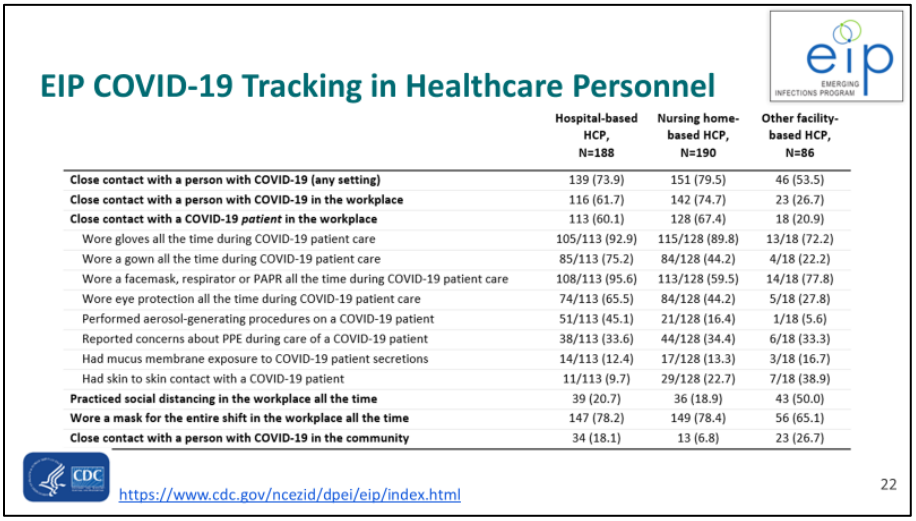
> **Healthcare Personnel** (HCP) are essential workers defined as **paid** and **unpaid** persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials.

CDC reports and routinely updates cases and deaths among healthcare personnel on the CDC website. As of July 27th, there have been 113,000 cases and 576 deaths among healthcare personnel. This is likely an underestimate, as HCP status was only available on 22% of cases.

The Emerging Infections Program (EIP) is a network of 10 state health departments and local health and academic partners that conduct sentinel or population-based surveillance for COVID-19 in HCP. The breakdown and type of surveillance among the 10 sites are listed here:

- ❑ 7 sites (Connecticut, Colorado, Maryland, Minnesota, New Mexico, Oregon, Tennessee) conduct sentinel surveillance
- ❑ 2 sites (California, Georgia) conduct population-based surveillance
- ❑ 1 site (New York—Rochester) uses a hybrid approach that includes sentinel hospitals, with population-based surveillance for nursing home HCP with COVID-19

These projects including surveillance for and interviews of HCP cases. Through June, over 1000 cases have been reported and 464 interviews have been conducted. Regarding the demographics of the HCP cases, stratified by facility type, most were female in all facility types. In hospital-based settings, over 40% of cases were nurses, while over 40% were assistants or technicians in nursing home-based facilities, likely representing differences in the workforce in these two settings. Risk factors for COVID-19 acquisition are shown here:



EIP COVID-19 Tracking in Healthcare Personnel

	Hospital-based HCP, N=188	Nursing home-based HCP, N=190	Other facility-based HCP, N=86
Close contact with a person with COVID-19 (any setting)	139 (73.9)	151 (79.5)	46 (53.5)
Close contact with a person with COVID-19 in the workplace	116 (61.7)	142 (74.7)	23 (26.7)
Close contact with a COVID-19 *patient* in the workplace	113 (60.1)	128 (67.4)	18 (20.9)
Wore gloves all the time during COVID-19 patient care	105/113 (92.9)	115/128 (89.8)	13/18 (72.2)
Wore a gown all the time during COVID-19 patient care	85/113 (75.2)	84/128 (44.2)	4/18 (22.2)
Wore a facemask, respirator or PAPR all the time during COVID-19 patient care	108/113 (95.6)	113/128 (59.5)	14/18 (77.8)
Wore eye protection all the time during COVID-19 patient care	74/113 (65.5)	84/128 (44.2)	5/18 (27.8)
Performed aerosol-generating procedures on a COVID-19 patient	51/113 (45.1)	21/128 (16.4)	1/18 (5.6)
Reported concerns about PPE during care of a COVID-19 patient	38/113 (33.6)	44/128 (34.4)	6/18 (33.3)
Had mucus membrane exposure to COVID-19 patient secretions	14/113 (12.4)	17/128 (13.3)	3/18 (16.7)
Had skin to skin contact with a COVID-19 patient	11/113 (9.7)	29/128 (22.7)	7/18 (38.9)
Practiced social distancing in the workplace all the time	39 (20.7)	36 (18.9)	43 (50.0)
Wore a mask for the entire shift in the workplace all the time	147 (78.2)	149 (78.4)	56 (65.1)
Close contact with a person with COVID-19 in the community	34 (18.1)	13 (6.8)	23 (26.7)

https://www.cdc.gov/ncezid/dpei/eip/index.html

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Through hospital and nursing home-based settings, around ¾ of cases had close contact with a COVID-19 case in any setting and 60% to 70% had contact through the workplace. Compliance with personal protective equipment (PPE) varied across settings and was highest among hospital-based personnel in the first column compared to nursing home-based personnel. The proportion using eye protection, the bottom row in this box, is lower than other PPE items, especially in nursing home settings.

Another study underway among HCP is COVID-19 Evaluation of Risk in Emergency Departments (Project COVERED) that is evaluating COVID risk in emergency departments (EDs), with a goal of 1600 participants enrolled in 20 medical centers for 20 weeks. Preliminary data through the first several weeks of data collection show that at baseline, 2% had positive serology, with none positive by PCR. Of the 29 who were positive at baseline, 75% reported previous symptoms compatible with COVID. Most had previously worked in the ED with symptoms. These interim results show that through the first 2 weeks of enrollment, there have been 9 incident cases of COVID-19. None who developed infection participated in an intubation of a COVID-positive patient. Using the preliminary data, there is a projected 2.4% infection rate over the 20-week observation period [https://medicine.uiowa.edu/content/covid-evaluation-risk-emergency-departments-covered-project].

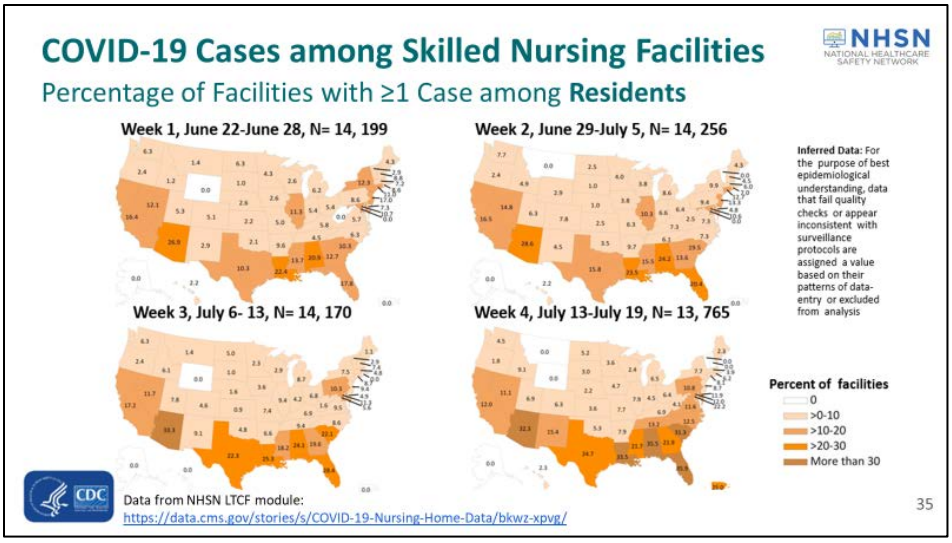
As discussed at the previous ACIP meeting, COVID-NET conducts hospitalization surveillance with 14 states, representing around 10% of the US population. Patients must be a resident of the surveillance area and have a positive SARS-CoV-2 test within 14 days prior to or during hospitalization, and chart reviews are conducted. Information on whether the patient is a HCP is collected as a part of the chart review [*MMWR* April 17, 2020; https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e3.htm].

Of the 36,000 hospitalizations within COVID-NET, 9195 cases had data on HCP status. Of those, 512, or 5.6%, were documented as HCP. Median age of HCP patients was 48 years. Among HCP, there was a higher proportion of non-Hispanic Black persons and a lower proportion of Hispanic persons. Additional data on type of HCP are collected. A small number of respiratory therapists have been hospitalized with COVID among whom 5% are physicians, 24% nurses, and the remainder from the "other" category. It is a free text variable, but an attempt was made to provide some additional detail to show the diversity of cases. Most were hospital-based patient care support, such as nursing assistants. But the cases also included housekeeping or environmental services, home health workers, emergency personnel, pharmacy, food services, et cetera. Among hospitalized HCP, 87% had an underlying condition (e.g., diabetes, hypertension, obesity, CKD, COPD, and/or asthma). For comparison, 91% of all hospitalized adults had an underlying medical condition. A higher proportion of HCP were obese and had asthma but had a lower proportion of other underlying medical conditions.

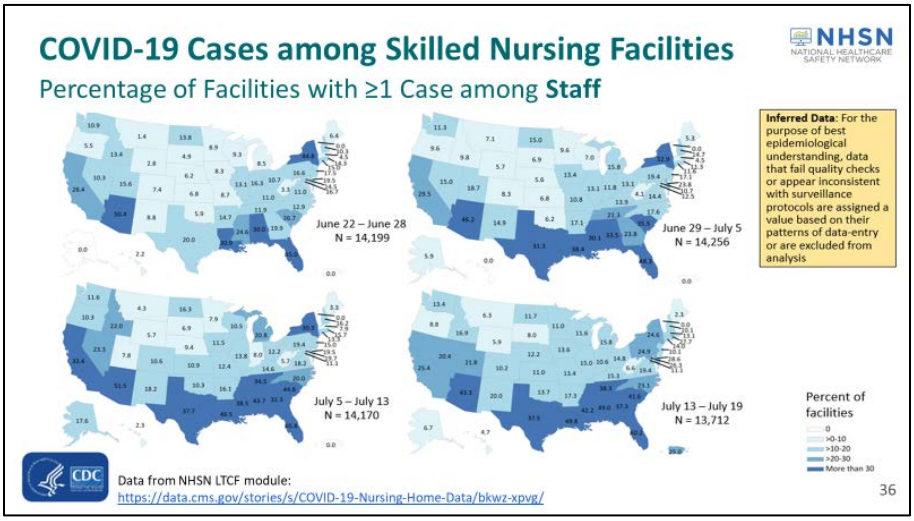
When the same data on underlying conditions were stratified by age, among adults 18-49 years and 50-64 years, HCP had a higher proportion of obesity and asthma, but a similar or lower proportion of other underlying conditions. Among adults 65 years of age and older, hospitalized HCP had a lower proportion of most underlying medical conditions. In terms of clinical outcomes, 3.7% of healthcare providers died, 13% required mechanical ventilation, and 26% required intensive care unit (ICU) admission. Overall, HCP had a lower proportion of severe clinical outcomes compared to all hospitalized adults.

To summarize information from the past few studies, HCP with COVID-19 are demographically diverse, including geography, occupation, race and ethnicity, and underlying conditions. Many HCP report direct contact with COVID-19 patients through work. Among hospitalized HCP, there were similar proportions with underlying conditions, a higher prevalence of obesity and asthma, and a lower prevalence of other underlying conditions including diabetes, hypertension, and chronic kidney or lung disease.

Now to focus on a specific subset of HCP—staff at LTCFs. Many US states publicly report COVID-19 cases among staff of LTCF, including nursing homes and assisted living facilities. As of July 16th, there were nearly 70,000 confirmed or probable cases based on data reported from 36 states. Of those, 342 confirmed or probable COVID-19 related deaths have been reported among staff at LTCF in 17 states. This series of maps demonstrates the number of skilled nursing facilities with at least 1 case among residents through the past 4 weeks. As the weeks progress, the states across the lower half of the country became progressively darker, representing a higher percent of facilities with at least one case:



This series of maps highlights COVID-19 cases among staff at skilled nursing facilities, which reflects a similar geographic pattern to the locations of staff and residents with COVID:



In terms of counts and incidence of COVID 19 cases among staff at skilled nursing facilities, the incidence of cases per 1000 resident weeks has increased through late June and July. The incidence of death has remained relatively stable over that time. The LTCF workforce consists of a variety of occupations with different levels of direct patient contact. They are disproportionately lower-wage workers. Nearly 40% are 50 years of age and older, 82% are female, and a quarter are non-Hispanic Black persons. Both of those are higher than what is reported among the general workforce. In addition, staff can be shared among multiple facilities, and in many instances, COVID-19 activity increases among LTCF staff first, and then residents.

Moving to COVID-19 among workers in food processing and agriculture, through April and May, among 23 states reporting COVID-19 outbreaks in meat or poultry processing plants, there were over 16,000 cases in 239 facilities, including 86 deaths. However, testing strategies and methods varied by workplace. Symptom status was reported for around 10,000 cases. Of those,

88% were symptomatic. Among 14 states reporting total number of workers in affected meat and poultry processing plants, COVID was diagnosed in 9.1% of workers. This ranged from 3% to 25% per facility. Among cases with race and ethnicity reported, nearly 90% occurred among racial or ethnic minorities. Over half were Hispanic or Latino and 12% were Asian persons, suggesting that Hispanic and Asian workers might be disproportionally affected among meat and poultry processing facility outbreaks [*MMWR* July 10, 2020; https://www.cdc.gov/mmwr/volumes/69/wr/mm6927e2.htm?s_cid=mm6927e2_w].

Outbreaks have been reported in other food production sectors, including food processing facilities and farms. Compared to all US salaried workers, individuals working in agriculture are more likely to be racial and ethnic minorities, lacking a high school diploma, and less likely to be born in the US. There are multiple factors that increase food processing and agriculture workers' risk for exposure to SARS-CoV-2, including prolonged close workplace contact with coworkers, frequent community contact with fellow workers, mobility of the work force, shared transportation to and from the workplace, lack of paid sick leave, and congregate housing, which can include living in employer-furnished housing and shared living quarters or living in crowded and multigenerational housing.
Regarding COVID-19 among workers in correctional facilities, in terms of the number of infections per 100,000 in the prison population and the US population from April through early June, the COVID-19 case rate is 5.5 times higher among incarcerated persons, compared to the general US population. Overall, there have been 985 correctional or detention facilities with at least 1 COVID-19 case. COVID was diagnosed in over 77,000 incarcerated persons and 18,000 staff, with 700 COVID related deaths among incarcerated persons and 56 among staff. However, actual case counts are likely higher than reported [UCLA COVID-19 Behind Bars Data Project; https://law.ucla.edu/academics/centers /criminal-justice-program/ucla-covid-19-behind-bars-data-project].

Testing of staff at correction and detention facilities does not always occur with larger investigations and may be self-reported. In an analysis of 16 US prisons and jails, 56% identified their first case of COVID-19 among staff members as opposed to incarcerated or detained persons[1]. This indicates that staff members can introduce the virus into correction and detention settings through their daily movements between the facility and the community [[1]Hagan et al. *MMWR* – projected publication date August 7. Results of Mass Testing for SARS-CoV-2 in 16 Prisons and Jails—Six U.S. Jurisdictions, April–May 2020].

Turning to the epidemiology among military personnel, there have been over 36,000 cases and 56 deaths among DoD personnel. Among those, a total of 960 were hospitalized; 15,122 recovered; and 56 died. The number of cases by branch of service include Army: 8623, Marine Corps 3003, Navy 6340, Air Force 3964, National Guard 3398, and DoD Agencies 262 [https://www.defense.gov/Explore/Spotlight/Coronavirus/].

Challenges that can be faced among military personnel are highlighted in the *MMWR* reporting an outbreak aboard the USS Theodore Roosevelt in April. During this time, approximately 1000 service members were determined to be infected with SARS-CoV-2. A portion of those associated with the ship provided specimens and answered questionnaires. In terms of the results, 37% had positive PCR results at the time of testing, 60% had positive antibodies to SARS-CoV-2 spike protein, and nearly 20% of those with previous or current infection were asymptomatic. Risk factors among military personnel faced here include congregate living

quarters and close working environments [Payne DC et al. June 12, 2020 MMWR; https://www.cdc.gov/mmwr/ volumes/69/wr/mm6923e4.htm?s_cid=mm6923e4_w].

In summary, there have been over 4 million cases of COVID-19 diagnosed in the US through July. Information on occupation for COVID-19 cases has not been systematically collected and reported for all cases. However, through available data, many occupations appear to have increased risk for COVID-19, including HCP and staff at LTCF, correctional and detention facilities, and food/agricultural settings. Surveillance and additional projects are ongoing to identify risk factors for COVID-19, including risk factors associated with occupations.

Discussion Points

Dr. Frey requested additional information, based on the knowledge that continues to accrue about bad outcomes and people regardless of whether they were ventilated or in the ICU, about people who end up with worsening lung disease or heart disease 3 to 6 months later. She wondered if at this point, it would be possible to look at statistics or data as it relates to those types of core clinical outcomes as opposed to just looking at death, mechanical ventilation, and ICU admissions.

Dr. Oliver indicated that they are collecting data on some longitudinal cohorts so that they will be able to follow up with individuals and look at potential readmissions for COVID-19 cases.

Dr. Hall added that they are standing up multiple longitudinal cohort studies that will attempt to address the issue of longer-term outcomes, sequelae, and functional status (including things like lung function). Essentially, cohorts will be established of infected individuals who will be followed prospectively. These are still in the early stages of award and implementation, so it will be some time before there are data from those studies. Some of the other studies that Dr. Oliver alluded to are looking at readmission from some of CDC's surveillance networks and some community cohorts that can follow people regardless of infections status prospectively through integrated healthcare systems and also affords an opportunity to look at the admission or subsequent follow-up for related conditions. These natural history studies are following infections prospectively and are specifically designed to look for functional outcomes and longer-term sequelae. There are no data yet, but there are plans in place to address this.

In terms of population sizes, Dr. Szilagyi asked whether the HCW are all part of the 12 million that are listed in the next presentation for critical healthcare and other workers and if Dr. Oliver could provide a sense of the population size of workers in LTCF, correctional facilities, et cetera.

Dr. Oliver said that in the upcoming presentations, they would be talking more about population size so she did not include all of those numbers in this presentation.

Dr. Poehling asked whether data would be forthcoming from the EIP, COVID-NET, and other ongoing studies about other people who may be considered essential workers such as teachers and other populations.

Dr. Oliver said that the short answer is that they are working on collecting occupation status, not necessarily just through COVID-NET and EIP, but across projects that are looking more at occupational status. The EIP-specific projects were set up more around HCW, but there is a

definite effort to collect more occupational status information moving forward. That is a part of the case-based surveillance data recently.

In terms of other populations, Dr. Finley (AIM) asked whether there are plans to look at college dorms and military barracks.

Dr. Oliver indicated that consideration is being given to what types of risk factors they will assess for future ACIP meetings. Individuals residing in congregate settings is an area of focus for upcoming ACIP meetings.

COVID-19 Vaccine Prioritization: Work Group Considerations

Sarah Mbaeyi, MD MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Mbaeyi reviewed the COVID-19 Vaccine WG's considerations for COVID-19 vaccine prioritization. Identifying priority groups for COVID-19 vaccination is essential to support vaccine implementation planning, such as the strengthening of vaccine distribution networks, creating communication strategies to reach the target population, developing state and local vaccine microplans, and implementing safety and effectiveness evaluations. To avoid delays once vaccine is available, it is important to start this prioritization and implementation planning now, as Dr. Messonnier mentioned earlier, despite the challenges due to incomplete information on vaccine safety and efficacy in population subgroups and vaccine dose availability. A prioritization framework for COVID-19 vaccines is being adapted from the 2018 pandemic influenza vaccine guidance. At the June 24th ACIP meeting, the WG proposed priority vaccination of essential workers, including HCP and high-risk populations.

The WG assumes that vaccination will occur through phased implementation. Initially, a limited number of doses will be available for vaccination of HCP and other essential workers, and other high-risk populations, such as LTCF residents. Subsequently, a large number of doses will become available. At this point, the objectives of the vaccination program will be targeting of specific populations at increased risk for severe COVID-19, as well as HCP and essential workers to ensure high uptake in these groups, as well as widespread access to achieve high coverage across the population.

Thus, the WG has been reviewing considerations for priority vaccination of essential workers and high-risk populations. This session focused on considerations for vaccination of essential workers, including HCP. During the August ACIP meeting, the WG will review considerations for other high-risk populations. The CDC definition of HCP that the WG used in its deliberations is as follows:

> Healthcare personnel are defined as all paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials. This includes persons not directly involved in patient care, but who are potentially exposed to infectious agents while working in a healthcare setting, including clerical, dietary, environmental services, laundry, security, maintenance, engineering and facilities management, administrative, billing, and volunteer personnel [https://www.cdc.gov/infectioncontrol/pdf/guidelines/infection-control-HCP-H.pdf].

From the WG's perspective, the goals of including essential workers, including HCP, in the earliest priority group for vaccination is to minimize the impact of COVID-19 on the healthcare infrastructure and societal functions, protect individuals who risk their health and safety to take care of others, and reduce the risk of transmission to vulnerable populations, such as LTCF residents. Considerations for prioritizing this group include the risk of exposure, infection, and severe disease; the risk of transmitting disease to vulnerable populations; disparities and equity; feasibility of implementation; and values of the target group and the public.
The overarching policy question is, "When COVID-19 vaccines become available, should essential workers (including healthcare personnel) be among the initial priority group?" To help answer this question, the WG reviewed elements of the Evidence to Recommendations (EtR) framework, which is the framework used by ACIP to make evidence-based, transparent policy decisions. The WG reviewed the following EtR criteria:

- ❑ Is the problem of public health importance?
- ❑ Does the target group, in this case healthcare personnel and other essential workers, feel that the desirable effects of vaccination are large relative to the undesirable effects?
- ❑ Is there important uncertainty about or variability in how much people value the main outcomes from vaccination?
- ❑ Is the intervention, in this case vaccination, acceptable to key stakeholders?
- ❑ Is vaccination feasible to implement?

Starting with the public health problem, occupational groups as defined by the Bureau of Labor Statistics (BLS) who are at greatest risk for exposure to infectious diseases include those in the healthcare support (e.g., home health aides, nursing assistants, massage therapists, dental assistants, medical assistants); healthcare practitioner (e.g., physicians, dentists, nurses, pharmacists, physical therapists, respiratory therapists); protective services (e.g., police officers, firefighters, correctional officers, security guards, transportation screeners); personal care and service (e.g., childcare workers, barbers, manicurists, fitness trainers, skincare specialists, gaming service workers); community support (e.g., social workers, therapists, counselors, probation officers, health educators); and education, training, and library categories (e.g., teachers (K-12), teaching assistants, librarians) according to a recent study [Baker MG, et al. PLoS One. 2020. 15(4), e0232452].

In addition, there are socioeconomic and racial disparities in worker risk to infectious disease exposures. People with lower income occupations are generally less likely to be able to work from home[1] and thus have a greater risk of exposure. In addition, racial and ethnic minorities are more likely to work in occupations deemed essential or with increased risk of infectious disease exposure. These include workers in the healthcare and social assistance, animal slaughtering and processing, and transportation industries[2] [Hawkins D. American Journal of Industrial Medicine. 2020 Jun 15].

These occupational groups at risk of infectious disease exposure are consistent with those observed to have an increased burden of COVID-19 disease. As discussed in the last presentation, over 110,000 cases of COVID-19 have been reported in HCP to date. This includes a substantial proportion of HCP who are at increased risk of severe COVID-19 disease, including those with high-risk conditions or those who belong to a racial or ethnic minority group. Outbreaks and increased incidence also have been reported in workers of congregate settings,

often among lower-wage workers or workers belonging to racial/ethnic minority groups, including LTCF, meat and poultry processing facilities, and correctional facilities.

Examining HCP in greater detail, 39% have a high-risk condition or are aged ≥65 years. Those in support roles (such as medical assistants or home health aides) or licensed practical nurses (LPNs), emergency medical technicians (EMTs), or others with less than a Bachelor's degree, have the highest rates of underlying conditions. These groups in general also have a higher proportion of workers who are African-American, Latinx, uninsured, or have an income of less than 200% of the federal poverty level. Thus, vaccination of HCP will help to reach populations who are otherwise at increased risk of severe COVID-19 disease, and help to address health equity concerns [Gibson D, J Gen Int Med, 2020].

Occupational setting is also an important consideration for vaccination of HCP, as the composition of the healthcare workforce varies widely by setting. For example, nursing care facilities have a greater proportion of healthcare support staff such as nursing assistants and personal care aides, as well as non-clinical staff such as cooks and housekeepers, than hospitals. It is important to make sure that prioritization deliberations take into account these differences [https://datausa.io/profile/naics/hospitals https://datausa.io/profile/naics/nursing-care-facilities].

Finally, health-related workplace absenteeism also has been observed in several essential workforce sectors. While overall there has been a relatively minor impact of COVID-19 on absenteeism at a national level, increased absenteeism was observed in the personal care and service, healthcare support, and production sectors [Groenewold MR, et. al. MMWR Morb Mortal Wkly Rep 2020;69:853–858].

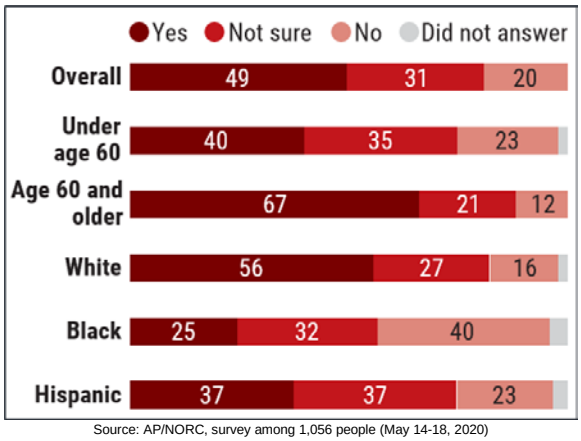
Turning to values and acceptability of vaccinating essential workers, including HCP, from June to July, CDC-sponsored focus groups were conducted to explore attitudes and beliefs about COVID-19 vaccines, including who should be among the first to get the vaccine once available. Virtual focus groups were led by trained qualitative moderators, with 33 of 49 planned sessions completed to date. Quota sampling was conducted through a professional recruitment company. The focus groups included participants from 12 audience segments: adults older than 60 years of age in both the low and median socioeconomic ranges, parents of children less than 18 years of age, adults 20-30 years of age without children, non-medical essential workers, and nurses. Focus groups for each of the segments were conducted among the general population, as well as specifically among African-Americans. The focus group participants overwhelmingly supported prioritization of healthcare and frontline personnel, essential workers, and high-risk populations for vaccination. These beliefs were similar across audience segments. The primary reasons stated by the participants are that these groups are most likely to be exposed to COVID-19, have higher rates of infection, and perform important public services. Additional analyses are ongoing to evaluate overall public attitudes, beliefs, and intended practices towards COVID-19 vaccines [CDC unpublished data].

Consistent with the focus group findings, stakeholders and the public consistently name HCP as a priority group for vaccination during pandemics. For COVID-19, the WHO has included HCP as a priority group in its Global Allocation Framework. Similarly, the United Kingdom's (UK's) vaccine policy body, the Joint Committee on Vaccination and Immunisation (JCVI), recently issued a report advising priority vaccination of frontline health and social care workers. For pandemic influenza, participants in a series of public and stakeholder meetings to identify

priority vaccination groups in the event of a pandemic identified healthcare personnel as a priority group. When the 2009 H1N1 pandemic occurred, ACIP recommended that HCP be included in the highest priority group for vaccination [https://apps.who.int/gb/COVID-19/pdf_files/18_06/Global%20Allocation%20Framework.pdf; https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi/interim-advice-on-priority-groups-for-covid-19-vaccination; University of Nebraska. Evaluation of the Public Engagement Project on Pandemic Influenza Vaccine Prioritization. February 7, 2008; https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5810a1.htm].

In terms of the general public's views towards COVID-19 vaccination, 49% to 72% of consumer survey respondents in May and June expressed vaccine intention. Differences in methodology and framing of the question likely account for some of the variation. However, there is likely substantial variation in the population views towards vaccination. As seen in the figure below, vaccination intention was substantially higher in persons aged 60 years and older compared to younger adults, and higher among White compared to Black and Hispanic participants, in one recent survey:

"If a coronavirus vaccine becomes available, do you plan to get vaccinated?"



Source: AP/NORC, survey among 1,056 people (May 14-18, 2020)

There is currently limited information on views and intentions towards COVID-19 vaccines among healthcare and other essential workers. However, coverage of influenza vaccination among HCP can help shed some insight into potential acceptance of COVID-19 vaccines. During the 2017-2018 influenza season, 78% of HCP received influenza vaccination, which is more than double that observed in the general adult population. However, one potential factor is workplace vaccination requirements, which is the greatest predictor of coverage among HCP. Coverage also varied by setting, with the highest coverage among hospital personnel and lowest among long-term care facility personnel [Black CL, et. al. *MMWR* Morb Mortal Wkly Rep 2018;67:1050–1054; https://www.cdc.gov/flu/fluvaxview/coverage-1819estimates.htm].

Healthcare providers are consistently rated as the most trusted source of information not only on vaccines, but also for COVID-19. Evidence shows that healthcare providers who are confident in vaccines and are themselves vaccinated are more likely to recommend vaccination to patients. This is important, given that provider recommendation is the strongest predictor of vaccine uptake. Thus, early acceptance of COVID-19 vaccines among HCP is likely to be important in building public trust in the vaccination program [Freed GL, et al. Pediatrics 2011; 127 Suppl 1: S107-12; Gust DA, et al. Pediatrics 2008; 122(4): 718-25; Paterson P, et al.

Vaccine 2016; 34(52): 6700-6; AP-NORC Center. https://apnews.com/1ca088a559803242579630f88b99b681].

Turning to feasibility considerations, a recent assessment of immunization programs showed that the majority have plans for vaccination of the critical workforce, but other than for HCP, implementation has not been fully tested during a pandemic. Several vaccine candidates require a 2-dose series. Series completion may be a challenge, given the experience with other multi-dose adult vaccines, such as zoster and meningococcal B. Furthermore, there may be multiple non-interchangeable products available which could add additional complexities. In addition, some vaccines may have different storage and administration requirements. These barriers apply to all target groups, but may be more manageable in targeted occupational groups than in the general population [CDC, Program Annual Progress Assessment of Immunization Awardees, January 1, 2018 – June 30, 2019; CDC unpublished data].

Limiting vaccine allocation to other essential workers during a period of limited initial supply may help to facilitate implementation. First, this would allow for coordinated vaccine distribution and tracking through occupational health services. It also would facilitate streamlined vaccine microplanning at the state and local levels, as well as efficient post-approval routine vaccination monitoring.

In summary, the WG feels that protection of the healthcare infrastructure is an important consideration in vaccine prioritization. Vaccination of healthcare and other essential workers is consistent with the principles of ensuring health equity in vaccine prioritization, as a high proportion of minority, lower income, or medically high-risk populations comprise the workforce of some sectors. In addition, there is likely broad public support for the prioritization of these groups for COVID-19 vaccine. Finally, although implementation will likely have challenges, vaccination of these occupational groups is likely more feasible than the general population.

The WG feels that the prevention of COVID-19 in healthcare and other essential workers is a problem of public health importance, that the target population probably feels that the desirable effects of vaccination are large relative to undesirable effects, that there is important uncertainty about or variability in how much people value the main outcome, that vaccination is probably acceptable to key stakeholders, and that vaccination is probably feasible to implement. Thus, the overall WG interpretation is that the initial priority group for COVID-19 vaccination should include healthcare and other essential workers.

In terms of how to prioritize vaccination in the setting of initial limited supply, the WG consensus is that both essential workers (including healthcare personnel) and high-risk populations are important priority groups. However, the WG acknowledges that sub-prioritization will be necessary given the initial anticipated supply, and that not all groups that are deemed a priority will be able to be vaccinated at once. There was also discomfort among some members of the WG about limiting the priority group to only HCP and other essential workers. As the WG and ACIP are largely comprised of HCP, and there was concern about appearing bias toward this group. There is also recognition that those at highest risk of death would not be included. However, given all the factors discussed during this presentation, the WG was in agreement that essential workers, including HCP, should be included as one of the priority groups for initial doses.

As not all healthcare and essential workers can be vaccinated at once during a period of initial limited supply, sub-prioritization among essential workers, which can be categorized as HCP, homeland and national security personnel, and other essential workers, likely will be necessary. The WG proposes the following criteria for which healthcare and other essential workers to include in the priority group:

- ❑ Risk of exposure, infection, and severe disease, including the risks that occur both in the occupational as well as community setting, as both have an impact on healthcare and societal functions.
- ❑ Other criteria, including protection of these healthcare and societal functions.
- ❑ Reducing the risk of transmission to vulnerable populations, such as LTCF residents.
- ❑ Equity and implementation considerations.

In terms of next steps, during the August ACIP meeting, the WG anticipates reviewing considerations for prioritization of high-risk populations, including persons:

- ❑ Who are older (e.g., ≥65 years)
- ❑ With high-risk medical conditions
- ❑ Residing in LTCF and other congregate settings
- ❑ Belonging to certain racial and ethnic minority groups
- ❑ Residing in geographic hot spots

During future ACIP meetings, the WG will continue to review evidence and considerations to develop an overall vaccine prioritization scheme.

To set the stage for the discussion period, the WG requested ACIP's feedback on the following questions:

- ❑ Does ACIP agree with the WG's assessment to include essential workers, including HCP, in the initial priority group for vaccination?
- ❑ Does ACIP agree with the proposed criteria for sub-prioritization of essential workers?
- ❑ What additional evidence would ACIP like to review?

Discussion Points

Dr. Bernstein asked whether epidemiology thresholds are established a priori for the various subpopulations that will help with prioritization, and whether prioritization includes compliance with important mitigation practices.

Dr. Mbaeyi said she thought that would be challenging given some of the limitations in knowing the occupation of all of the cases, so they have not focused on developing thresholds. There are a number of other considerations other than the epidemiology that will be guiding those decisions as well. It is an all-encompassing effort to take all of the factors into consideration, including the epidemiology. The WG feels that vaccination and other mitigation measures are complementary in helping to control this disease. It is known that in certain settings, there are periodic shortages of PPE. On a national level in terms of trying to develop national policy, it is somewhat challenging to prioritize based on other mitigation factors. However, the WG has certainly discussed some other mitigation measures and how they are complementary to vaccine and how that might relate to prioritization.

Dr. Szilagyi supports the prioritization of HCP and pointed out that vaccination of HCP in skilled nursing facilities would be an excellent way to protect the group that is at the most high-risk from death, even though the residents would not be prioritized. In Los Angeles County, 47% of deaths from COVID-19 were individuals in skilled nursing facilities. In earlier studies for influenza vaccination demonstrated that high rates of vaccination in these kinds of facilities, among the staff, significantly reduced influenza disease throughout these facilities.

Dr. Mbaeyi indicated that the WG has discussed vaccination of HCP in skilled nursing facilities and completely agrees.

Regarding the data Dr. Szilagyi mentioned, Dr. Poehling pointed out that there clearly was a difference in vaccine uptake in LTCFs than some of the others for HCP and said she is excited that they are talking about this. This also highlighted what Dr. Messonnier mentioned earlier about making sure they communicate about and really work on that component, because it will be a very important strategy. She requested further clarification about the definition of “essential workers.”

Dr. Mbaeyi indicated that they reviewed a couple of sources, one of which was an independent influenza guidance in which essential workers are listed out. CISA and the Department of Homeland Security (DHS) also have some groupings. While the WG began with those, they also looked at some categories that traditionally have not been included as essential workers in some of the previous iterations such as teachers and other educators. They have tried to think through other groups who are essential to society and where those impacts on society may occur. This certainly has been seen with school closures.

Dr. Hunter pointed out that there is a best case scenario in which the supply ramps up quickly. It would be extremely important to change messaging quickly to make it clear that the initial prioritization categories no longer apply to avoid people not getting the vaccine because they think they are not in a priority category.

Dr. Ault wondered what guidance ACIP might offer about pregnant HCW, given that it did not seem there would be pregnancy data from the planned Phase 3 trials.

Dr. Mbaeyi called upon Dr. Bell to comment on this based on the WG discussions pertaining to pregnancy.

Dr. Bell acknowledged the importance of addressing pregnancy among HCP in terms of vaccination, which the WG is mindful of. There are some liaisons on the WG who have thought very deeply about this issue. While the WG has not finished discussing this, they have taken into consideration issues of personal choice, informed consent, and so forth. The WG has not reached any conclusions, but is committed to thinking about it further.

Dr. Bernstein asked whether, once the prioritization plans are crystalized, if there will be discussion about this being a universal recommendation for those particular groups or if it would be shared clinical decision-making. They have seen that influenza vaccination rates are highest in hospitals where influenza vaccines are mandated, which certainly could have quite an impact in terms of COVID-19 transmission.

Dr. Mbaeyi indicated that while the WG has not reached the specific phase of reviewing proposed recommendations, they would anticipate that this would be a regular recommendation rather than a shared clinical decision-making recommendation.

Dr. Sanchez emphasized that while it is easy to say “all essential HCW” a lot of prioritization occurs within that category. With that in mind, he wondered whether ultimately this would have to be decided on a local basis to determine which of the groups have the highest contact with COVID-19 patients. Another important consideration is HCW who are breastfeeding, which perhaps should be considered to be a contraindication.

Dr. Mbaeyi said that in the presentation they tried to lay out the WG criteria that might be thought of in terms of how to sub-prioritize essential workers. This harkens back to Dr. Messonnier’s point about how important state and local microplanning will be so that decisions can be made appropriately at the local level.

Dr. Hunter observed that someone who is a middle-aged, older, African American, female, medical assistant with diabetes and hypertension would be at the top of the list to get a vaccine. He wondered whether any outreach had been done to the professional society for medical assistants.

Dr. Mbaeyi indicated that they have not spoken specifically with them yet, but they are planning additional stakeholder engagement as Dr. Messonnier mentioned. There is very robust representation on the WG of other professional societies, such as the American Nurses Association (ANA) and others. The professional society for medical assistants is a great suggestion for further stakeholder engagement.

Dr. Lee pointed out that as the WG deliberations continue to take their course, one of the challenges is not knowing which populations will be under the potential EUA. Who those populations are will need to be included in the WG’s decision-making process. A lot of this is also about risk/benefit assessment in the various subpopulations and making sure that the vaccine gets to the areas where the benefit/risk balance is known to be the greatest.

Dr. Arthur (BIO) asked whether in the future there would be some data on how the population that has had the most cases is transmitting into the community, which would be interesting data to examine as they consider the role of HCP in their workplace as well as at home in their communities.

Dr. Mbaeyi indicated that they would look into these data and would bring that back to ACIP. There are plans for future meetings to have some presentations on some modeling that will look at transmission factors.

Dr. Romero added that careful assessment of transmission outward into the community via essential workers, such as those who work in meat packing and poultry industry, will be particularly important. In a recent outbreak in Arkansas, there was extensive transmission outside of that group of individuals into the community.

Dr. Atmar added that transmission into healthcare facilities is also important, as highlighted by the data from LTCFs. One thing they have seen locally in Texas as they investigate HCP who become infected is that their significant exposures or contacts did not occur in the work setting

where they had PPE. Instead, it occurred in community settings including home and other contacts outside the workplace.

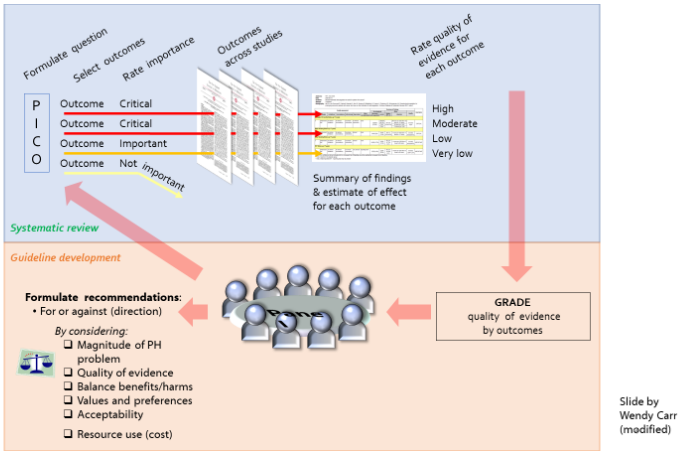
Dr. Duchin (NACCHO) indicated that they too are seeing that a significant amount of community transmission is occurring locally in Seattle and that many of the HCW infections are community-acquired and not healthcare facility-acquired.

COVID-19 Vaccine WG Considerations: EtR Framework

Kathleen Dooling, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Dooling reminded everyone what the WG considers the objectives of the COVID-19 Vaccine Program to be: 1) ensuring the safety and effectiveness of COVID-19 vaccines; 2) reducing transmission, morbidity, and mortality of COVID-19 disease; 3) helping minimize disruption to society and the economy, including maintaining healthcare capacity; and 4) ensuring equity and vaccine allocation and distribution.

In order to realize those program objectives, the ACIP WG will rely on a transparent pathway for evidence-based decision-making. Evidence from published in gray literature is systematically collected and rigorously assessed and GRADE'd (Grading of Recommendation Assessment, Development, and Evaluation). Next that evidence is evaluated within the EtR framework, which contains domains critical to the success of any vaccine program. These include assessment of the magnitude of the public health problem; balancing of expected benefits against any possible harms; understanding the values of the target population as they relate to the vaccine; understanding whether the target population will accept a proposed vaccine; the feasibility of a vaccine program, including allocation and distribution plans; and the resources needed for success. This compilation of evidence, as well as the understanding of the uncertainty therein, forms the foundation upon which ACIP recommendations may be rendered. An ACIP recommendation may come in one of three forms: 1) a recommendation for a given population to receive a vaccine; 2) a recommendation for individuals within a certain group to receive a vaccine based on shared clinical decision-making with their healthcare provider; or a decision not to recommend the vaccine. This schematic diagram represents some of the more granular details:



The WG has begun the process of systematic review of the evidence by formulating the policy question in a format that can facilitate systematic review of the evidence and transparent GRADE'ing of the quality of that evidence.

Dr. Dooling reported on WG progress toward formulating the policy, or PICO question. PICO stands for: Population, Intervention, Comparison, and Outcomes. The WG envisions the entire US population as the population of interest. Understanding the evidence may be generated at different times for different groups. For example, the Phase 3 trials sub-populations will be defined moving forward. With respect to the intervention, the WG agreed that the recommendations should be specific to an individual vaccine, not by class or group, and that evidence be directly comparable regarding the number of doses, routes of administration, and the schedule used in the studies. There are several comparison groups against which vaccine performance could be measured. Placebo groups might include saline or a non-COVID-19 vaccine; no vaccine, including community comparisons that may be informative in some circumstances; and in the future, if a COVID-19 vaccine is approved, it may be possible to use that vaccine to compare against other COVID-19 vaccines in non-inferiority type study designs. Next, the WG considered outcomes of interest. The outcomes discussed included both potential benefits as well as possible harms of a vaccine. Additionally, WG members selected outcomes that are important or critical to vaccine policy deliberations.

Following WG discussion and a modified Delphi process, important and critical outcomes to be considered by the WG for inclusion in the GRADE process were determined. The critical outcomes that ACIP considers to be essential for making a recommendation are prevention of symptomatic COVID-19 disease and possible severe adverse events (SAEs), including vaccine enhanced disease. Important outcomes include reactogenicity, prevention of SARS-CoV-2 seroconversion, COVID-19 hospitalization, mechanical ventilation, and death. The WG looks forward to ACIP's feedback on these outcomes.

The evidence pertaining to each selected outcome will be GRADE'd, and the resulting assessment of the quality of evidence will be considered in the EtR framework to adjudicate the domains of "Balance of Benefits" and "Risks." Ultimately, COVID-19 recommendations may be thought of in two broad categories. The first is the specific vaccine recommendations, which are generally stable, usually applicable to broad populations, and for which the purpose is a to set a standard of clinical practice. In the case of COVID-19, the specific vaccine recommendation also could inform prioritization recommendations. This recommendation would be much more dynamic and expand as vaccines are approved for different populations and as supply and demand change over time. The purpose of the prioritization recommendation is primarily to facilitate implementation.

Dr. Dooling next reviewed WG considerations of equity. Dr. Mbaeyi introduced this concept on the last ACIP meeting, but the WG was considering the pandemic influenza framework as a starting point for COVID adaptation and also the EtR recommendation framework. In addition to this, the WG considered it important to employ ethics and equity principles to accomplish program goals, especially reducing disproportionate burden on members of groups with existing disparities. This desire is featured prominently in the WG's "Proposed Guiding Principles" as a cross-cutting theme for the COVID-19 Vaccine Program and is highlighted in the need for inclusive clinical trials and equitable distribution of approved vaccine.

As described earlier in the day, NASEM has struck a committee on Equitable Allocation of Vaccine for the Novel Coronavirus. The purpose of this committee is to develop a framework for planning for equitable allocation of vaccines, which can inform decisions by ACIP. The committee has certainly proposed questions of mutual interest to ACIP, including the following:

- ❑ What criteria should be used in setting priorities for equitable allocation of vaccine?
- ❑ How should the criteria be applied in determining the first tier of vaccine recipients?
- ❑ How can communities of color be assured access to vaccination?

ACIP looks forward to working with NESEM's committee in the shared goal of equity in allocation and distribution of COVID-19 vaccines.

There is certainly a lot of work ahead for the WG. The WG's next steps with regard to vaccine recommendation are to: 1) complete the definition of the policy question for inclusion in the EtR framework; 2) review clinical trial data for candidate vaccines as they become available; 3) build the understanding of AE reporting and surveillance systems in clinical studies and post-approval use—identifying gaps and strengthen systems; and 4) further refine the Tier Groups for allocation of early vaccine, including persons at high risk, by reviewing proposed vaccine implementation to understand the needs at the state and local levels; reviewing modeling analyses of vaccine implementation strategies; and reviewing results of focus groups and other public engagement as they become available.

Discussion Points

Dr. Atmar noted that as he was listening to Dr. Dooling's presentation, one of the things that occurred to him was that some of the groups potentially being targeted for initial allocation of vaccine could include individuals who are not part of the persons participating in the Phase 3 efficacy trials, such that the groups who are participating in the Phase 3 efficacy trials may not be initially prioritized for vaccine allocation or use once there is an EUA or vaccine is licensed. It raises in his mind the question of equity that the individuals who are assuming the risk participating in trials may not be some of the initial groups who have or will be targeted for vaccination. This gets at the definition of essential personnel, such as people working in the grocery store. He had not heard a discussion about that kind of equity in terms of rolling out the vaccine and was wondering if that had been discussed by the WG.

Dr. Dooling indicated that representation and inclusive clinical trials has certainly been discussed by the WG in that everyone they think is at risk for COVID-19 should be represented in clinical trials to maximize their generalizability. She was encouraged to hear Dr. Ledgerwood's presentation earlier in the day about the lengths to which the recruiting entities have gone and are committed to going to make sure that these Phase three clinical trials are truly representative of all communities. In terms of ensuring equity across essential workers, including all of those people whose duties have demanded that they go into public settings and put themselves at risk to do their jobs (people in the food system, grocery store workers, et cetera), that is absolutely front of mind in the WG considerations. They hope to move the prioritization work forward so that mechanisms to reach those populations can be developed in a timely way so that people who need to be at the front of the line can be.

Dr. Fryhofer (AMA) said that speaking as a primary care physician and on behalf of the AMA, they greatly appreciate the WG's considerations for vaccine prioritization. The AMA Ethics Committee is also assessing these issues. The AMA and its Center on Health Equity strongly support attention to equity and diversity in this process, and they want to reinforce the importance of safety and transparency and also the spirit of health equity. It is so important to make sure that these Phase 3 trials that are looking at safety and efficacy include ethnic and racial diversity; are representative of the US population; and take into account age, individuals with comorbidities, and vulnerable populations.

Dr. Lee said that as they are thinking about the benefits and risks of vaccine balanced against the benefits and risks of disease, they recognize the benefit/risk balance of the populations who are incorporated in the clinical trials. That will be better known at the end of the Phase 3 clinical trials. The benefit/risk balance of vaccine and populations not included in trials, such as pregnant women, will continue to be a challenge. With that in mind, her thinking on this is that there are still risks of having disease and those still need to be considered. Even though the benefits and risks of the vaccine may be less well-known, the risk of disease can be substantial in certain populations. She does not think it is necessarily a contraindication, but rather further discussion is needed and it is very important that access is not limited to populations who might need it. She continues to hope that those clinical trials will be as inclusive as possible.

Certification

Upon reviewing the foregoing version of the July 29, 2020 ACIP meeting minutes, Dr. Jose Romero, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
July 1, 2019 – June 30, 2020

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