

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

**Advisory Committee on
Immunization Practices (ACIP)**



**Summary Report
January 27, 2021
Atlanta, Georgia**

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MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention

Atlanta, Georgia 30329

January 27, 2021

<u>AGENDA ITEM</u>	<u>PRESIDER/PRESENTER(s)</u>
Wednesday, January 27, 2021	
10:00 Welcome & Introductions	Dr. José Romero (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary, CDC)
Coronavirus Disease 2019 (COVID-19) Vaccines	
Introduction	Dr. Beth Bell (ACIP, WG Chair)
AstraZeneca COVID-19 vaccine (AZD1222)	Dr. Tonya Villafana (AstraZeneca)
11:15	Break
11:30 COVID-19 Epidemiology among Children	Dr. Angela Campbell (CDC/NCIRD)
Pediatric COVID-19 Clinical Trials	Dr. Emily Erbeling (NIH)
12:30	Break
1:00 Vaccine Safety Technical Subgroup (VaST) introduction	Dr. Grace Lee (ACIP, VaST Co-chair)
COVID-19 Vaccine Safety Update	Dr. Tom Shimabukuro (CDC/NCEZID)
VaST assessment of safety data	Dr. Grace Lee (ACIP, VaST Co-chair)
2:30	Break
2:45 Update on COVID-19 Vaccine Administration	Dr. Amanda Cohn (CDC/NCIRD)
COVID-19 Vaccine Effectiveness Studies	Dr. Katherine Fleming-Dutra (CDC/NCIRD)
Work Group Interpretation and Next Steps	Dr. Sara Oliver (CDC/NCIRD)
4:15	Break
4:30 Public comment	
5:00 Adjourn	
Acronyms	
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
COVID-19	Coronavirus disease 2019
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
SARS-CoV-2	Severe acute respiratory syndrome coronavirus
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
Ad.26	Adenovirus 26
ADE	Antibody-Dependent Enhancement
AE	Adverse Event
AECI	Adverse Events of Clinical Interest
AESI	Adverse Events of Special Interest
AGS	American Geriatric Society
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIM	Association of Immunization Managers
AMA	American Medical Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APTR	Association for Prevention Teaching and Research
ARDS	Acute Respiratory Distress Syndrome
ASTHO	Association of State and Territorial Health Officers
BARDA	Biomedical Advanced Research and Development Authority
BMI	Body Mass Index
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CID	Clinical Infectious Diseases
CISA	Clinical Immunization Safety Assessment
CISA	Cybersecurity and Infrastructure Security Agency
CIVICs	Collaborative Influenza Vaccine Innovation Centers
CKD	Chronic Kidney Disease
CLD	Chronic Liver Disease
CMS	Center for Medicare and Medicaid Services
COD	Cause of Death
COI	Conflict of Interest
COID	Committee on Infectious Diseases
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CSTE	Council of State and Territorial Epidemiologists
CVD	Center for Vaccine Development and Global Health
DNA	Deoxyribonucleic Acid
DNI	Do Not Intubate
DNR	Do Not Resuscitate
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
EHR	Electronic Health Record
EMA	European Medicines Agency
EUA	Emergency Use Authorization
EV	Enterovirus
FDA	Food and Drug Administration
GACVS	Global Advisory Committee on Vaccine Safety

GMT	Geometric Mean Titers
HCP	Health Care Personnel / Providers
HCW	Health Care Workers
HHS	(Department of) Health and Human Services
HRSA	Health Resources and Services Administration
IB	Investigator Brochure
ICF	Informed Consent Form
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IFN γ	Interferon Gamma
IHR	Institute for Health Research
IHS	Indian Health Service
IIS	Immunization Information Systems
IL	Interleukin
IM	Intramuscular
ISO	Immunization Safety Office
ISTM	International Society for Travel Medicine
KFF	Kaiser Family Foundation
KPCO	Kaiser Permanente Colorado
LTCF	Long-Term Care Facilities
MAAE	Medically-Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MIS-C	Multisystem Inflammatory Syndrome in Children
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>
mRNA	Messenger Ribonucleic Acid
NAAT	Nucleic Acid Amplification Test
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
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
NFID	National Foundation for Infectious Diseases
NHP	Non-Human Primates
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NMA	National Medical Association
NPI	Non-Pharmaceutical Intervention
NS3	National SARS-CoV-2 Strain Surveillance
NVAC	National Vaccine Advisory Committee
OID	Office of Infectious Disease
OIDP	Office of Infectious Disease Policy and HIV/AIDS
OVS	Operation Warp Speed
PALISI	Pediatric Acute Lung Injury and Sepsis Investigator's Network
PHAC	Public Health Agency Canada
PhRMA [®]	Pharmaceutical Research and Manufacturers of America [®]
PI	Principal Investigator
PICFLU Study	Pediatric Intensive Care Influenza PICFLU Study
PIDS	Pediatric Infectious Disease Society
PPE	Personal Protective Equipment

PreVAIL kids	Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence
PRISM	Pediatric Research Immune Network on SARS-CoV-2 and MIS-C
PT	Preferred Terms (MedDRA)
RADx SM	Rapid Acceleration of Diagnostics SM
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RR	Relative Risk
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SHEA	Society for Healthcare Epidemiology of America
SII	Serum Institute of India
SMEs	Subject Matter Experts
SNF	Skilled Nursing Facilities
SPHERES	SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology and Surveillance
SVI	Social Vulnerability Index
TNF	Tumor Necrosis Factor
UK	United Kingdom
UMB	University of Maryland Baltimore
UMMC	University of Mississippi Medical Center
UMSOM	University of Maryland School of Medicine
US	United States
USG	US Government
USPHS	US Public Health Service
VA	(US Department of) Veteran's Affairs
VA ADERS	VA Adverse Drug Event Reporting System
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VaST	ACIP COVID-19 Vaccine Safety Technical Subgroup
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VP	Viral Particles
VRBPAC	Vaccines and Related Biological Products Advisory Committee Meeting
VSC	Vaccine Safety Coordinator
VSD	Vaccine Safety Datalink
VTEU	Vaccine Treatment Evaluation Unit
WG	Work Group
WGS	whole genome sequencing
WHO	World Health Organization

January 27, 2021: Opening Session

José Romero, MD, FAAP
ACIP Chair

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Romero called to order the January 27, 2021 emergency meeting of the Advisory Committee on Immunization Practices (ACIP), the purpose of which was to discuss Coronavirus Disease 2019 (COVID)-19 vaccines.

Dr. Cohn welcomed everyone and noted that the final agenda and webcast link could be accessed on the ACIP website, and that copies of the slides for this meeting could be accessed at the following URL:

<https://www.cdc.gov/vaccines/acip/meetings/slides-2021-1-27-21.html>

Additionally, the slides to be presented during this meeting were made available through a ShareFile link for ACIP Voting, Liaison, and *Ex-Officio* members. The live webcast videos will be posted approximately 1 week following the meeting, and the meeting minutes also will be posted to the ACIP website.

In terms of meeting logistics, participants were instructed to raise their hands virtually when Dr. Romero opened the floor for discussion and to disable their video or mute their phone lines to reduce issues with the Zoom connection. 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 as much as possible.

The next regularly scheduled ACIP meeting will be convened on February 24-25, 2021. An emergency meeting will be scheduled and announced if data become available that ACIP needs to consider before that time.

Dr. Cohn explained that there would be an oral public comment session at 4:30 PM EST. Given that many more individuals registered to make oral public comments than could be accommodated, selection was made randomly via a lottery. Those individuals who were not selected and any other individuals wishing to make written public comments may submit them through <https://www.regulations.gov> using Docket Number CDC-2021-0002. Further information on the written public comment process can be found on the ACIP website.

ACIP members 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, 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 those vaccines, but are prohibited from participating in committee votes. Regarding other vaccines of the concerned company, a member may participate in discussions with the provision that he/she abstains on all votes related to that

company. At the beginning of each meeting, ACIP members state any COIs. No votes were on the agenda for this meeting.

Dr. Romero indicated that Dr. Grace Lee will serve an additional term from July 2020 through June 2021 as a bridging period in preparation to become the next ACIP Chair. In addition, he introduced the following incoming ACIP members:

- ❑ Dr. Wilbur Chen, who is a Professor of Medicine at the Center for Vaccine Development and Global Health (CVD) within the University of Maryland School of Medicine (UMSOM). He also is the Director of the University of Maryland Baltimore (UMB) Travel Medicine Practice. His research interest is in developing vaccines against pathogens which afflict low and middle income countries. He is a Co-Investigator of the NIAID-funded Vaccine Treatment and Evaluation Unit (VTEU) and the NIAID-funded Collaborative Influenza Vaccine Innovation Centers (CIVICs).
- ❑ Dr. Matthew Daley is a Senior Investigator at the Institute for Health Research (IHR) within Kaiser Permanente Colorado (KPCO). He has extensive experience in the areas of vaccine safety, parental vaccine hesitancy, and immunization services delivery. He is an Investigator in the Vaccine Safety Datalink (VSD) and an Associate Professor of Pediatrics in the Department of Pediatrics at the University of Colorado School of Medicine.
- ❑ Dr. Camille Kotton is the Clinical Director of the Transplant and Immunocompromised Host Infectious Diseases in the Infectious Diseases Division of Massachusetts General Hospital, and an Associate Professor of Medicine at the Harvard Medical School. She is an Infectious Diseases Clinician with special expertise in the area of care of complex patients undergoing solid organ transplantation with cancer. She also is a national expert in vaccination and zoonotic infectious diseases in the immunocompromised host.
- ❑ Dr. Sarah Long is a Professor of Pediatric Infectious Diseases at Drexel University College of Medicine. She is an Attending Physician in Infectious Diseases at St. Christopher's Hospital for Children. She has over 4 decades of contributions in the field of pediatric infectious diseases. She has been a member of the Food and Drug Administration (FDA) Vaccines and Related Biological Products Advisory Committee (VRBPAC) and the American Academy of Pediatric (AAP) Committee on Infectious Diseases (COID).

Dr. Romero then conducted the roll call. No COIs were declared for this meeting. A list of Members, *Ex Officio* Members, and Liaison Representatives is included in the appendixes at the end of the full minutes for the January 27, 2021 ACIP meeting.

Coronavirus Disease 2019 (COVID-19) Vaccines: January 27, 2021

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 introduced the session, first drawing attention to the following publications that appeared in December 2020:

- The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine — United States, December 2020¹
- The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Moderna COVID-19 Vaccine — United States, December 2020²
- The Advisory Committee on Immunization Practices' Updated Interim Recommendation for Allocation of COVID-19 Vaccine — United States, December 2020³

In January 2021, the COVID-19 Work Group (WG) covered a number of topics in terms of the current situation and looking forward, including safety updates, COVID-19 in children, plans for clinical studies of COVID vaccine in children, plans for vaccine effectiveness studies, and a number of issues related to clinical guidance for the use of messenger ribonucleic acid (mRNA) COVID-19 vaccines.

Dr. Bell indicated that the day's agenda would include presentations on the following topics, which would be followed by a public comment session:

- AstraZeneca COVID-19 Vaccine (AZD1222) Development Program
- Update on COVID-19 Vaccine Administration
- Vaccine Safety Technical Subgroup (VaST) Introduction
- COVID-19 Vaccine Safety Update
- VaST Assessment of Safety Data
- COVID-19 Epidemiology among Children
- Pediatric COVID-19 Clinical Trials
- COVID-19 Vaccine Effectiveness Studies
- Work Group Interpretation and Next Steps

¹ MMWR Morb Mortal Wkly Rep 2020;69:1922-1924. DOI: <http://dx.doi.org/10.15585/mmwr.mm6950e2>

² MMWR Morb Mortal Wkly Rep 2021;69:1653-1656. DOI: <http://dx.doi.org/10.15585/mmwr.mm695152e1>

³ MMWR Morb Mortal Wkly Rep 2021;69:1657-1660.

DOI: <http://dx.doi.org/10.15585/mmwr.mm695152e2externalicon>

AstraZeneca COVID-19 Vaccine (AZD1222)

Tonya Villafana, PhD, MPH
VP Global Franchise Head, Infection

Dr. Villafana presented on the AZD1222 adenoviral vector platform and the early clinical data that supported moving forward into the US Phase III study, non-investigational new drug (IND) Phase III efficacy and safety trials from which an interim analysis was recently published in *The Lancet* and for which the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) issued a temporary supply authorization, and vaccine storage and handling.

The Phase III trial in the US is ongoing and enrollment is complete. This trial will be the primary basis for the Emergency Use Authorization (EUA) application to the FDA, with supporting data from the non-IND trials conducted outside the US. In April 2020, AstraZeneca committed to a partnership with the University of Oxford to ensure broad and equitable vaccine access globally and not-for-profit during the pandemic. Vaccine immunogenicity, efficacy, and safety were demonstrated for AZD1222 in four ongoing Phase I-III non-IND trials conducted in the UK, Brazil, and South Africa. As mentioned, data from these trials supported UK MHRA authorization for temporary supply. AZD1222 also has EUA in several markets. The vaccine is supplied in 5 ml preservative free, non-latex multidose vials to be stored at 2°-8°C for at least 6 months.

In terms of background on the platform and the early clinical data that supported moving forward to Phase III, AZD1222 is a non-replicating chimp adenovirus-vectored vaccine expressing the spike SARS-CoV-2 antigen⁴. The chimp adenovirus avoids issues with pre-existing immunity that is commonly seen with human adenoviruses⁵. The vaccine has been shown to induce strong B- and T-cell responses after a single vaccination⁴. Prior to April 2020, the group at Oxford had conducted several Phase I studies and early stage studies with this vector platform used for a variety of disease pathogens. About 330 subjects had been vaccinated with various vaccines using the platform. These data were instrumental to leverage moving forward very quickly into clinical studies with the AZD1222 vaccine. The dose that was selected for clinical development moving forward is 5×10^{10} viral particles (VP) as an intramuscular (IM) injection, 0.5 ml⁴.

In collaboration with the University of Oxford, AstraZeneca has conducted a global clinical development program to support the goal of equitable access. The first trial that was started in April 2020 began in the UK and was a Phase I/II study⁶. The interim results from that study supported moving forward into Phase II/III studies in the UK⁷, a Phase III study in Brazil⁸, and a Phase I/II study in South Africa. The results were instrumental in moving forward into the US Phase III study⁹, which also includes enrollment in sites in Chile and Peru¹⁰. AstraZeneca has a number of studies ongoing globally, which are mostly safety and safety and immunogenicity studies to support licensure and use in those locations.

⁴ Folegatti PM, et al. *Lancet* 2020;396:467–478

⁵ Dicks MDJ, et al. *PLoS One* 2012;7:e40385

⁶ Study NCT04324606. [ClinicalTrials.gov](https://clinicaltrials.gov) website

⁷ Study NCT044400838. [ClinicalTrials.gov](https://clinicaltrials.gov) website

⁸ Study NCT04536051. [ClinicalTrials.gov](https://clinicaltrials.gov) website

⁹ Study NCT04444674. [ClinicalTrials.gov](https://clinicaltrials.gov) website

¹⁰ Study NCT04516746. [ClinicalTrials.gov](https://clinicaltrials.gov) website

COV001 was the first in-human study and the Phase I/II study that enrolled in the UK. This study enrolled 1077 participant 18-55 years of age. The study was originally designed to evaluate a single dose of the vaccine candidate, but a cohort of 10 participants was initially included who received 2 doses of the vaccine 28 days apart. Participants were randomized to receive either a dose of the vaccine or a control vaccine for meningitis. After a single dose of the vaccine, there was a nice rise in antibody titers in response to vaccination. When given a second dose 28 days later, there was a boost of these antibody responses. For both a single and two doses of vaccines, the responses were similar in range to what is seen with convalescent sera antibody titers. In an assay run by Public Health England (PHE) looking at neutralizing activity against the SARS-CoV-2 virus, approximately 91% of vaccinees had a neutralizing antibody response after a single dose of the vaccine. After 2 doses, 100% of vaccinees had a response. These data were very supportive in moving forward with a 2-dose vaccine strategy, which was implemented for the rest of the clinical development program¹¹.

Older adults are disproportionately impacted by COVID-19 with severe outcomes. They are a priority population for vaccination and inclusion in clinical trials. Prior to being able to enroll older adults in AstraZeneca's large-scale efficacy studies, they were included in the Phase II portion of the COV002 trial, which is a Phase II/III study. In terms of antibody responses in older adults when compared to younger adults, the older adults have similar immune responses in terms of neutralizing antibody activity to the younger adults 18-55 years of age. These data were supportive in allowing AstraZeneca to move forward to older adult populations in its Phase III program¹².

A key question for COVID-19 vaccine development regards whether vaccines causes antibody-dependent enhancement (ADE). Pre-clinical animal studies demonstrated no evidence of ADE for AZD1222. From previous SARS-CoV-1 and other vaccines, it is known that Th2 polarization is associated with ADE. In terms of results from inter-cytokine staining to determine the cytokine profile of CD4 T-cells in vaccinated individuals, participants vaccinated with AZD1222 demonstrated a Th1-biased T-cell response, with induction of interferon gamma (IFN γ), interleukin-2 (IL-2), and tumor necrosis factor (TNF) cytokines. Notably, Th2 cytokines were not detected. These are all spike-specific responses. These data were also supportive for moving into the Phase III study¹³.

AZD1222 was well-tolerated in Phase I/II studies. Most adverse events (AEs) were mild to moderate in severity and the majority resolved within 7 days. Local and systemic reactions were approximately 20% less frequent after the second dose. AEs were similar in nature to those previously reported for the viral vector platform and included injection site pain, feeling feverish, muscle ache, and headache. Local and systemic reactions were more common in participants given AZD1222 than the control vaccine (MenACWY). Less reactogenicity, both local and systemic, was observed in older adults. About 30% of participants >70 years of age experienced fewer mild/moderate local reactions than those <55 years of age. A similar trend was seen for systemic reactions when comparing those over 70 years of age to those less than 55 years of age¹⁴.

¹¹ Folegatti P et al. *The Lancet*. 2020

¹² Ramasamy M et al. *Lancet*. 2020

¹³ Exploratory analysis; unpublished results

¹⁴ Ramasamy MN et al. *Lancet*. 2020. [https://doi.org/10.1016/S0140-6736\(20\)32466-1](https://doi.org/10.1016/S0140-6736(20)32466-1). Accessed January 21, 2021

In totality, the antibody responses observed, the Th1 cytokine profile, and the safety data were supportive in moving forward to the Phase III study in the US. Other data have been published in the *Lancet* and *Nature* that profiles the immunology of immune responses in the vaccinees in more detail.

The Phase III trial in the US, D8110C00001, was designed to evaluate the safety and efficacy of the vaccine in over 30,000 volunteers. The study began in August 2020. Volunteers were randomized 2:1 to receive either 2 doses of AZD1222 or a saline placebo control vaccine. This study is ongoing in 88 sites in the US, Chile, and Peru (Study NCT04516746; clinicaltrials.gov). Adults 18 years and older were included, with a target to include 25% of subjects above the age of 65 years. Study enrollment included diversity targets selected in agreement with the US Government (USG). It was very important to AstraZeneca to have a very diverse population represented in its Phase III study.

The primary efficacy endpoint is the first case of SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR)-positive symptomatic illness occurring more than 14 days post-administration of study intervention. Participants are included if they meet the following criteria at any point from Day 1 (initial visit) through Day 14:

Subjects will be counted as a case if they have: 1) One or more category A findings OR 2) Two or more category B symptoms		
Specificity (Pathogen Confirmation)	Category A: Lower respiratory tract involvement (one or more)	Category B: Systemic/ other symptoms (two or more)
SARS-CoV-2 confirmed • Positive RT-PCR	<ul style="list-style-type: none"> • Pneumonia diagnosed by chest x-ray, or CT scan • O₂ sat of ≤ 94% on room air or 2 percentage point drop from baseline • New or worsening dyspnea/ shortness of breath 	<ul style="list-style-type: none"> • Fever > 37.8° C (100° F) or feverishness • New or worsening cough • Myalgia/ muscle pain • Fatigue that interferes with activities of daily living • Vomiting or diarrhea • Anosmia or ageusia

The safety endpoint is occurrence of AEs for 28 days post-each dose and AE, medically-attended adverse events (MAAEs), and adverse events of special interest (AESI) are assessed from Day 1 post-treatment throughout the study.

In terms of diversity targets and older adults, US enrollment includes 11.2% Hispanic/Latin, 9.8% Black or African American, 5.3% Asian, 1.8% American Indian, 0.4% Hawaiian or Pacific Islander, and 71.5% White. Older adult enrollment came very close to the target of 25% over the age of 65 years, with about 23.6% 65+ years old and 76.4% <65 years old. The majority of participants (57.8%) had a comorbidity such as chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), heart failure, coronary artery disease, diabetes, asthma, high blood pressure, liver disease, and/or body mass index (BMI) of 30 or higher to highlight a few. A total of 32,459 participants were enrolled, of whom 26,327 received a second dose by January 21, 2021.

There was a clinical hold during the course of study D8110C00001. The study was initiated on August 28, 2020. AstraZeneca paused the study on September 6, 2020 in response to an event of transverse myelitis that was reported in the Phase II/III study conducted by the University of Oxford in the UK. This was done out of an abundance of caution for the safety of participants in the study. During the clinical hold, AstraZeneca provided a lot of information to the FDA,

including additional details on neurological events in studies sponsored by AstraZeneca and the University of Oxford, as well as any analyses of available clinical safety data from AZD1222 and other ChAdOx-1 viral vector platform studies that were requested by the agency. A number of changes were implemented in the study conducted in response to the event. The risk language in the Informed Consent Form (ICF) and Investigator Brochure (IB) was updated and a number of protocol changes were made, including accelerated and increased safety reporting and the establishment of an independent expert neurology panel. Dr. Villafana emphasized that both for the US study and the studies conducted outside the US that were sponsored by the University of Oxford, there are DSMBs that review the safety information in these studies on an ongoing basis. The participant who experienced the event continues to recover and AstraZeneca continues to provide the FDA and other agencies with information requested regarding safety events that occur in these studies.

Regarding the non-IND Phase II/III program interim results for the outside US studies that were sponsored by the University of Oxford from a data cut on November 4th, the interim analysis was a pooled analysis across 4 ongoing studies. The analysis included 23,745 participants across these studies as follows: UK COV001 (N=1,077) Phase I/II single-blinded study of adults aged 18–55 years, UK COV002 (N=12,390) Phase II/III single-blinded, ≥18 years (including elderly), Brazil COV003 (N=10,300), Phase III single-blinded, ≥18 years (including elderly), and S. Africa COV005 (N=2,070), and Phase I/II double-blinded, adults aged 18–65 years¹⁵. The primary endpoint of the study is nucleic acid amplification test (NAAT) positive for symptomatic COVID-19. Prior to conducting any analyses, a global statistical analysis plan for pooling data across the studies was developed and discussed with regulators. Prespecified analyses that would contribute to assessment of efficacy were discussed and agreed upon. The population in the primary efficacy analysis included 11,636 participants from the UK/Brazil Phase III studies, which are the 2 studies that met the inclusion criteria for the interim analysis with 5 cases of COVID-19. A total of 23,745 participants were included in the safety analysis across all 4 studies. The median for follow-up for post-Dose 1 was 105 days and for post-Dose 2 was 62 days¹⁶.

In terms of the results for the Phase III interim efficacy analysis for AZD1222, the pooled analysis demonstrated 70.4% (95.8% CI: 54.8% to 80.6%) vaccine efficacy at preventing symptomatic COVID-19. The subgroup analysis with standard versus low dose of the vaccine demonstrated efficacy at preventing symptomatic COVID-19 of 62.1% (41.0% to 75.7%). There were no hospitalizations or severe COVID-19 in vaccinated participants from 21 days after the first dose. Across the 4 studies, the vaccine exhibited a favorable safety profile. SAEs occurred in 168 participants, 79 of whom received AZD1222 and 89 of whom received MenACWY or saline control. Among the 168 participants, there were 175 SAEs, of which 4 were considered possibly related to intervention of either the experimental vaccine or the control. In the AZD1222 group, 1 of the SAEs was a case of pyrexia 2 days after Dose 1 that was treated with paracetamol and resolved the same day and the second was the case of transverse myelitis that occurred 14 days after Dose 2. In the control group, there was 1 case of autoimmune hemolytic anemia 10 days after MenACWY and 1 case of transverse myelitis 2 months after the first control dose. The majority of SAEs resolved within a few days of vaccination. The reactogenicity profile was similar to the Phase I/II study conducted in the UK and were generally milder and reported less frequently after Dose 2 in older adults ≥65 years old¹⁵.

¹⁵ Voysey M, et al. Article and supplementary appendix. *Lancet*. 2020. [http://dx.doi.org/10.1016/S0140-6736\(20\)32661-1](http://dx.doi.org/10.1016/S0140-6736(20)32661-1). Accessed January 21, 2021.

¹⁶ COVID-19 Vaccine AstraZeneca, solution for injection in multidose container COVID-19 Vaccine (ChAdOx1-S [recombinant]).

Moving to vaccine storage and handling, the vaccine can be stored in the refrigerator at 2° to 8°C. It has a shelf life of 6 months and cannot be frozen. In terms of administration, the vaccine will be provided as a multi-dose vial. After the first puncture, it can be stored up to 6 hours at room temperature or up to 48 hours at 2°-8°C, with a total storage time not to exceed 48 hours. No dilution or reconstitution of the vaccine is needed.

In summary, AstraZeneca believes that AZD1222 offers a potential to address the global COVID-19 crisis. AZD1222 induces robust immune responses against the SARS-CoV-2 spike protein. Spike antibodies increased after a second dose with geometric mean titers (GMTs) comparable to convalescent sera. Neutralizing antibody titers were observed in all participants following Dose 2. There was a strong Th1-biased CD4+ T-cell response observed. A lot of immunology data have been published already on the vaccine. The US Phase III study is ongoing with 32,459 participants enrolled with co-morbidities, older adults, and people with diverse backgrounds. A total of 26,327 participants received a second dose by January 21, 2021. Efficacy and safety were demonstrated in 4 Phase I-III studies in the UK, Brazil, and South Africa. AZD1222 has the potential to address the SARS-CoV-2 pandemic and has been authorized in 18 countries under emergency use or full approval as of January 25, 2021.

Discussion Points

Dr. Romero asked whether the vaccine's effect has been assessed on the variants that have arisen and if the prevalence was known of the variants reported in the literature from South Africa and Brazil at the time of the study.

Dr. Villafana indicated that AstraZeneca is continuing work to understand the activity of AZD1222 against variants that are circulating in the places the studies are being conducted.

Dr. Pollard added that an analysis is currently underway for the UK B.1.1.7 variant that is assessing neutralizing antibody data, which is anticipated to be completed and submitted for publication in the next few days. Since the middle of December, that variant has been dominant in the UK since it spread so rapidly. Therefore, it should be possible to conduct an analysis on efficacy against that within a week. That is very much related to the ability to get sequence data. In parallel, they are looking at neutralizing activity against the South African variant. There is a possibility in the trial to look directly at efficacy against the South African variant, which has increased rapidly in the country since November. About 90% of the disease there is thought to be caused by the new variant. The trial site in Brazil is not directly around the epicenter for the origin of the Brazil variant, so it is not clear whether they will be able to make a direct comment about efficacy in Brazil. However, they are working with local teams on sequencing the virus from the individuals in the trials who have symptoms and are looking at neutralizing antibody against the virus. That will take a little longer because they are slightly behind on the sequencing.

In response to a question from Dr. Poehling regarding Th1 and Th2 responses, Dr. Kelly indicated that there were 70 participants all from the UK studies, COV001 and COV002. Approximately 40 subjects were between the ages of 18-64 years and 30 subjects over 65 years of age. In that analysis, they looked at lineage markers (CD3, CD4, and CD8), functional markers (Th1 and Th2 cytokines), and additional phenotypic markers (CD69, CD28, CDR7, and CD45RA). There was strong induction of Th1 cytokines in those study participants after Dose 1. Those cytokines did not rise but remained elevated after Dose 2. No induction was seen of Th2 cytokines.

Dr. Talbot inquired about the number of trial participants who have dropped out as they have become eligible for vaccine in the US and how that might impact data collection and duration of follow-up.

Dr. Gonzalez-Lopez responded that 30,000 participants have already decided to stay in the study because they are susceptible to receive the vaccine in the US. This number is random and the potential impact on efficacy is going to be very limited because the efficacy is driven by the number of cases and they are very close to having the number of cases needed for the interim and primary analyses. If the number of cases continue to increase in the future, they probably will have to consider what will be the impact in the long-term safety follow-up. They are working on a potential plan for a safety follow-up system to guarantee they can keep as many participants in the study as possible.

Dr. Quach (NACI) requested information about whether there is a difference between the AstraZeneca vaccine and the one that is produced by the Serum Institute of India (SII), which seems to use the same platform, and whether they have any lot-to-lot comparisons of immunogenicity.

Dr. Villafana indicated that it is the same vaccine construct. AstraZeneca has a sublicense with the SII for them to manufacture the vaccine for India and for lower-middle income countries. The SII product is called COVISHIELD™. A study was conducted in India that included 1600 participants. Within that study, AZD1222 and COVISHIELD™ were included.

In terms of the neutralizing antibody, Dr. Long thought it seemed in the middle age group there was either no or very modest booster response from Dose 2. She also noted in the *Lancet* publication that there was an amendment to the protocol for the prophylactic use of paracetamol in some of the sites and that reactogenicity was less on the second dose, and she wondered if those were related. She also wondered if they assessed antibody responses in those who received paracetamol and those who did not. It is known that prophylactic acetaminophen in the US has been associated with diminished response to pneumococcal conjugate vaccine for instance.

Dr. Villafana indicated that prophylactic use of paracetamol did not have any impact on immunogenicity in AstraZeneca's studies.

Dr. Pollard added that they have seen consistently with the second dose of this viral vector that reactogenicity is lower, so they had a subgroup in which they tried the prophylactic paracetamol and saw that there was some impact, particularly on the more severe systemic reactogenicity. However, it is a modest effect so the subsequent studies have not had prophylactic paracetamol. It is just reactive in those who have symptoms.

Dr. Lee expressed gratitude for the investigation of the variants and how that might impact vaccine efficacy. Recognizing that this is a different platform from the mRNA vaccines, she requested comments on whether there were any severe allergic reactions, Bell's Palsy, and pregnancies during the trial. If there have been pregnancies, she asked whether there is a registry and if the pregnancies are being followed.

Dr. Pollard noted that in the current trial of about 23,000, there are a lot of younger adults who are healthcare workers among whom there are a large number of pregnancies. They are being followed-up through the birth of the child. Because of the relatively short duration, they do not have the data yet. However, they are making good progress on that. It is a challenge to obtain

all of the sequence data from the various counties, so it make take some time before the final analysis is done. Dr. Lindgren added that in the University of Oxford studies, there were 3 reports of Bell's Palsy in the AZD1222 group and 3 in the control group. Regarding pregnancy, the pharmacovigilance plan calls for a pregnancy registry. In terms of severe allergic reactions, hypersensitivity was reported in the clinical trials. There were no reports of anaphylaxis in the clinical trials that could be seen as associated with the vaccine. As with any vaccine, with broader exposure, hypersensitivity reactions will be assessed through active surveillance post-authorization. Dr. Pollard added that from the ingredients that are in the vaccine, the only one that might be associated with that is polysorbate 80, which is a widely used product that is not particularly associated with anaphylaxis to his knowledges. It is one of the ingredients in the adjuvanted influenza vaccine, which does not have any excess rates of anaphylaxis associated with it.

Referring to Slide 15 with the racial and ethnic demographics, Dr. Kimberlin (AAP Redbook) requested clarification about the total number of US participants enrolled. Thinking about the global aspects for this particular product, he inquired as to whether there are pre-existing chimp adenovirus antibodies in different populations on different continents.

Dr. Villafana indicated that of the 32,459 total population enrolled in Study D8110C00001, about 3600 were from Peru and Chile. Dr. Kelly added that there have been historic studies on the population from Gambia in which there was low existing immunity to the chimp adenovirus. In general, in populations in the Northern Hemisphere in many of their sites, they do not see pre-existing immunity. Dr. Villafana added that in non-African populations, the seroprevalence is well under 10%. Dr. Pollard added that seroprevalence is low in all populations, but there is some variability. The key question regards whether that impacts on responses to spike protein. They have not seen any significant differences in responses in different countries in the immune response to spike protein. Indeed, there is no correlation after the second dose to the anti-vector neutralizing antibody that is induced and the response to spike protein.

Dr. Bell inquired as to whether AstraZeneca has been able to do any subgroup analyses they could share with ACIP either stratified by age, comorbidities, or racial/ethnic composition.

Dr. Villafana indicated that VE was about 73.4% in the comorbid population. For the interim analysis, they did not have a large number of older adults so the confidence intervals are wide. With subsequent analyses, they will be able to report out efficacy in the older adult population since there will be more older adults at that time.

Given that adenovirus platforms regardless of serotype can trigger innate immune responses, Dr. Maldonado (AAP) asked about the potential for development of subsequent specific adaptive immunity to the adenovirus platform and the likelihood of that impacting booster responses over time.

Dr. Pollard responded that the fact that the data they have so far does not show a relationship between anti-vector immunity and the spike protein response after the second dose provides some reassurance. In the UK trial, there is a small subgroup who were in previous trials of the same viral vector who have been brought back and received 2 doses of the coronavirus vaccine with viral vector, so they will be able to answer that question very soon.

Dr. Maldonado (AAP) asked whether there was a possible explanation for the biological plausibility between the differential responses and efficacy between the 2 regimens, given that one is a low-dose standard versus the standard dose.

Referring to Slide 30, Dr Villafana indicated that within this study participants received 2 doses at varying intervals depending upon where they were located and enrolled in the study. Participants who received 2 of the standard doses or the low-dose/standard dose combination and interval was accounted for, the responses look very much the same. Therefore, they think that interval is probably associated with the increased efficacy being seen for the low-dose/standard dose group just because many of those participants were in the longer interval group.

Dr. Eckert (ACOG) asked how many pregnant women are included in the trial.

Dr. Lindgren indicated that in the dataset that was analyzed before Christmas, there were 21 women who became pregnant during the trial who based on the exclusion criteria were not pregnant upon enrollment. The pregnancy registry is not yet up and running, but there is a commitment to establish this as quickly as possible.

COVID-19 Epidemiology among Children

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Dr. Campbell presented on COVID-19 in the US, COVID-19 epidemiology in children and teens, and Multisystem Inflammatory Syndrome in Children (MIS-C), which is a complication of SARS-CoV-2 infection.

Beginning with the US COVID-19 epidemiology, from the CDC COVID Data Tracker as of January 24th, more than 24.8 million COVID-19 cases had been reported to CDC, with the most recent 7-day average of more than 168,000 cases per day and over 416,000 deaths, with a 7-day moving average of 3,070 deaths per day¹⁷.

In terms of COVID-19 incidence per 100,000 population by age group, the reported incidence of COVID-19 cases is lowest for children 0-4 and 5-17 years. Multiple factors have contributed to under-detection of overall SARS-CoV-2 infections in children, including limitations in testing availability, assay sensitivity, testing and reporting practices, care seeking behaviors, and under-recognition of mild or asymptomatic infection¹⁸. Dr. Campbell's colleagues at CDC have published a statistical model, based on methods previously used to estimate the disease burden of influenza, to account for under-ascertainment and adjust nationally reported COVID-19 case counts to better reflect the true number of SARS-CoV-2 infections. Adjusting for under detection, estimated SARS-CoV-2 infection rates per 100,000 population are lowest in children 0-4 years, but for children 5-17 years are basically the same as for adults¹⁹.

A study that evaluated SARS-CoV-2 seroprevalence in children <18 years, using residual serum samples from May to September, was performed by the University of Mississippi Medical Center (UMMC) which provides clinical laboratory services for university hospitals statewide. Among the 1,603 people tested, the overall seroprevalence was 10.9%. Seropositivity was higher among non-White children. Specifically, seropositivity among Black, non-Hispanic, and Hispanic children was 2.4 and 4.3 times higher respectively than that among White non-Hispanic

¹⁷ <https://www.cdc.gov/covid-data-tracker/index.html#trends>

¹⁸ <https://www.cdc.gov/covid-data-tracker/index.html#demographics>

¹⁹ <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html>

children. Seropositivity among children increased over time from 3.5% among samples collected in May of 2020 to 18.2% by September. These estimates help to track infections among children. In fact, compared with seroprevalence data from older age groups in Mississippi, data from this sample suggested that cumulative infection rates by mid-September among children were similar to those among adults 18–49 years, which was the age group with the highest seroprevalence²⁰.

To gather data on susceptibility and understand the role of children in transmission, CDC is supporting a case-ascertained household transmission study with Vanderbilt University in Tennessee and Marshfield Clinic in Wisconsin. An initial analysis of the data was published in an *MMWR*. The data shown during this session included enrollments between the study start in April and November. In brief, index patients are enrolled from outpatient clinics if they have lab-confirmed SARS-CoV-2, symptoms for <7 days, and live with at least 1 other person who has not had acute illness in the past week. All enrolled index patients and their household members were followed for 14 days, with daily symptom reporting and self-collected nasal swabs to look for secondary transmission²¹.

Thus far the study sites have enrolled 147 index cases, who were enrolled a median of 3.5 days after illness onset, and 306 of their household contacts have been enrolled. The index patients are more middle-aged than the household contacts. In total, the sites have enrolled 22 index cases who are children and 118 household contacts who are children. For this analysis, Dr. Campbell showed only households that had co-primary cases and contacts who were likely tertiary cases were excluded. After these exclusions, 78 household contacts (49%) were positive for SARS-CoV-2 in follow-up. Among these 78 people with secondary infection, younger children <12 years, in general, were less likely to be symptomatic and had many fewer symptoms than adults. In terms of the secondary infection rates plotted by the age of the index case to help understand age-related differences in transmission from the index case, in general, symptomatic children in the top two age categories can transmit SARS-CoV-2. The sample size is most robust in the adults 18-49 years of age and there are overlapping confidence intervals around the estimated secondary infection rates, but in looking at the point estimates, symptomatic children seem to transmit SARS-Cov-2 less frequently than adults 18-49 years of age. Regarding the secondary infection rates by the age of the household contacts in order to look at how susceptible different age groups are to SARS-CoV-2 infection, children who were exposed in the household had a similar risk of secondary infection as adults²².

A similar study was conducted as a field investigation in Utah and Wisconsin earlier in the spring of 2020. These data are published in *Pediatrics* and they found that secondary infection rates were similar among pediatric and adult household contacts or, in other words, children were as susceptible to SARS-COV-2 infection as adults²³.

Moving from an outpatient look at susceptibility and transmission to the hospital, based on data from the COVID-Net hospital surveillance system showing laboratory-confirmed COVID-19 hospitalization rates per 100,000, children <18 years of age have the lowest cumulative rate of COVID-19 associated hospitalizations. Those are 35.4 and 21.2 per 100,000 for 0-4 and 5-17

²⁰ C. Hobbs, et al. CDC COVID-19 Response Team, unpublished data

²¹ FLUTES-C Study. Grijalva, et al. *MMWR* 2020;69(44):1631-34

²² FLUTES-C Study. Preliminary data, subject to change

²³ Laws RL, et al. *Pediatrics*. 2020; doi:10.1542/peds.2020-027268

years, respectively for simplicity compared with all people age 18 and older with a rate of 460.1 per 100,000²⁴.

Although children with COVID-19 may have mild or no symptoms, children can get severely ill from COVID-19. While there is still a lot to learn, children with certain underlying conditions may be more likely to have severe illness. These include asthma or chronic lung disease; diabetes; genetic, neurologic, or metabolic conditions; sickle cell disease; heart disease since birth; immunosuppression; medical complexity; and obesity²⁵. Looking at further data from COVID-NET, 52% of Children <18 years of age hospitalized with COVID-19 had an underlying condition. Based on these data, the leading condition was obesity at between 35%-40% of the children. This is followed by asthma, and other chronic medical conditions. It is important to note that for influenza, the obesity proportion is more on the order of 9%-10% of hospitalized children with influenza. The leading underlying condition for influenza is generally asthma at about 15%-20% of laboratory-confirmed influenza hospitalizations²⁶. Additional data from COVID-NET show that children are about similarly likely to be admitted to the intensive care unit (ICU) at around 30% of hospitalized children and adults. Children <18 years of age who are hospitalized with COVID-19 are less likely than adults to experience mechanical ventilation or in-hospital death²⁷. In terms of COVID-19 mortality rates, there is a 0.4-0.3 per 100,000 mortality rate for children, which increases significantly in older adults²⁸.

Moving MIS-C, MIS-C is a severe inflammatory syndrome that was first recognized last April in the UK, occurring in children with current or recent infection with SARS-CoV-2. MIS-C is thought to result from delayed, dysregulated host immune response. It is generally delayed 3-4 weeks, but this can be a wider range of 2-6 weeks from preceding COVID-19 illness. Often, MIS-C occurs with no known preceding illness. By May of 2020, cases were reported in New York City and New York State. On May 14th, CDC issued a Health Advisory²⁹ requesting healthcare providers to report patients <21 years of age meeting MIS-C criteria to local, state, or territorial health departments. This is the case definition:

An individual aged <21 years presenting with feverⁱ, laboratory evidence of inflammationⁱⁱ, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**

No alternative plausible diagnoses; **AND**

Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

An *MMWR* published on August 14, 2020 reported results from a latent class analysis to identify similarities and group the first 570 MIS-C cases reported from March through July into distinct classes. Patients in Class 1 had a “typical” MIS-C picture in which 98% tested positive for SARS-CoV-2 by serology. All patients had cardiovascular and nearly all had gastrointestinal

²⁴ https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html

²⁵ <https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/symptoms.html>

²⁶ https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html

²⁷ https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html

²⁸ <https://www.cdc.gov/covid-data-tracker/index.html#demographics>

²⁹ <https://emergency.cdc.gov/han/2020/han00432.asp>; <https://www.cdc.gov/mis-c/hcp/>

manifestations, often with a number of additional organ systems involved and markedly elevated laboratory values of inflammation and markers of cardiac damage. These patients had significantly higher frequencies of shock and myocarditis relative to the other two classes with a very high percentage of ICU admissions. Patients in Class 2 had more of an acute COVID-19/MIS-C combination picture in that 100% tested positive by PCR and patients were significantly more likely to have respiratory involvement with cough, shortness of breath, pneumonia, and acute respiratory distress syndrome (ARDS). Patients in Class 3 were generally younger with a median age of 6 years compared with 9 and 10 year olds in the previous two classes. They had milder illness and relatively higher frequency of rash and mucocutaneous lesions, most similar to Kawasaki disease³⁰.

The CDC MIS-C website shows the health department-reported cases. The most recent January update shows 1659 cases reported and 26 deaths from 47 states, New York City, and Washington, DC. The average age is 8 years, 57% are male, 33% are Hispanic/Latino, and 30% Black, non-Hispanic persons. In terms of the epidemiologic curve of daily MIS-C cases, the first peak was from March to June, primarily in the Northeast. The second peak was from June to September, largely in the South and to a lesser extent the Western US. These peaks followed the first two national COVID-19 peaks by 2-5 weeks. These patterns were consistent by US Census Region. The most recent third peak of the COVID-19 pandemic rose in December and into January in the US and may result in another MIS-C peak, although such an increase may not be apparent for several months because of the delay in the occurrence of MIS-C and additional delays associated with identification and reporting of cases. A surge is beginning to be observed in many states³¹.

Based on data in which CDC estimated the incidence of MIS-C cases from that first peak time period from April to June 2020 in 7 participating jurisdictions, the population-based incidence estimates using a denominator of population of persons <21 years were 1 to 8.5 MIS-C cases per million person-months across the jurisdictions. In addition to population-based incidence estimates, CDC estimated the incidence of MIS-C across groups using a denominator representing total SARS-CoV-2 infections in children, for which the incidence would be expected to be much higher than in the general population. CDC wanted to assess whether certain racial and ethnic groups may be disproportionately represented among MIS-C cases in these groups, even controlling for total SARS-CoV-2 infections, and found that indeed there is a 6-fold higher incidence of MIS-C among Black/African American children relative to White children and a 4- and 3-fold higher incidence among Hispanic and Asian/PI children compared with White children³².

In summary, as of January 24th, over 24 million cases of COVID-19 and over 410,000 COVID-19-associated deaths were reported in the US. Children <18 years have lower rates of COVID-19 reported incidence, hospitalization, and mortality than adults. Children are susceptible to SARS-CoV-2, though younger children tended to have fewer respiratory symptoms than adults. Symptomatic children can transmit SARS-CoV-2. MIS-C is a complication of COVID-19 and has varied clinical presentations. MIS-C is highest, and disproportionately so, among Black/African American children and Hispanic/Latino children. Further studies are needed to fully understand the role of children and teens in SARS-CoV-2 transmission and risk factors for severe illness and complications of COVID-19.

³⁰ Godfred-Cato, et al. *MMWR* 3030;69:1074-80

³¹ <https://www.cdc.gov/mis-c/cases/index.html>; last updated January 8, 2021

³² A. Payne, et al, CDC COVID-19 Response Team, unpublished data

Discussion Points

Dr. Poehling requested more details about the percentage of MIS-C cases that were Types 1, 2, and 3.

Dr. Campbell said that while she did not have the actual percentage, 570 total cases were included. Class 1 included 203, Class 2 had 169, and Class 3 had 198.

Dr. Romero inquired as to whether Dr. Campbell had any information on the impact of the variants that are being seen around the world on the number of cases and/or severity of MIS-C.

Dr. Campbell said that all she could say at this point is that they do not know, but are very interested in this question. There is no evidence to support this right now, but CDC is certainly concerned and is encouraging its partners to submit samples for surveillance MIS-C surveillance for SARS-CoV-2. There is enhanced surveillance now to which they can submit up to 20 additional samples for sequencing per week. There have been discussions with a couple of states about considering submitting additional samples for sequences if they think they are seeing something different. For example, one state was concerned that perhaps they were seeing more severe MIS-C. It is just not possible to figure that out right now because the expected surge following the rise in COVID-19 cases through the winter is being experienced right now.

Dr. Lee expressed appreciation for the deeper dive into understanding the epidemiology in children a little better. Regarding understanding the disproportionate burden of MIS-C in Black and Hispanic children accounting for two-thirds of cases, she wondered if there is any further exploration about whether there is biologic plausibility for that versus disparities in testing rates, particularly in communities of color. If the disparities in testing rates are impacting the denominator in terms of estimating the proportion of MIS-C cases by race/ethnicity, she wondered if perhaps that has an impact on under-ascertainment regarding the overall burden of infection.

Dr. Campbell said she thinks that the information on race/ethnicity is somewhat limited. For example, in the incidence study she showed, there was considerable missing data for race/ethnicity on many of the children, certainly for the reported cases and somewhat from the MIS-C. They are putting out an encouraging call for more complete race/ethnicity data. With respect to the under-ascertainment bias, she did not think the multipliers that take into account all of the different factors related to under-detection for the different races/ethnicities have been done yet. They suspect that there are multiple factors involved that are not all biologic by any means. The CDC analysis is not the only one that has found this, but if it is a testing bias, other analyses would show it also. Nevertheless, they are trying to get a finer level of detail. She is happy to follow-up more about what is being done to help get at under-ascertainment of various races and ethnicities.

Dr. Kimberlin (AAP Redbook) expressed gratitude of the expansion of focus at this appropriate time to be considering children and adolescents moving forward through this pandemic. Regarding the list of risk factors, the CDC website generally lists "Diabetes Type 2," though Dr. Campbell's slides focused on Diabetes. He wondered whether Type 1 diabetics could be considered to be at the same risk as Type 2 diabetics. With the potential to expand over the next several months to recommend COVID-19 vaccine to adolescents, down into children, and perhaps using a phased approach that could include risk factors, he thinks of Type 1 diabetes. He was concerned that the Type 2 listing of risk factors for COVID disease or severe COVID

disease is simply a bias that this is what most adults have. Perhaps the listing on the CDC website should simply be “Diabetes” instead of “Diabetes Type 2.”

Dr. Campbell said that she generally thinks of Type 1 more with regard to children. COVID-NET does not differentiate between Types 1 and 2 diabetes mellitus. Given that these are children, Type 1 is likely to be predominantly represented. There is a separate COVID-19 in children webpage where she got the list that she showed.

Dr. Oliver added that the general list with “Diabetes Type 2” is not managed by anybody on the Vaccine Task Force, but they will take this feedback back to the people who manage the list.

Dr. Long noted that they see children who are identified as having MIS-C but who are not sick enough to be treated for it who get better, and it is known that this virus causes a signature innate immune response. If they looked at Class 2 and applied the criteria to adults with COVID-lung disease, she wondered whether a considerable percent would have MIS-A. Regarding the epidemiology, as she looked at the *MMWR* in January of the trends in the latest surge, she observed that 14 to 17 year olds are as commonly affected as those over 65 years of age. She wondered if the data that showed 14 to 17 year olds included the latest surge in the younger population (Slide 35).

Dr. Campbell indicated that several of her colleagues are looking through adult charts with a general case definition searching for MIS-A and not necessarily excluding those with primarily respiratory involvement, but also looking for the multi-system involvement and other more classic features. It is harder in adults because there is so much more of the severe COVID spectrum. Cases of MIS-A have been reported in adult patients, but they are still in the information gathering stage about adults because there is certainly some aspects that seem quite classic, but then there is also the spectrum that is harder to tease out.

Referring to Slide 7, Dr. Campbell clarified that the COVID-19 cases went through January 24th, so it did include the latest surge. The younger section of that age group and the children 0 to 4 years of age were under-tested early in the pandemic. To speculate, the bar for 14 to 17 year olds may be so low just because it had a long way to catch up, but they have certainly increased and essentially lead in percent positive now.

Dr. Maldonado (AAP) emphasized the importance of these data as their colleagues begin to dig into the different social and biological determinants of COVID disease for prevention and therapeutic interventions in these populations. She asked about the status of the MIS-C studies from the Request for Applications (RFA) released last year focused on more biological bases for MIS-C and in particular whether there are racial or ethnic differences in expressions of different biological markers for risk and evolution of this disease.

Dr. Campbell said that she did not want to speculate. They recently had MIS-C in a Broad Agency Announcement (BAA) topic list that went out. Those white papers are under review. In addition to national surveillance, one large system that she did not mention that is CDC-funded is the network called Overcoming COVID that initially was the Pediatric Acute Lung Injury and Sepsis Investigator’s (PALISI) Network then the Pediatric Intensive Care Influenza (PICFLU) Study, which basically is a pediatric ICU network that CDC already had been working with to assess severe influenza and vaccine effectiveness against severe influenza outcomes. That pivoted to include COVID and MIS-C surveillance and a number of scientific questions pertaining to COVID and MIS-C in children last year. CDC is still working closely with that network. NIH has a number of MIS-C focused studies that they published funding requests for

and have since awarded, such as the Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM), the Rapid Acceleration of Diagnostics (RADxSM) initiative, and Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence (PreVAAIL klds). There is a lot going on in that sphere.

Dr. Romero noted that while there was a lot of focus on MIS-C, less than 5% of adults have freestanding myocarditis which has been seen in athletes. He asked whether there are any data on myocardial inflammatory disease in children as a freestanding condition not related to MIS-C. With enterovirus (EV), there is a syndrome of chronic debilitating cardiomyopathy that appears years after a primary infection, which can many times be asymptomatic. He wondered if they could see this in 5 to 10 years in young athletes who are developing myocardial disease isolated without MIS-C.

Dr. Campbell indicated that those data are coming from the Overcoming COVID-19 study. There is a paper under review comparing MIC to severe COVID-19 children who were hospitalized. They do have quite a bit of information on the cardiac outcomes in that manuscript. There is an entire Community of Practice at CDC devoted to long COVID-19 outcomes. While they do not want to lose sight of acute COVID and its complications, so they are thinking through these things.

COVID-19 Vaccines for Children

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Dr. Erbelding reported that the USG effort in vaccine trials that was previously called Operation Warp Speed (OWS) is in the process of transitioning to a different name. The goal of the OWS effort was to bring about SARS-CoV-2 vaccines for the whole of the US population. The USG is committed to providing the resources for vaccine trials in pregnant women and the pediatric population. Under the framework of the USG effort, a company can elect to be the sponsor and most do. The protocols must be approved by USG partners, including the National Institute of Allergy and Infectious Diseases (NIAID), the Biomedical Advanced Research and Development Authority (BARDA), and those on the protocol team. The protocol chairs include NIAID-funded investigators. The USG partners and company jointly oversee operationalization of the studies. A joint oversight team has been stood up to resolve any conflicts that might arise in the course of the protocol.

In terms of the rationale for conducting studies in pediatrics, the pediatric burden of disease is significant even though it is not as high as in adults and there is a disproportionate burden among children in minority communities. There are direct and indirect effects to children and all of society. This burden will continue if vaccination is not done and natural "herd" effects are waited for to occur over time. There are early data from the Moderna VRBPAC briefing package that suggests that the vaccines that we have might actually prevent asymptomatic carriage. If this can be done safely, it would reverse the pandemic more rapidly and be good for everyone. As far as clinical trials go, safety data do need to be collected and this is best done in clinical trial settings.

A number of pediatricians months ago thought that this was a very important issue to begin to plan for as soon as possible. Anderson et al published a thought piece in *Clinical Infectious Diseases (CID)* and made the case for this based upon not even a full year of surveillance data in the US that the impact on the children, including the burden of hospitalizations and deaths in some cases, compared to other diseases for which childhood immunization is standard in the pediatric schedule³³. Based on this and the thought pieces of others, the importance was realized of beginning to plan for pediatric trials even before adult efficacy trials could be completed.

NIAID asked a number of pediatric investigators and their colleagues in obstetrics and gynecology who had previously conducted vaccine studies to work off of pandemic preparedness protocols for influenza that were designed but not implemented in prior times of pandemic threat for influenza. They were asked to develop a shell protocol that would define approaches to age de-escalation and have healthy children for testing these vaccines and to have maternal protocols for immunization in pregnant women should those be required as vaccines were proven to be efficacious and rolled out.

This table depicts the status of the efficacy trials that initially were recruiting only adults and how the timeline in those products in the US might relate to clinical development plans for testing these vaccines in children:

Vaccine Clinical Development Children				
				
Platform/ Design	mRNA: encodes stabilized spike; lipid NP	mRNA: encodes 2P - stabilized spike; lipid NP	Replication incompetent Ad26; stabilized spike	Replication incompetent ChAdOx1 chimp Ad; wild type spike
Dose/ Schedule Adults	IM 2 doses X 30 µg 21 days apart	IM 2 doses 100 µg 28 days apart	IM 1 dose at 5×10^{10} vp (also testing 2 doses (0, 56 days))	IM 2 doses at 5×10^{10} vp, (0, 28 days)
Current Status	EUA ages 16 and up	EUA ages 18 and up	Phase 3 adults	Phase 3 adults
Adolescents	Fully enrolled	TeenCOVE	Start 4-6wks after results from adult trials	Begin Early 2021
Younger Children	Planning early 2021	Planning early 2021	Planning early 2021	Planning early 2021
Comments			Platform used widely in teens, infants, children	

Others supported by USG: Novavax (Ph3 enrolling), Sanofi

The EUA for the Pfizer/BioNTech mRNA vaccine allowed for authorized use in individuals aged 16 years and up because Pfizer amended their efficacy trial protocol to expand from age 18 and up down to age 12 and up. By the time that they applied for EUA, they had sufficient data in the age 16 and up category to have its use authorized in that age group. They announced the previous week that they have fully enrolled down to 12 years of age. In public statements, they have anticipated that this vaccine may be licensed for use down to 12 years of age sometime in the first half of 2021. It also has been publicly reported that they are planning studies in children under 12 years of age some time in 2021.

³³ Anderson EJ, Campbell JD, Creech CB, Frenck R, Kamidani S, Munoz FM, Nachman S, Spearman P. Warp Speed for COVID-19 Vaccines: Why are Children Stuck in Neutral? *Clin Infect Dis*. 2020 Sep 18:ciaa1425. doi: 10.1093/cid/ciaa1425. Epub ahead of print. PMID: 32945335; PMCID: PMC7543330.

The Moderna mRNA vaccine was authorized for use in those 18 years of age and up and they now have launched a standalone adolescent protocol that will recruit a cohort of ages 12 to 18 years called TeenCOVE. They have announced that they are planning to begin studies in younger age groups sometime in early 2021.

The Janssen product is an Ad26 non-replicating viral platform that is being tested with 2 dosing schedules in efficacy studies. The schedule supported by the USG is a single dose and the one being supported by other sources that is recruiting globally is 2 sequential doses spread 56 days apart. Both of those studies are in Phase III efficacy trials in the US and beyond. It has been announced publicly that there is an expectation for Janssen to announce the main results of their US-supported trial very soon. They also have announced publicly that they plan to start trials that would gather data for use in adolescents 12 to 17 years of age and younger age groups, which would be initiated 4 to 6 weeks after the results from their adult trials. It is worth noting that the Janssen Ad26 platform has already been used widely in infants, children, and teens. It is licensed for use by European Medicines Agency (EMA) for Ebola, so there is a lot of clinical experience and safety data related to this platform in younger age groups.

They heard earlier in the day about the AstraZeneca chimp Ad vaccine, which is a replication incompetent adenovirus vector vaccine. The efficacy trial is fully enrolled in the US and the company has plans to test the vaccine in adolescent trials and younger children. However, the details of those trials have not yet been announced.

In terms of additional products, Novavax is the fifth vaccine that is in efficacy trials in the US. It is currently about halfway enrolled. However, Dr. Eberding did not have details on the company's plans for conducting clinical trials in younger age populations at this time. Sanofi will probably be the next USG-supported vaccine to enter clinical trials sometime in early 2021.

To recapitulate the three approaches to getting a label indication for SARS-CoV-2 vaccination in younger age cohorts and the teenage cohort 12 to 17 years of age, there was the Pfizer/BioNTech approach that was to expand the eligibility in the adult efficacy trials down to younger ages while they were ongoing. It seems as though that approach was relatively efficient. Their vaccine was proven to be safe enough down to age 16 and now they are accruing more safety down to age 12. There is the approach that was chosen by Moderna, the TeenCOVE standalone trial for safety using the adult dose, which has been proven to be efficacious in the adult efficacy trial. Then there are other approaches to expand eligibility into lower age groups from Phase II trials that originally enrolled adult participants. The outcome measures of these would be immunogenicity and safety and they might explore different dosing schedules. In order for these perhaps to get regulatory approval, there may need to be a correlate of protection of efficacy from completed adult trials.

The TeenCOVE study, which focuses on the adolescent group, opened around December 8th or so and is currently recruiting. The target enrollment is 3000 teenagers with 2:1 randomization of active product to placebo given in 2 100µg doses spread 28 days apart that has been demonstrated to have efficacy and is authorized for use in adults in the US. That is one approach to a standalone teen protocol.

An example of a dose-ranging study that would occur in younger children uses an age de-escalation approach with children divided into 3 age groups. The traditional divisions are 6 to <12 years of age, 2 to <6 years of age, and infants to <2 years of age. This is more complicated because there are 3 different cohorts. In some cases, the vaccine developers are testing 2 different doses, with the idea being that many of these vaccines are relatively reactogenic in the

adult population and may be more so in younger age groups, and the immunogenicity and level of protection with lower doses might be very good in children. Full, half, and quarter doses will be considered by age group. The idea is that once a dose is identified that is safe and appears to be immunogenic, the study would move from a smaller sample size in the dose-finding and age de-escalation study to a safety and immunogenicity study over time. If the trials begin in early 2021, it is possible to infer when the results might become available in younger aged children based on the fact that typically these trials are designed to be 13 months long.

Discussion Points

Given the significant burden of MIS-C alone in pediatric disease, Dr. Romero inquired as to whether there is an effort as with the adult trials to ensure that there is a very robust inclusion of Latino, African American, and Asian children in these studies. In addition, he inquired as to whether children of African descent and Latino children experience similar incidence of MIS-C in countries outside of the US.

Dr. Erbeling emphasized that the trials funded by the USG certainly would try to help optimize recruitment strategies so that diverse populations would be well-represented. She said she did not know about the similarity of MIS-C among children inside versus outside the US.

Dr. Poehling expressed appreciation for the concept of the shell protocols. She recalled that in the prior presentation they saw that children with high-risk medical conditions had an increased incidence of severe disease for COVID-19 similar to that seen in adults. It appeared that the focus was on healthy children in the shell protocols for children and pregnant women, so she wondered if there would be an attempt to be diverse on the medical conditions as well.

Dr. Erbeling indicated that in the adult efficacy trials, recruitment targeted people at high-risk for poor outcomes of COVID illness and complications of COVID because they were all supposed to be powered to prevent disease not just prevent asymptomatic infection. Because children have a much lower rate overall of COVID illness, the focus would be on the safety profile of the vaccine. If the indication for a lower dose was part of the objective of the clinical development plan, immunogenicity would be the other outcome in some of these protocols. It would be important to have the children who are likely to get vaccinated when vaccines are allowed to be included in the clinical trials. The effort should be made to include ambulatory children who might represent the US population enrolling in these trials.

Dr. Hayes (ACNM) requested elucidation on what is occurring with OWS in terms of whether it is just changing its name or is changing its structure within NIH. In addition, she requested a presentation in the near future about what the protocol will be for enrolling pregnant women.

Dr. Erbeling clarified that NIH was a partner in what was formerly known as OWS along with the Department of Defense (DoD), BARDA, and CDC. The partnership remains intact and they still meet on a regular basis many times weekly to continue to move the vaccine development effort and therapeutics forward as fast as can possibly be done safely. All of that is the same, but the branding may be changing. In terms of a presentation on the protocol for pregnant women, ACIP could invite a representative of the protocol team to present on that as the planning evolves.

Dr. Cohn added that CDC would continue to keep ACIP and everyone listening informed on trials in pregnant women.

Ms. Stinchfield (NAPNAP) expressed excitement about the forward path for children and vaccines. In terms of the age de-escalation studies, she requested information about what placebos will be considered.

Dr. Erbeling indicated that none of these trials have launched yet. The active vaccine to placebo ratio is usually 2:1 or 3:1. In the US, the control condition has not been proposed to be another vaccine such as tetanus or meningococcal. While she has not heard that being proposed as a control condition, but it would be a consideration if that is the best approach ethically. It also might be a true saline placebo.

Regarding the slide on label indication approaches for vaccination into teenage cohorts 12 to 17 years of age, Dr. Kimberlin (AAP Redbook) observed that the third bullet was “to expand age eligibility in Phase II trials for immunogenicity and safety and there was mention of a correlate of immune protection. He requested a status on where that stood if possible in the multitude of studies and data coming in, and whether they were closer to getting a correlate of protection in adults.

Dr. Erbeling clarified that that was from the outset when the government was planning these studies together with the companies. They knew that the correlates of protection would be a high priority. Identifying a correlate of protections usually requires breakthrough infections in the vaccine arm. The first two vaccines authorized for use, the mRNA vaccines, were so highly efficacious that there were very few vaccine breakthroughs. More data accrued because a lot of virus is being transmitted and there were a lot of COVID cases in the trial after the authorization was granted. Groups of laboratorians, biostatisticians, and the companies are actively engaged in identifying correlates of protection for the authorized vaccines. There are also non-human primate (NHP) studies underway with all of these vaccines that are in efficacy trials to determine whether correlates can be identified with breakthrough infections in those groups. That might actually provide more robust data once a correlate is identified or implicated in the efficacy trials in humans. If the correlate correlates with what was seen in NHP, then there would be even more validity in using that for a marker of protection moving forward into studies for licensure that might rely upon a correlate of protection. People are hopeful that a correlate of protection will be identified in the next month or two for these early authorized vaccines. The question remains whether it will be different for a different platform.

Dr. Maldonado (AAP) said she just learned that the MIS-C studies were just recently awarded and looks forward to hearing updates on them because they are biological correlates that potentially could be useful for understanding some correlates of protection as well. AAP is excited that the pediatric trials are moving forward and hopes that they will move forward quickly, efficiently, and safely. Some of AAP's community partners, OB/GYNs particularly, have expressed concern about the potential ethical implications of enrolling pregnant women in a placebo-controlled trial when vaccines are already being given to pregnant women, especially in the healthcare Phase 1a sector. Perhaps it would be helpful to partner with ACOG and other groups to make sure that these trials are carefully spelled out and are ethical. There already is refusal among this important group to participate in trials.

Dr. Daley request further information about the steps involved in getting to authorization for 12 to 15 year olds for Pfizer and 12 to 17 year olds for Moderna and the anticipated timing of that.

Dr. Erbeling indicated that Pfizer announced that it was fully enrolled down to age 12, so one could infer that they have had prior discussions with the FDA on what an adequate number would be and that they achieved enough enrollment to reach their objective, which is going to

get authorization down to that age group. It would depend upon what the required follow-up for safety would be and what Pfizer's timeline is for moving forward to licensure. Based on what she has read in the newspaper, it is anticipated that vaccination might be an option for down to age 12 in the first half of 2021. The Moderna approach was to conduct a teen-specific trial, which also is open and enrolling. However, it is not fully enrolled so the timeline there would depend upon how quickly they can enroll and what they would view as a sufficient amount of safety data for that age group.

Dr. Fink (FDA) added that FDA is continuing to engage with individual vaccine manufacturers regarding the contours of their pediatric development programs, not just the studies that are currently underway. Some of the issues being considered include the number of subjects in certain pediatric age groups that would support an acceptable safety database or a regulatory decision that might first involve EUA, and then with some longer-term follow-up be supportive of biologic licensure. They also are continuing to discuss the immune marker parameters that would support bridging of effectiveness from the adult population into pediatric age groups. Certainly if there were to be an immune marker scientifically established to predict protection against COVID-19, that would make the job easier. However, the absence of such an established marker is not necessarily prohibited. There is regulatory experience with immunobinding approaches in situations where there is no immune marker that is established to predict protection. Although there are a variety of considerations that make it more or less easy to navigate such an approach, including a safe dosing regimen as was evaluated in the adult efficacy population, and also whether there is reason to believe that the parameters of the immune response in the pediatric age group would be similar to that in adults or different, and that in the adolescent group there is a high degree of confidence with the immune response parameters would be similar to those in younger adults.

Introduction of the New CDC Director

Rochelle P. Walensky, MD, MPH
Director, Centers for Disease Control and Prevention
Administrator, Agency for Toxic Substances and Disease Registry

Dr. Walensky thanked Dr. Cohn and ACIP for the invitation to address the committee. She said she is very proud to serve as the new CDC Director and is grateful to be part of the incredible CDC community. She recognized the critical importance of immunization practices. While CDC and ACIP have doubled down during COVID-19, she also recognized that their work is critical not only during times of COVID-19, but also in terms of childhood and adult immunization practices overall. She is happy to have ACIP as the advising body for CDC guidelines and recommendations, and recognized the very important and independent role that the committee plays in the review of safety and efficacy data prior to recommending vaccines to the American public. She also recognized the enormous dedication that this represents on the part of all of the ACIP members. The timely assessment of safety data and detailed plans for real-world effectiveness being discussed during ACIP meetings are really value-added for CDC and are critical to what ACIP provides. Everyone recognizes that this is a dynamic process and that as more is learned, implementations and recommendations may change as the vaccines are used to their maximize benefits. She especially thanked ACIP for its commitment to this process and for the members' ability and scientific expertise to deliberate on all of this in real-time and in a systemic way. Dr. Walensky highlighted the importance of health equity in all CDC discussions and recommendations. She realizes that there is a huge amount of work ahead to communicate the effectiveness and safety of vaccines—not just for COVID-19, but vaccines for all Americans and to support immunization as part of the COVID-19 pandemic response. She looks forward to

learning more from ACIP as they continue to deliberate new vaccines that are on the horizon. She expressed appreciation for ACIP's work to date. Until about a month ago, she was a practicing infectious disease physician who has relied on ACIP throughout her career and is proud to call many of the ACIP members colleagues and friends. She expressed gratitude for the opportunity to address ACIP and recognized that this was a newly planned meeting and that everyone had put in an extraordinary amount of time and energy throughout their careers and over this last year especially in thinking about vaccine safety and effectiveness, and probably would have a lot more of that to come as new vaccines emerge. She thanked ACIP for all that they offer to CDC and to the American public.

On behalf of the ACIP voting members, *ex officio* members, and liaisons, Dr. Romero welcomed Dr. Walensky and said that they were happy to hear that ACIP's work is recognized and is beneficial in advising CDC. ACIP looks forward to working with Dr. Walensky and providing her recommendations into the future. Dr. Romero thanked Dr. Walensky for taking time out of a very busy schedule to address the committee.

Vaccine Safety Technical Subgroup (VaST) Introduction

Grace M. Lee, MD MPH

VaST Co-Chair

Associate Chief Medical Officer for Practice Innovation

Lucile Packard Children's Hospital

Professor of Pediatrics, Stanford University School of Medicine

Dr. Lee thanked Dr. Walensky for her leadership and emphasized that ACIP is very much looking forward to collaborating with her moving forward. During this session, Dr. Lee provided an update on behalf of the Vaccine Safety Technical Subgroup (VaST) group, which includes her Co-Chair, Dr. Bob Hopkins who is the current Chair of the National Vaccine Advisory Committee (NVAC).

As a reminder, the objectives of the COVID-19 VaST Subgroup are to: 1) review, evaluate, and interpret post-authorization/approval COVID-19 vaccine safety data; 2) serve as the central hub for technical subject matter expertise from federal agencies conducting post-authorization/approval safety monitoring; 3) advise on analyses, interpretation, and data presentation; 4) provide updates to the ACIP COVID-19 Vaccines WG and the ACIP on COVID-19 vaccine safety; and 5) ensure independence, transparency, and public accountability for COVID-19 vaccine safety monitoring. The composition of the VaST Subgroup includes Dr. Lee from ACIP, Dr. Hopkins from NVAC, members from ACIP and NVAC serving as independent expert consultants, 2 CDC Co-Leads (Drs. Lauri Markowitz and Melinda Wharton), and 8 ACIP *ex officio* (FDA, NIH, ODP, CMS, HRSA, IHS) and liaison (VA, DoD) members. All are providing critical expertise through their work and surveillance systems.

In the pre-authorization phase from June to October 2020, VaST met 10 times to prepare for COVID-19 vaccine safety surveillance. In November, VaST transitioned its membership to the current Vaccine Safety Data Review Group focused on reviewing the safety data. Between November and mid-December 2020, they had 4 meetings to review the methods for vaccine safety monitoring and to finalize VaST procedures. As a reminder, the ACIP voted to recommend use of the Pfizer/BioNTech vaccine on December 12, 2020. On December 14, 2020, the very first dose of COVID-19 vaccine was administered in the US. On December 19, 2020, the ACIP voted to recommend use of the Moderna vaccine. On December 21, 2020, VaST convened its first call to review the safety data exactly one week after the start of vaccine

administration in the US. From December 21, 2020 to the present, VaST has had 6 meetings to review the post-authorization data—just 6 weeks into the vaccination program in the US.

At this point in the vaccination program, VaST has been primarily reviewing information from V-SAFESM, the VA Adverse Drug Event Reporting System (VA ADERS), which feeds into the national Vaccine Adverse Event Reporting System (VAERS) data bases and the Clinical Immunization Safety Assessment (CISA) system. VaST is just beginning to see some very early data from the two systems that have population-based data available.

As a brief description of its process, VaST is currently conducting a weekly review of available data on vaccine administration and AESI. VaST believes in a model of shared learning with regard to safety. All members, federal partners, and subject matter experts (SMEs) are present for presentation of data from multiple systems. In order to ensure independence, VaST members also have a separate session to discuss the findings independently. Finally, VaST provides a summary and interpretation of the aggregate data to the ACIP Secretariat on a regular basis and is committed to ensuring ongoing and regular communication with ACIP COVID-19 Vaccines WG and the ACIP in its open public meetings.

In closing, Dr. Lee expressed gratitude to the VaST members, CDC Co-Leads, and ACIP *Ex Officio* and Liaison Representatives. All of these individuals have gone above and beyond in dedicating their time and expertise to support the vaccine safety system in the US since day 1 of the vaccination program.

COVID-19 Vaccine Safety Update

Tom Shimabukuro, MD, MPH, MBA
CDC COVID-19 Vaccine Task Force
Vaccine Safety Team
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Shimabukuro provided an update pm v-safeSM, VAERS, CISA, VSD, anaphylaxis following COVID-19 vaccination, and reports of deaths and mortality following COVID-19 vaccination.

As a reminder, v-safeSM is CDC's smartphone-based text to web survey monitoring system. For the data presented during this session, Dr. Shimabukuro focused on Week 1, Days 0 to 7, when daily check-ins are done and questions are asked about reactogenicity and a health impact assessment is conducted. After the first week, weekly check-ins and health impact assessments are done for up to 6 weeks and then at 3, 6, and 12 months. A VAERS customer service representative conducts active telephone follow-up on any medically-attended health impact events identified by participants during a check-in and takes a report if appropriate. As of 1/20/21, about 21.8 million people had received 1 or more doses in the US. Of the registrants completing at least 1 v-safeSM health check-in, just under 1 million received the Pfizer-BioNTech vaccine and just over 1 million received the Moderna vaccine. To date, just over 15,000 pregnancies have been reported to v-safeSM. Individuals have been enrolled into the v-safeSM pregnancy registry, and not all of these 15,000 are actually pregnancy reports. People do make mistakes on the smartphone, so there are some males or individuals who are out of the age group. That is just one of the limitations of the system.

In terms of the reactogenicity that enrolled individuals are reporting in Days 0-7 for all vaccines combined, pain is a commonly reported reaction as are systemic reactions such as fatigue, headache, myalgia, chills, fever, swelling, joint pain, nausea. The reactogenicity profiles for Dose 1 are very similar for the Pfizer-BioNTech vaccine versus Dose 1 of the Moderna vaccine. Pain and other systemic reactions are commonly reported at similar proportions for both vaccines.

Because Pfizer-BioNTech began earlier and the doses are 21 days apart, there are meaningful Dose 2 data only for that vaccine at this point. Comparing Doses 1 and 2 for the Pfizer-BioNTech vaccine, substantially more reactogenicity is being reported after Dose 2 from 2-fold to 3-fold higher. If the data are broken down further, it is primarily on Day 1 of the 0-7 observation period. That is consistent with what was observed during the clinical trials in that there was more reactogenicity reported after Dose 2. Follow-up phone calls are ongoing to v-safeSM participants who report medically-attended health impact events. The pregnancy registry had enrolled 227 pregnancies as of January 22, 2021.

As a reminder, VAERS is the nation's early warning system for vaccine safety. It is a spontaneous reporting or passive system that is co-managed by the CDC and FDA. The strengths of VAERS is that it can rapidly detect safety signals and rare AEs. The main limitation for VAERS is that it is not designed to assess causality. However, VAERS accepts all reports from anyone regardless of the plausibility of the vaccine causing the event or the clinical seriousness of the event. As a hypothesis-generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems if necessary.

In terms of a general breakdown of the reports in VAERS for the two vaccines, there are substantially more Pfizer-BioNTech reports than Moderna and a difference in the serious versus non-serious. This is thought to be an artifact of report processing times in that the Pfizer-BioNTech came out earlier and that as more reports continue to accrue, the focus is on processing, reviewing, and coding of the serious reports initially. Looking at the total of the two combined, about 90% are non-serious AEs. The median age is 43 years and there are about 77% females, which likely represents the demographics of the healthcare workforce. In general, there are more female reporters in VAERS than males. The reporting rates for non-serious AEs are 372 per million doses administered and serious AEs are 45 per million doses administered. These are comparable to what is observed to other vaccines that are given to adults. Looking at the specific AEs being reported for the two vaccines, systemic and injection site reactions are the most commonly reported AEs. These are not mutually exclusive, meaning that an individual can have more than one AE in a single report. The AE profiles for the reporting to VAERS are remarkably similar for both Pfizer-BioNTech and Moderna vaccines.

CDC's colleagues at FDA conduct empirical Bayesian data mining in VAERS. FDA uses data mining to identify disproportional AEs reporting for vaccines, including COVID-19 vaccines. This identifies, with a high degree of confidence, AE-vaccine pairs reported at least twice as frequently as expected for a COVID-19 vaccine compared to the VAERS database. That means that the lower bound of the 90% confidence interval surrounding the empirical Bayesian geometric mean, EB05, is 2 or more compared to all other US-licensed vaccines. No empirical Bayesian data mining alerts (EB05 ≥ 2) were detected for any AE-COVID-19 vaccine pairs as of the January 22, 2021 weekly results.

The CISA project, is a collaboration between CDC and 7 medical research centers with vaccine safety experts³⁴. CISA has implemented Project COVIDvax, which is an extension of the CISA Project's clinical consultation service for US healthcare providers and health departments for complex COVID-19 vaccine safety questions/issues that are about an individual patients residing in the US that are not readily addressed by CDC or ACIP guidelines. The CISA Project has vaccine safety SMEs with expertise in multiple specialties and sub-specialties (e.g., infectious diseases, allergy/immunology, neurology, OB/GYN, pediatrics, geriatrics). Requests for a CISA consult about COVID-19 vaccine safety can be made by contacting CDC-INFO: 800-CDC-INFO (800-232-4636) or webform and indicating that the request is for a "CDC CISA" consult. No patient identifiers should be included³⁵.

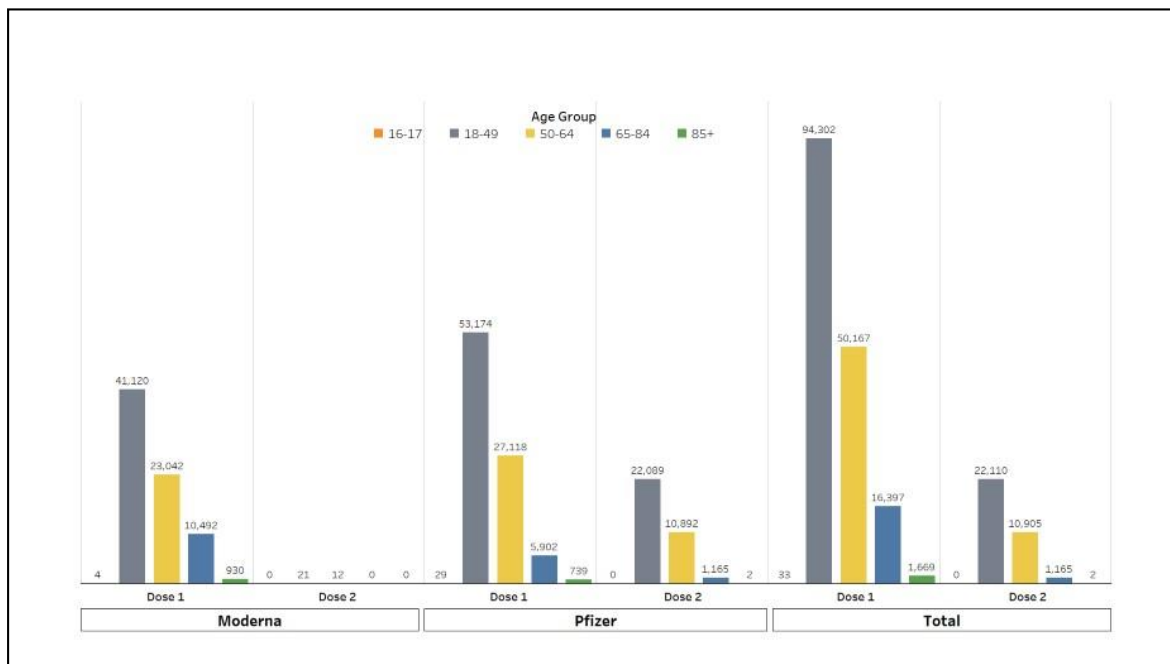
As of January 24, 2021, CISA has responded to 143 clinical inquiries or consultation requests about COVID-19 vaccine safety. Many of these have been about allergic reactions and anaphylaxis or about individuals who might be at high-risk for AEs. They also have assisted state health departments with evaluation of complex medical issues pertaining to COVID-19 vaccines safety. They convened a CISA Project WG with allergy and immunology specialists who provided input for CDC's guidance on clinical considerations for use of the mRNA COVID-19 vaccines and how to prepare for managing anaphylaxis after vaccination. They also have contributed to *MMWR* publications on anaphylaxis and allergic reactions after Dose 1 of both the Pfizer-BioNTech and Moderna COVID-19 vaccines. The CISA Project also is engaged in ongoing work to investigate possible mechanism for anaphylaxis in collaboration with FDA, NIH, and other partners.

The VSD is a collaboration between CDC and 9 participating integrated healthcare organizations with data on over 12 million persons per year. The VSD has electronic health record (EHR) and administrative data on immunization records, encounters with the healthcare system, birth and death certificate information, and demographics all linked by unique study IDs. The VSD also has access to charts and EHR for review of cases if necessary to confirm incident cases. The VSD Rapid Cycle Analysis (RCA) aims are to: 1) monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes of interest among VSD members; 2) assess each pre-specified outcome for a 1-21 and 1-42 day risk interval; and 3) describe the uptake of COVID-19 vaccines over time among eligible VSD members. The 1-21 day risk interval is largely based on the dosing interval for the Pfizer-BioNTech vaccine, which has a recommendation to obtain Dose 2 within 3 weeks. The 1-42 risk interval is the more traditional window used for vaccine safety.

As of January 16, 2021, the total number of the two vaccines combined were 162,575 doses administered of Dose 1 and 34,182 doses administered of Dose 2. Substantial vaccine is anticipated in the VSD population once the immunization program moves to more broad-based administration to begin vaccinating the general population. This graphic breaks down the number of doses through this time period by age group:

³⁴ <http://www.cdc.gov/vaccinesafety/Activities/CISA.html>

³⁵ <https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html>



The smaller numbers in the 65- to 84-year-old and 85+ age groups likely represents the VSD vaccinating a lot of healthcare workers, many of whom fall into the 18 to 49 year old age group.

In terms of the preliminary results of the VSD unvaccinated concurrent comparator analyses for COVID-19 vaccine safety, 22 outcomes are being monitored. The type of analysis that is being done right now, the unvaccinated concurrent comparator analyses, allows CDC to get the quickest data. Other analyses will come online fairly shortly. The signal is currently based on a rate ratio and the p-value. For a lot of the 22 outcomes, there have been no events in the vaccinated individuals so an analysis cannot be done. For the ones that can be analyzed, there have been no signals as of January 16, 2021.

In terms of the next steps for the VSD RCA, the vaccinated concurrent comparator analysis will begin when informative comparator follow-up data are available. These data are expected to be available within a week or so. Dose 1 and Dose 2 analyses will be performed for each vaccine with both the 1-21- and 1-42-day risk intervals. A historical comparator analysis will come online around mid-March 2021 and will assess general age comparable background rates and rates following well care visits among those who received influenza vaccine in the past 18 months.

Suspected anaphylaxis reports to VAERS through the analytic period January 18, 2021 were detected through early screening to identify suspected anaphylaxis reports prior to formal processing and Medical Dictionary for Regulatory Activities (MedDRA) coding, and also were detected through a MedDRA code search strategy after formal processing and coding. This is like a Venn diagram. There are two categories of reports and for most of these two methods, there is overlap. CDC has reported all of the reports captured through both of these methods. The suspected anaphylaxis reports were assessed by physicians at CDC who conducted medical record review and additional follow-up as necessary by contacting the treating physician, the healthcare facility where they were treated, and in some cases the patients themselves—many of whom were healthcare providers. These cases were classified according to the Brighton Collaboration case definition criteria. Brighton Levels 1, 2, and 3 are considered cases, with 1 being the highest level of diagnostic certainty. Cases classified as 4 and 5 are

considered not to be cases. CDC and FDA met daily to discuss and further adjudicate cases if necessary³⁶.

In terms of the characteristics of the confirmed cases through January 18th, there were 50 cases for the Pfizer-BioNTech vaccine and 21 cases for the Moderna vaccine that met the Brighton criteria. The median age and range were very similar between the two vaccines, which might be expected given that this was during a time when basically Phase 1a groups were being targeted and included a large number of healthcare workers. There is a strong female predominance for both vaccines, with 94% of the cases for Pfizer-BioNTech and 100 % of the cases for Moderna being female. Just over 60% of the initial doses have been administered in women. Prior surveillance reviews in VAERS of anaphylaxis also have noticed this female predominance at as high as 80% on a previous review that examined mostly influenza vaccine. These cases tended to occur quickly after vaccination, with a median onset of 10 minutes for both vaccines. The overwhelming majority had symptom onset within 15 minutes and 90% for both had onset within 30 minutes. High percentages of cases for both of the vaccines had documented histories of common allergies and allergic reactions, including to drugs and foods. A substantial percentage had a history of prior anaphylaxis cases following drugs, foods, contrast media, vaccines, insect stings, and unspecified sources in some cases. Most of the cases for both vaccines occurred after Dose 1, which likely represents where we are in the immunization program. There were a handful of Dose 2 anaphylaxis cases as well.

Based on updated vaccine doses administered counts and updated anaphylaxis cases, with approximately 9.9 million doses of Pfizer-BioNTech vaccine and 7.5 million doses of Moderna vaccine administered through the analytic period, CDC estimates a reporting rate of 5.0 per million doses for Pfizer-BioNTech doses administered and 2.8 per million for Moderna doses administered. The previously reported rate for the Pfizer-BioNTech vaccine was 11.1 per million doses administered (Dec 14-Dec 23)³⁷ and 2.5 per million doses administered for Moderna (Dec 21-Jan 10)³⁸. The rate for the Pfizer-BioNTech vaccine has come down substantially and the rate for the Moderna vaccine has remained about the same as more information has continued to be gathered.

Upon receipt or notification of a reported death after COVID-19 vaccine, the VAERS contractor expedites processing of the report the day of report, contacts the reporter for additional information (e.g., medical records, death certificate, autopsy report, et cetera), notifies the state Vaccine Safety Coordinator (VSC) of the death, and provides a copy of the initial report to the VSC via Epi-X. Physicians in CDC's Immunization Safety Office (ISO) and at FDA review all reports of deaths following COVID-19 vaccination as soon as notified in the daily VAERS priority report and make an assessment if any immediate action is necessary. Attempts, multiple if necessary, are made to obtain death certificates and autopsy reports when an autopsy is conducted to ascertain the cause of death (COD). Through January 18th, there have been 196 reports to VAERS of deaths due to any cause following COVID-19 vaccination. The median age is 79 (25–104), 22% of the 196 deaths were in individuals less than 65 years of age, 66% of the reports were in LTCF residents, and 113 were reported following receipt the Pfizer-BioNTech vaccine and 83 following receipt of the Moderna vaccine. These reports to VAERS involve

³⁶ Rüggeberg et al.; Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2007;25(31):5675-84.

³⁷ <https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm>

³⁸ <https://www.cdc.gov/mmwr/volumes/70/wr/mm7004e1.htm>

temporally associated deaths following vaccination due to any cause. AE reports to VAERS, including deaths, should not be assumed to be causally related to vaccination.

Focusing first on reports of death, it is important to know about background mortality in general to put the reports into perspective. Focusing on LTCF, it is estimated that about 2 million COVID-19 vaccine doses have been administered in LTCFs through January 18, 2021 based on the CDC COVID Data Tracker. Based on National Healthcare Safety Network (NHSN) data, it is assumed that 65% of dose were administered to LTCF residents and that about a third were administered to employees. That is about 1.3 million residents vaccinated during the analytic period. A 22% annual mortality rate ($n = 286,000$) is assumed based on published literature³⁹. The risk period assumes that December 21st was when vaccinations commenced in LTCFs. Therefore, the risk period is 29 days (December 21-January 18). Because some people could have 1 day of risk and others could have 29 days of risk, the difference was split to assume that each resident contributed 14.5 person-days or the approximate mid-point of the risk period. The 14.5 days equates to 4% of a calendar year.

Among the 1.3 million LTCF residents (2 million x 65%) vaccinated over the 29-day risk period of December 21-January 18th, about 11,440 deaths would be expected among LTCF residents following vaccination due to chance alone due to natural causes/background all-cause mortality rate in this population. By comparison, VAERS has received 129 reports of deaths following COVID-19 vaccination in LTCF residents through January 18, 2021. Mortality in LTCF residents is high and substantial numbers of deaths in this population will occur following vaccination as temporally-associated coincidental events.

Dr. Shimabukuro discussed some additional analyses from CDC's colleagues at Brown University using the Genesis Healthcare data. Genesis Healthcare is the largest nursing home company in the US, spanning 24 states. The analysis included 284 Skilled Nursing Facilities (SNF) with about 25,000 residents. COVID-19 vaccination began in these facilities on December 18, 2021. By December 31st, the first dose of vaccine was administered in 118 facilities among 7006 residents (61.4% in those facilities). The Brown University investigators assessed 7-day mortality rates among the vaccinated and unvaccinated residents in these 118 facilities as well as 17,076 residents in the 166 facilities that started vaccinating after January 1, 2021. After excluding residents with a positive SARS-CoV-2 diagnostic test within 20 days prior to their 7-day observation window, mortality was lower among vaccinated versus unvaccinated residents within the same facilities and compared to residents in not-yet-vaccinated facilities, with overlapping 95% confidence intervals. The findings suggest that short-term mortality rates appear unrelated to vaccination for COVID-19 in SNF residents. This study underscores the value of having an analytic infrastructure to support near real-time monitoring of AEs and safety during rapid vaccine deployment in this vulnerable population⁴⁰.

As mentioned earlier, there were 129 reports of deaths following COVID-19 vaccination in LTCF residents based on VAERS data through January 18th. The median age was 84 years and about half of these were female. About a third of these reported deaths involved individuals in hospice or who had Do Not Resuscitate (DNR) or Do Not Intubate (DNI) status. Very few of these were autopsy cases ($n=2$). Death certificates were available for 18 cases. A death certificate was unavailable or autopsy results were pending for 112 cases. The initial assessment indicated that many case reports documented ill health and a history of multiple co-morbidities and common

³⁹ Thomas et al, J Gerontol A Biol Sci Med Sci, 2019, Vol. 74, 219–225

⁴⁰ Presented on behalf of: Barbara Bardenheier, PhD, MPH, MA; Assistant Professor of Health Services, Policy, and Practice; Assistant Professor of Epidemiology; Brown University School of Public Health

age-related diseases (e.g., heart disease, type 2 diabetes, dementia, et cetera). The causes of death from the death certificates in the 18 individuals for whom death certificates were available are shown in the following table:

Cause of Death From the Death Certificate
Hypertension, leading to acute myocardial infarction, leading to anoxic brain injury
Atherosclerotic cardiovascular disease, acute myocardial infarction
Arteriosclerotic Disease
Cardiac arrest, cardiopulmonary arrest
Acute congestive heart failure, non-ischemic cardiomyopathy
Congestive heart failure, non-ischemic cardiomyopathy
Congestive heart failure
Congestive heart failure
Heart failure, hypertension
End stage chronic obstructive pulmonary disease
Acute kidney failure, resulting from acute liver failure, resulting from liver masses
Hypertension, hypothyroidism, bipolar disorder, peripheral vascular disease
Pneumonia, cardiac arrest and shock
Aspiration, frontotemporal dementia
Hypertension, mixed Alzheimer's and vascular dementia
Dementia
Chronic alcohol abuse and severe malnutrition, alcohol withdrawal, electrolyte derangement, ventricular arrhythmia, cardiogenic shock
Failure to thrive

The overall impression on deaths and mortality in LTCF residents following COVID-19 vaccination is that mortality in LTCF residents is high due to the underlying health status of the LTCF resident population. The available evidence from VAERS monitoring and Genesis population-based surveillance does not suggest a safety problem with respect to deaths in older adults residing in LTCFs. Case reports of deaths in LTCF residents following COVID-19 vaccination to VAERS include many persons such as those with multiple co-morbidities, including some with cognitive impairment, those in ill health and in declining states of health, and those in hospice or DNR or DNI status. Deaths in LTCF residents following COVID-19 vaccination are consistent with expected all-cause mortality in this population. CDC's findings are consistent with the findings of the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) COVID-19 Vaccine Safety Subcommittee that the data do not suggest any unexpected or any untoward increases in fatalities in frail elderly individuals and that the causes of death were consistent with expected numbers of all-cause mortality in this population⁴¹.

There have been reports of deaths following COVID-19 vaccination in community-dwelling adults aged <65 years. The background rate of sudden cardiac death among community-dwelling individuals is 29.6 per 100,000 person-years. This estimate is based on a study by Tseng et al that looked at out-of-hospital cardiac arrest in people 18–90 years of age in San Francisco County. The study inclusion criteria were sudden unexpected death either within 1 hour of symptom onset for witnessed events, or within 24 hours of having been observed alive and symptom free for unwitnessed events. Exclusions criteria included subjects with

⁴¹ <https://www.who.int/news/item/22-01-2021-gacvs-review-deaths-pfizer-biontech-covid-19-vaccine-bnt162b2>

chronic/terminal illness in which imminent death was not unexpected; hospice residents; subjects with identifiable non-cardiac etiology of death at presentation, including drug abuse/overdose, trauma, homicide, or suicide; and subjects with hospital admission within the prior 30 days for noncardiac illness or surgical procedure⁴².

Using similar calculations to assess the number of individuals vaccinated, the risk period, and calculated person years, CDC calculated an expected number of sudden cardiac deaths of 168 in the 13.7 million community residents estimated to have been vaccinated between December 14, 2020 –January 18, 2021 based on the CDC COVID Data Tracker. The risk period was 35 days, it was assumed that each resident contributes 15 person-days (~ mid-point of risk period, adjusted downward to account for Moderna not used until December 21), and total person-years contributed of 566,650 ($[13.7\text{million} \times 15 \text{ days}] / 365.25$). Based on these calculations, the expected sudden cardiac death count was 168 deaths. The sudden cardiac death count reported to VAERS following COVID vaccination was 18, or substantially more expected than reported to VAERS.

In the VAERS database through January 18th, there are 28 reports of deaths following COVID-19 vaccination in community-dwelling adults less than 65 years of age. The median age in these reports is 54 years (range 25–63) and the median time from vaccination to death is 5 days (range day of vaccination to 25 days after). Death certificates and autopsy reports are available for 11 of these deaths. There is 1 completed autopsy and 4 pending. This table lists the causes of deaths following COVID-19 vaccination in the community dwelling adults aged <65 years with death certificate or autopsy report available:

Cause of Death from Death Certificate or Autopsy Report
Atherosclerotic cardiovascular disease
Atherosclerotic cardiovascular heart disease, hypertension
Cardiac arrest, COVID-19
Cardiac arrest, hypertension, morbid obesity
Cardiopulmonary arrest, hypertensive heart disease, hypertension, DM type II
Hypertensive cardiovascular disease
Myocardial infarction, ventricular fibrillation
Drug overdose
Pulmonary hemorrhage from squamous cell cancer of the lung
Subarachnoid hemorrhage, intraparenchymal hemorrhage, intraventricular hemorrhage
COVID-19 stroke, COVID-19 acute respiratory failure

In summary, 23.5 million COVID-19 vaccine doses have been administered in the US as of January 26, 2020. During this time, the US government has implemented the most intense and comprehensive vaccine safety monitoring program in history. Overall, the safety profiles of COVID-19 vaccines are reassuring and consistent with that observed from the pre-authorization clinical trials. Though rarely, anaphylaxis has been observed following mRNA COVID-19 vaccines. The data do not suggest a signal with respect to overall safety or deaths following vaccination in older adult residents of LTCFs. Additional population-based monitoring systems will continue to gather safety data as vaccination increases and the immunization program broadens, including CDC's VSD, FDA monitoring in CMS data, and VA EHR data.

⁴² Tseng et al, *Circulation*. 2018;137:2689–2700

VaST Assessment of Safety Data

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Dr. Lee reported that VaST believes that these well-established vaccine safety surveillance systems remain the cornerstone of COVID-19 vaccine safety monitoring in the US. In addition, novel approaches to surveillance such as v-safesm have enriched the understanding of COVID-19 vaccine safety in the early phases of vaccine deployment. As mentioned earlier, VaST meets weekly to review all available data and to ensure a coordinated approach across multiple safety surveillance systems.

Consistent with previously published clinical trial data, local and systemic reactions are commonly reported following vaccination in v-safesm and VAERS. This appears to be qualitatively similar at this point for both the Pfizer-BioNTech and Moderna vaccines. During the early phases of the US vaccination program, particularly in first few months, reliance is primarily on data reported to VAERS. However, the limitations of these data are that they are numerator only data, they are descriptive in nature, and they are subject to reporting bias. As the COVID-19 vaccination program matures, it will be possible to rely more on the data from population-based surveillance systems (e.g., VSD, CMS, Genesis) to understand the risk of AESIs following vaccination. These systems have both numerator and denominator data in a well-defined population and comparison groups are available to ensure that there is a good contextual understanding of the benefit-risk balance.

Anaphylaxis following COVID-19 vaccination is being closely monitored. The estimated rates currently range from 2.8 to 5.0 per million doses using Brighton Collaboration criteria. In response, CDC has recommended risk mitigation strategies, including screening for risk prior to vaccination, monitoring for symptoms post-vaccination, and early recognition and management of anaphylaxis on-site. In addition, provider and patient education is ongoing by CDC and partners.

As an example of the timeliness of the response to potential vaccine safety signals, federal safety colleagues published the available data on allergic reactions following the Pfizer-BioNTech vaccine on 6 January⁴³, the Moderna vaccine on 22 January⁴⁴, and a clinical update in the *Journal of the American Medical Association (JAMA)* on 21 January⁴⁵. In addition, anaphylaxis has been a topic of discussion during ACIP meetings, on COCA calls, and on other calls with broad clinical audiences to ensure that vaccines are being safely delivered to patients and the public. CDC has developed a pre-vaccination checklist that incorporates questions

⁴³ Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14–23, 2020. *MMWR Morb Mortal Wkly Rep* 2021;70:46–51. DOI: <http://dx.doi.org/10.15585/mmwr.mm7002e1>

⁴⁴ Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine — United States, December 21, 2020–January 10, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:125–129. DOI: <http://dx.doi.org/10.15585/mmwr.mm7004e1> external icon

⁴⁵ Shimabukuro T, Nair N. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine. *JAMA*. Published online January 21, 2021. doi:10.1001/jama.2021.0600

about prior known history of severe allergic reactions⁴⁶. Clinical guidance documents are continually and in real-time updated to ensure that individuals who are at risk for an allergic reaction are monitored for 30 minutes post-vaccination⁴⁷, and that all vaccination sites are prepared to diagnosis and manage severe allergic reactions on site⁴⁸. Over the course of the past 6 weeks, it is clear to see that safety systems are working quickly to ensure a timely response.

Serious AEs following COVID-19 vaccination are being closely monitored. Data in the US and Europe suggest that case reports of deaths are consistent with all-cause mortality rates, particularly in frail, elderly individuals. It is important to remember that COVID-19 vaccines are designed to prevent COVID-19-related mortality, but not mortality due to other causes. It is anticipated that additional vaccine safety surveillance systems will begin reporting data as a larger proportion of the US population begins to be vaccinated. VaST will continue to update the ACIP COVID-19 Vaccines WG, the ACIP Secretariat, and the ACIP on a regular basis.

Discussion Points (Lee & Shimabukuro)

Dr. Ault inquired as to when the pregnancy data generated from v-safesm, VAERS, and VSD are anticipated to be assessed.

Dr. Shimabukuro indicated that VAERS data are being reviewed as they come in. Limited data are available at this point, but they would be happy to present those data during a future ACIP meeting. For the v-safesm, they are in the process of enrolling individuals into the pregnancy registry and hope to begin assessing those data pretty quickly. There would be an opportunity to present those data during a future ACIP meeting as well. A couple of surveillance projects are planned in the VSD. Once they feel that there are sufficient data to present meaningful results, they will be happy to present that information to the ACIP.

Dr. Chen noted that there was recent updated guidance about severe but non-anaphylaxis reactions. Some of his colleagues in the allergy and immunology community have mentioned desensitization protocol guidelines or something like that to offer further guidance for these non-anaphylaxis events. He wondered whether there is any movement within the safety group to discussion some of these approaches or if any of these events were Brighton Classification Level 4 or 5.

In terms of the allergic reactions that were in the publications, Dr. Shimabukuro said that they cast a very wide net to look for any allergic reactions that were severe or suggestive of anaphylaxis and then reviewed those. These basically fell into 3 categories. Either they were anaphylaxis according to the Brighton, or they did not meet Brighton criteria but were judged to be allergic reactions, or they were judged to be non-allergic reactions like vasovagal anxiety-related reactions.

Dr. Goldman (ACP) emphasized that it is incumbent upon those who are vaccinating patients to stress to them and make them well aware of the potential reactions. He personally experienced fever and chills after the second dose and they were quite severe. They must make patients aware of it so they will return for their second dose. He wondered if patients who experienced

⁴⁶ <https://www.cdc.gov/vaccines/covid-19/downloads/pre-vaccination-screening-form.pdf>

⁴⁷ <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html>

⁴⁸ <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/testing-after-allergic-reaction.html>

reactogenicity or anaphylaxis had been assessed for having previously had COVID-19 infection and received the vaccine.

Dr. Shimabukuro said that while they did not specifically assess this, that information may be captured in the VAERS reports. Anecdotally, they have heard about previous infection and the possibility of more severe reactogenicity when getting a dose of COVID-19 vaccine. Options are being explored to use the v-safesm data to determine whether it is possible to further investigate that potential safety issue. There are limited data on that now, they are looking at ways to obtain better information on that.

Dr. Sanchez said that he too has heard a lot of anecdotes about people who have had COVID-19 previously who are having reactions to the vaccine that are worse than the original infection. It is very important to be able to capture that in v-safesm. In addition, he inquired as to whether breastfeeding mothers and infant outcomes would be assessed in the pregnancy registry in terms of women who were vaccinated while breastfeeding. In terms of reactogenicity being reported out to 7 days, it was reported in the *New England Journal of Medicine (NEJM)* that erythema and swelling has been noted 7 to 14 days out.

Dr. Shimabukuro said that recognizing the concern about prior infection, they are exploring some options for conducting a nested study within v-safesm to further assess that issue. In terms of maternal safety activities, the v-safesm pregnancy registry is enrolling women through the duration of their pregnancies and then following the infants out for 3 months, so there will be information on infant outcomes. Regarding erythema and swelling, he believes there are ways to get at AEs beyond the 7-day period and into the 7- to 14-day window in v-safesm.

Dr. O'Leary (PIDS) asked whether there have been any reports of any MIS-like syndromes in younger adults, and if CDC is monitoring vaccination in patients with so-called "long COVID" with persistent symptoms long after an initial COVID infection.

Dr. Shimabukuro indicated that MIS-C and MIS-A are AESIs that are being monitored in VAERS and the VSD and that he was not aware of any reports of MIS-A in younger adults to date that met the case definition. The "long COVID" individuals would be captured in VAERS, provided that the past medical history was documented. There is information about COVID infection in VSD. While this may not have been incorporated specifically into the monitoring, it is certainly something that could be considered in the future more as a research project.

Knowing that these data are early and the risk estimates continue to change as more data come in, Dr. Drees (SHEA) wondered what criteria would need to be met to cease the recommendation for 15 minutes of monitoring post-vaccination, particularly among those without a known allergy history. The risk for anaphylaxis seems exceptionally low and as vaccination is expanded and high throughput events are being planned, a limiting factor is often finding space for people to hang out following vaccination, as well as the need for additional clinical staff to perform the monitoring.

Dr. Shimabukuro said he thought there were sufficient data to say that anaphylaxis can occur following mRNA vaccines. Anaphylaxis can occur following any vaccine. As far as adjusting the post-vaccination observation period, he deferred to those who developed the clinical guidance on if and when that would be warranted.

Dr. Daley emphasized that the presentations by Drs. Lee and Shimabukuro were important reminders to them all that vaccine safety knowledge certainly would evolve over time. It is important to keep in mind that as Dr. Shimabukuro described, this is the most intense and comprehensive vaccine undertaking ever by the USG. This also seems to be the timeliest safety evaluation, given that this has all occurred in just the last 5 or 6 weeks. It is very fortunate to have such well-established systems in place and to have been able to add new systems like v-safesm. These safety data are critical for public confidence and clinical considerations around vaccination, so it is reassuring to know what careful attention is being paid to vaccine safety.

COVID-19 Vaccine Implementation

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Dr. Cohn provided a high-level update on the status of vaccine administration. As of January 25, 2021, there are 11 states that report being in Phase 1a, 38 states that report being in Phase 1b, and 2 states that report being in Phase 1c. The Kaiser Family Foundation (KFF) publishes a report that updates this regularly and also talks about variation between the different phases, including age group and differences in essential worker populations. That is very helpful in terms of getting a sense of all the different things that the states are doing⁴⁹.

The ACIP prioritization recommendations are intended as a framework to support equitable and efficient administration of COVID-19 vaccine and jurisdictional flexibility. As discussed during multiple other ACIP meetings, it is not necessary to complete one phase before expanding to the next group. Jurisdictions should start to move into other age groups as, for example, demand starts to decrease in persons aged greater than 75 years. A critical part of this is to use all available doses and to minimize waste, even if that means giving doses to somebody who may not be in an eligible group at that moment. However, a key principle is to continue to offer vaccine to persons in earlier phases—even if they refused vaccine the first time they were offered.

CDC is committed to transparency on vaccine administration data. Vaccine administration is getting to somewhat of a steadier state with vaccine ramping up and with reporting. On February 1, 2021, CDC will be publishing two MMWRs showing early administration data in LTCFs and general demographic characteristics of the early groups who have been vaccinated. Vaccines have been shipped to over 18,000 providers. It is important to understand that these vaccines require larger minimal doses of 100 doses for Moderna and over 950 doses for Pfizer. This results in high inventory when doses are received. For example, if a vaccination site receives 100 doses of Pfizer vaccine once or twice a week, there will always be days when they are reporting a large amount of inventory. Social distancing requirements reduce throughput and necessitates scheduling of vaccine appointments and an increased workforce to manage the need to watch patients in a socially distanced way for 15 minutes after vaccination and other requirements of remaining socially distanced. Finally, it is important to understand that doses administered per day increased, especially after the holidays, which means an increased number of doses now at 3 to 4 weeks later are being assigned to be administered as second doses.

⁴⁹ <https://www.kff.org/other/state-indicator/state-COVID-19-vaccine-priority-populations/>

Overall COVID-19 vaccine distribution and initiation are posted on CDC's COVID Data Tracker. In the very near future, CDC will be increasing the amount of data that can be shown in the COVID Data Tracker. As of January 26, 2021, over 44 million doses of vaccines have been distributed. "Doses distributed" means that this number of doses have been received by the jurisdictions. "Doses administered" refers to the number of vaccine doses that have been reported to have gotten into arms. The total doses administered is over 23 million. This includes nearly 20 million persons receiving one or more doses and nearly 3.5 million people who are fully vaccinated with two doses. As expected, Pfizer vaccine was being administered slightly earlier, but both products are now being used broadly⁵⁰.

In terms of the total number of doses administered by date of administration, it is important to note that it takes time for vaccines to be reported. Doses are administered and then have to be entered through a reporting system. Since early January, over 1 million doses of vaccine have been administered most days of the week. The Saturday number of doses administered declines, and the Sunday doses administered is extremely low and continues to be low. However, in the last week after Martin Luther King Day on January 18th, over 1.2 million doses were administered per day over several days⁵¹.

Through the Federal Pharmacy Partnership for Long-Term Care (LTC) Vaccination Program, over 2.7 million doses have been administered overall. Over 2.4 million people have received one dose and just under 250,000 have received both doses. Over 1.2 million residents of LTCFs have been vaccinated and over 800,000 staff have been vaccinated. These LTCF clinics and LTCFs are reporting low vaccine uptake and vaccine hesitancy among LTCF staff, especially in some states. Vaccination clinics will go to the LTCFs 3 times. Early information is showing that when the clinics return for the second or third time, additional staff are accepting vaccine. Therefore, continuing to capture those staff who do not accept vaccine early will be really important in terms of eliminating outbreaks and protecting both staff and residents in LTCFs.

There are a lot of questions about why it appears that more doses are being distributed compared to the number of doses administered. A couple of reasons for this are time from administration to reporting and inventory being resupplied on a regular basis. However, there is clearly a need to improve efficiency of vaccination at administration sites. It is important to ensure the demonstration sites can handle the supply they have and better match demand to where supply is. CDC is working with jurisdiction and administration sites to improve throughput at sites through workflow and additional staffing, improve scheduling, better match of supply to throughput capabilities, improve vaccine supply and demand mismatch, and share best practices from states that are doing this well. This sounds super straightforward and incredibly rational, but it is it takes a very large amount of work.

In conclusion, unprecedented roll-out of a new vaccination program has reached nearly 20 million people over a short period of time during a surge in the epidemic. However, supply continues to be a rate-limiting factor. While everything possible can be done to increase efficiency and get doses into arms more rapidly, there is likely to be limited supply for the near future. As vaccination expands and vaccine uptake continues to increase, it is important to focus on rapidly administering doses and reducing bottlenecks in the system. These bottlenecks can occur anywhere in the system from manufacturing, to shipping, to distribution, to administration. No person should be left behind. It is important to continue to focus on equitable access, even

⁵⁰ <https://covid.cdc.gov/covid-data-tracker>

⁵¹ Data Source: IIS, Federal Pharmacy Program, Federal Entities Program

with the focus on vaccinating as many people as rapidly as possible. This means it will be necessary to reduce barriers to vaccination and increase engagement to build trust in communities. Particular communities of concern in terms of access and demand include essential worker populations, homebound adults, and persons with disabilities. It is much easier to communicate and get older adults vaccinated than it is essential workers, so vaccinating essential workers is going to require an incredible amount of work. Many persons with disabilities will not be able to go to vaccination clinics that are currently available, so it will be important to find ways to vaccinate in people's homes or to set up designated spaces that can vaccinate persons with disabilities. CDC continues to focus efforts on increasing demand, but also bringing vaccinations to racial and ethnic minority communities. Access and building trust are both needed, so it is critical to continue to listen to and engage with these communities. Vaccinating the country will take all of society working together and requires persistence, engagement, and community.

In closing, Dr. Cohn called upon all who were listening to this meeting to take action and do something to support the vaccination program, whether it is checking in with neighbors who may be eligible for vaccine and driving them to their appointment or working with a community to set up a vaccination clinic in a school or church. This takes more than a village. It takes an entire country and it will be a lot of work, but vaccination remains one of the best ways to end this pandemic and get life back to normal.

Discussion Points

Dr. Duchin (NACCHO) expressed gratitude for the update and the tremendous work that CDC is doing to support states, and emphasized how gratifying it was to hear President Biden acknowledging that the unpredictable supply of vaccine and the inability to forecast from week to week is a major barrier for getting vaccines into the communities and the eligible populations at the local level throughout the country. He requested additional information about the vaccine supply in terms of what states can expect and how the inability to forecast can be overcome. He heard the President say that more reliable information and predictable data would be provided.

Dr. Cohn stressed that one of the more challenging barriers is not knowing the prediction and being able to predict and forecast out supplies so that people know when they'll be getting doses and can schedule more than just a couple of weeks out. The question about resolving this issue is being worked on currently. There was additional discussion about that on a White House briefing earlier in the day. They are trying to understand the data better and work with companies to have a better sense of forecasting and to increase the supply to jurisdictions when possible. It is important to be careful not to increase supply so much that it is too close to the edge of supply management. While she did not have specifics on ways that is being managed, she is hoping to get more details in the coming days. That will be a collaborative process with HHS, CDC, and the White House Task Force to resolve this.

Dr. Duchin (NACCHO) asked whether CDC would be providing any guidance to states about how to manage the second dose issues. Initially those doses were being reserved, so there was no need to do anything special to ensure that everyone who got a first dose would be guaranteed a second dose. At this point, that is no longer being done so he wondered if CDC would be recommending strategies to ensure that second doses are received and administered on time.

Dr. Cohn clarified that second doses are still being allocated when the initial doses are allocated. Second doses are made available 3 or 4 weeks out depending on the product. This is being managed to ensure that there is a second dose for everyone who gets the first dose. It is not being held back in that inventory is not being held back, but inventory is being prioritized and directed through the supply management system to ensure that there are second doses available.

Dr. Romero thanked CDC for being very flexible in allowing states to use vaccine that was dedicated to LTCFs where that dosing was over-calculated. In his state, the formula used to calculate the amount of doses given for the LTCFs provided extra doses that were sitting there and they were able to reach out to CDC to have that moved out of the category and used in the community. There still is a deficit in the ability to reach out to communities that are linguistically challenged or have cultural differences that need to be addressed. He stressed that this is very important as they begin the move out of the Phase 1a groups and into Phased 1b and 1c. They must continue to focus on that and provide guidance and materials for the states in order to forward on that.

In terms of equity and allocating doses, Ms. Bahta expressed concern that speed is being pushed over equity. Based on working specifically with African American and Latino communities and liaisons from the health department, there is a lot of hesitancy that is due to historical trauma, past injustices by public health and the healthcare system, and current injustices that are occurring. There needs to be a lot more conversation at both the local and national levels in order to give people the information they need to make the best decision for vaccination. In her state, those who are 65 and older are starting to get the vaccine but they consist of 97% white individuals. So, this vaccine is not getting into the communities that have been the most severely impacted by COVID-19. While she heard the commitment in the presentation, it is important to keep acting as well.

Dr. Cohn stressed that the CDC and USG approach is to not leave anyone behind and continue to focus on equity while expanding vaccination into new populations. They are monitoring this very closely and will be reviewing the data as it comes in on race and ethnicity to ensure that. They are also looking at the data to help jurisdictions identify which parts geographically of their state may be getting under-served either because of access or because of hesitancy, so looking at distribution compared to uptake in socially vulnerable communities, rural communities, and other places. In response to the comments about racial and ethnic minority communities and the large amount of vaccine hesitancy in those communities, one of the key things that CDC thinks is critical is to engage national and local Black organizational partners, such as BlackDoctors.org, the National Medical Association (NMA), the National Black Nurses Association (NBNA), organizations that support Latina communities, and many others to give them what they need to talk to and engage and vaccinate their communities. It is important for jurisdictions to work with these organizations that really understand the challenges that their communities face, and for CDC to do this at a national level. The agency will be laser-focused on this in the coming weeks.

Dr. Sonja Hutchins (NMA) indicated that she is a Professor in the Department of Community Health and Preventive Medicine at Morehouse School of Medicine and a retired Captain in the United States Public Health Service (USPHS) where she spent her entire 30-year career at CDC working on vaccines, prevention of vaccine-preventable diseases, and emergency public health preparedness and response, particularly as it related to vulnerable populations. As a member of the NMA and also someone who has a lot of experience in working with the most vulnerable populations in our society, NMA has been working on hesitancy from the very

beginning of the pandemic as the oldest and largest organization of African American physicians. They have had webinars as early as the end of March and throughout the year and set up a COVID-19 Task Force that has been meeting with the manufacturers, CDC, and other organizations to combat the hesitancy problem. It was gratifying for her to hear of the robust vaccine safety monitoring, because that really helps communities better understand the safety of the vaccines and that goes a long way in promoting confidence in the vaccinations. They are also concerned about the administration of the vaccine in their communities and know that there are supply issues that need to be overcome so that the vaccine is equitably administered in the underserved populations throughout the country. The NMA spoke with CDC the previous week about that, shared some ideas, and are continuing to work on distribution and administration of vaccines in the communities where people are accepting the vaccines. The NMA is very hopeful that they will continue to work together with CDC and other partners to reach the most vulnerable sectors and communities and the nation.

Dr. Goldman (ACP) expressed concern that while many of his colleagues want to be able to provide the vaccine, have access to communities, but are being denied the ability to do that. Plus, it is known that on a state-by-state level each Governor can choose to follow the guidelines or not. Many Governors are completely ignoring the CDC's Ethical Framework and healthcare workers on the frontline and essential workers are being denied the ability to get a vaccine in favor of different guidelines being enacted. With that and the unethical occurrences of those with a lot of money donating to facilities and getting vaccinated above and beyond those who should get it first based on the Ethical Framework, he wondered whether CDC anticipated any stronger federal involvement or a more national strategy to take over in some of the states that are not quite following an ethical framework so that they can ensure equity and actual vaccine distribution in a more fair manner for some of the states that are not following the framework. For example, firefighters are eligible but policemen and teachers are not allowed to get vaccines.

Dr. Cohn said that incorporating primary care physicians to be vaccinators and administrators of COVID-19 vaccine is something CDC would really like to do in the near future as supply increases enough. She thinks there are ways that they can do it in a limited way so that providers who serve large portions of the population or can act as vaccinators for other practices. There are a lot of challenges right now with the limited number of doses and the high minimal requirement to order. There are groups of people that they need primary care doctors to vaccinate and many people still will want to wait to get vaccinated at their primary care doctors, or someplace that an individual recognizes as a provider. CDC is absolutely thinking about several ways that they can support jurisdictions to get vaccine distributed and administered equitably and efficiently. There are lots of reports about certain administration sites and locations where individuals who are not eligible for vaccination are getting vaccinated. They do not want to be so rigid that doses are wasted, but they do believe that for any vaccination there should be provider fairness. Fairness should be a critical factor. CDC's preference would be for pharmacies and other organizations that are vaccinating to have wait lists of people who are eligible for vaccine. Most organizations are doing this. They are just hearing the stories of some places. From a federal perspective, CDC is there to support the jurisdictions and anticipate continuing to provide them guidance as needed, but primarily around improving their programs. ACIP has made the recommendations and provided a framework for people to use, but jurisdictions do have flexibility in how they implement those recommendations.

Dr. Lee requested that they keep two metrics visible. The one they are all aware of and should be aware of is the one on efficiency. She absolutely agreed that they do not want doses in freezers or any wasted doses. But they also have to bring into view measures of equity. Holding them to both standards is really important in order to be sure that there is accountability for how vaccines are being delivered. In addition, having a standard way to measure equity and recognizing all the challenges with measuring equity, will allow them to redouble the efforts in communities where there are known to be high rates of disease and high rates of vaccine hesitancy, and it will allow them to focus those efforts in a more specific manner as opposed to a general approach, which is needed as well. Race/ethnicity was mentioned specifically as one dimension. In the past there have been discussions about zip code, the Social Vulnerability Index (SVI), or the COVID-19 Pandemic Index as a proxy for understanding risk in communities and how well they are doing in vaccinating those communities. They also need to ensure that healthcare delivery systems are also looking at primary or preferred language to ensure that rates of vaccination are similar among English and non-English speakers. Having examples of these measures of equity, even if they are not ideal or the thing they want to measure, anything they bring into vision will help ensure that they are doing a good job.

Dr. Cohn indicated that CDC is actively working on the measures Dr. Lee was speaking about and anticipates being able to report in those ways in the near future. Race and ethnicity are about 50% unreported, so provider reporting of race and ethnicity is critical. CDC is also attempting to use SVI and other measures and proxies.

Carol Hayes (ACNM) expressed gratitude to HHS and CDC for the funding that has come along not only with the vaccines themselves, but also the other types of monies that have been given. In the state where she resides, the vast majority of how they have been able to roll out the COVID vaccine was from federal funding. She suggested assessing the Immunization Information Systems (IIS) systems in different states. For instance, her state is the worst in vaccinating individuals in the US because their IIS system is from 1996 and it has not been updated since. They are so slow at reporting doses given, OWS would not give them more doses. So, they are in a horrible catch-22. Her state also has punted the vast majority of how to roll out the vaccine to the counties. Some of their counties are so poor and so underfunded that they have had a difficult time developing their own registration systems and their own drive through systems. Her state has 159 counties. This feudalism presents a horrible situation where no one is really coordinating in a really global way, so she was very happy to hear that CDC is going to recommend that the states that have had an efficient system can share their best practices with other states.

Dr. Long emphasized that they all have different experiences and have all been very concerned about being sure that disparities, deaths, and disease do not get any worse. Despite the best attempts, they will because those who have colleagues, family, members, friends who are not paid by a healthcare institution know how much self-advocacy it takes to get an immunization. Even when someone is on the right list and in the right ballpark, it is very difficult. It took hours for her to get an immunization for her husband who is now retired because by the time she completed all of the information to try to get an appointment online, there were no more slots for that time. This is happening in lots of ways. She suggested that President Biden's administration could be very useful. She does not think it will help to educate people who do not trust the system about how safe the vaccines are if it is the government telling them. She thinks a grassroots organization is needed with people knocking on doors talking to their neighbors. Perhaps an Obama-Biden approach might be the way to do this, because she thinks there are going to be very disparate numbers in who is able to get immunized. The other thing where she thinks there has been a complete failure, at least in Philadelphia, is that the big university

institutions who take care of millions of patients still have no plans for immunizing their patients. Perhaps they could get people who have some time like retired physician, nurses, et cetera to be able to give immunizations on weekends. It is not clear why vaccines are not being given on weekends when people are dying on weekends. She felt great relief when she and her husband got their first dose and said that if they were not infected in the next 10 days, they would not die from coronavirus. There are people who still will, so she is upset and passionate about the haves still getting more vaccine than that have nots.

COVID-19 Vaccine Effectiveness Studies

Katherine Fleming-Dutra, MD
Vaccine Effectiveness Team, Vaccine Evaluation Unit
Vaccine Task Force, COVID-19 Response
Centers for Disease Control and Prevention

Dr. Fleming-Dutra explained the reasons COVID-19 post-authorization VE estimates are needed. First, real-world performance of vaccines can vary from efficacy in control trial settings. This can only be understood from observational VE studies. Both authorized COVID-19 vaccines have recommended 2-dose schedules with dosing intervals of 3 and 4 weeks. It is known that outside of clinical trials and actual practice, the timing and coverage of second doses can vary from what is recommended. Both authorized vaccines have specific cold-chain requirements that may be difficult to implement in practice. Additionally, post-authorization VE estimates also will build on evidence from the Phase III clinical trials, including VE in key sub-populations and outcomes for which the trials may have had limited power, follow-up time, or were not designed to address. Examples of these outcomes include severe disease, SARS-CoV-2 infection and transmission, and duration of protection.

While it would be ideal to have observational data on all outcomes in all populations, the need is recognized to prioritize and focus on information that will be most useful for guiding policy. The Vaccine Effectiveness Team's priorities have been developed based on the results of internal and external input. The most immediate priority in the first 2 to 4 months of vaccination is to answer the question, "Does vaccine protect against symptomatic disease as expected?" After that, the subsequent priorities include: 1) estimating VE against key outcomes of severe disease, non-severe disease, and SARS-CoV-2 infection and transmission; estimating VE in key sub-populations, including for adults 65 years of age, those living in LTCFs; people with key underlying health conditions, such as those who are immunocompromised or have obesity or diabetes; and racial and ethnic populations that have been disproportionately affected by COVID-19; and 2) estimating VE for regimen-related questions, such as single dose and prolonged dosing intervals and mixed-dose schedules. In the later stage, additional key policy questions include those around viral evolution and whether genome changes threaten VE, duration of protection, and estimating comparative VE in terms of whether one product is better than another.

While there is undoubtedly a need for post-authorization VE studies, there are some challenges inherent to observational COVID-19 VE studies that can bias VE estimates. One of the biggest challenges is that the decision to be vaccinated may correlate with the risk of disease and people who choose to get vaccinated may also adopt other prevention behaviors that would decrease the risk of disease, or they may engage in more risky behavior because they feel protected. Prior infection may bias the VE estimates as it confers protection against disease and known prior infection may be associated with the likelihood of vaccination. In addition, COVID-19 epidemiology is highly dynamic, which makes it tricky to plan when and where to do VE

studies. Multiple products are in use simultaneously, further complicating VE studies. Given these inherent limitations, a portfolio has been developed using a diversity of methods to address policy priorities.

The following table provides a summary of currently planned COVID-19 VE assessments. For each of the policy priorities listed in the left column, there are plans to start both studies with prospective data collection, which are listed in the middle column, and settings that leverage big data such as EHRs or claims datasets listed in the right column:

Currently Planned COVID-19 VE Assessments		
VE priority	Prospective data collection	Electronic health record (EHR) and claims analyses (coordination across US government)
Immediate priority		
Does vaccine work as expected to prevent symptomatic disease?	Test-negative design case-control among healthcare personnel	
Subsequent priorities		
Older adults, including residents of longterm care facilities (LTCF)	Case-control among adults ≥65 years (CONNECT-linked to CMS); National Healthcare Safety Network	CMS cohort (FDA, CMS) EHR datasets (CDC, VA, FDA)
Infection and transmission	Prospective longitudinal cohorts, including among healthcare personnel & frontline workers; case-ascertained household cohorts for transmission	
Severe disease/hospitalization	Test-negative design (for adults and children); conventional case-control using hospitalized controls; screening method	EHR datasets (CDC, VA, FDA): Retrospective cohort or test-negative design
Nonsevere disease	Test-negative design among outpatients	Potentially using EHR datasets
Those with key underlying conditions (e.g., immunocompromised)	Captured in above studies	CMS (FDA, CMS); EHR datasets (CDC, VA, FDA)
Disproportionately affected racial/ethnic groups	Captured in above studies; test-negative design in American Indian/Alaska Native population	CMS (FDA, CMS); EHR datasets (CDC, VA, FDA) Exploring IHS EHR (IHS)
Vaccine impact	Ecologic analyses of disease incidence/seroprevalence and vaccine coverage; comparisons of vaccine impact from models with observed impact	

Prospective studies allow for richer data through interviews or surveys of participants and chart review, while larger datasets offer greater statistical power and efficiently make use of existing data resources. For this work, the aim is to facilitate rapid launches of these assessments by leveraging existing platforms and to harmonize across platforms and USG.

Starting with the most immediate question of whether vaccine works as expected to prevent symptomatic disease, a prospective assessment will be conducted among HCP using a prospective test-negative design among HCP. A test-negative design is a type of case-control study which enrolls people with a certain clinical syndrome, in this case HCP with a COVID-like illness who are tested for the disease of interest, in this case COVID-19. Cases are those who test positive and controls are those who test negative. The primary objective of this assessment is to evaluate the VE of a complete schedule of COVID-19 vaccine against laboratory-confirmed, symptomatic COVID-19. If feasible, this will be done by vaccine product. The secondary objectives are several and will include assessing VE by the number of doses received if this is feasible based on the number of participants who received 1 or 2 doses assessment. This assessment launched in January 2021 and will enroll until sites have reached a vaccine coverage of greater than 80% with 2 doses. Interim analysis may occur as early as March, but the timing depends on vaccine coverage at the sites and the rate of case accrual.

This VE assessment is being conducted across 26 states in 34 sites that have over 500,000 HCP.

Turning toward the next priority of assessing VE among older adults, including residents of LTCs facilities, several assessments are planned among adults 65 years of age and older. These include a CDC-led case-control assessment of VE linking hospitalized COVID-19 cases from CDC's COVID-NET surveillance system with claims data from CMS and an FDA-led cohort analysis of CMS claims data. Both of these assessments will conduct separate analyses among adults 65 years of age and older who reside in the community and those who reside in LTCFs. For these analyses, the results are not expected until at least this summer to allow time for vaccination to occur in this age group, cases to accrue, and the data to be available.

Among residents of LTCFs, the plan is to use data from the National Healthcare Safety Network (NHSN) LTCF surveillance and vaccine coverage modules. These data will have weekly aggregate counts at the facility level of new laboratory-confirmed COVID-19 cases and vaccination status among all residents and among new COVID-19 cases. Using these data, weekly attack rates will be calculated among vaccinated and unvaccinated to estimate VE among residents of LTCFs. The first transmissions with these data will be available starting in early February. The initial analysis will require at least 8 weekly transmission from facilities with at least 50% vaccine coverage. There are plans to conduct ongoing analyses as reporting into these NHSN modules will be ongoing.

Additionally, there are plans for assessments of vaccine impact in LTCFs facilities that have the potential to be more rapid, including ecologic analyses of vaccine coverage and COVID-19 disease rates among residents of LTCFs. Assessments of vaccine impact may also come from outbreaks with descriptive analyses before and after vaccine use. Another key priority is to assess the VE against infection, including asymptomatic infection, and importantly against transmission, which can only be evaluated prospectively. In order to do this, an ongoing cohort of more than 5000 HCP and first responders will be leveraged with weekly testing for SARS-CoV-2 infection and assessment of secondary transmission among household members. The cohort began in July 2020 and will continue through March 2022. Work is currently underway to expand case-ascertained household transmission studies to include the general population during widespread adult vaccination.

A test-negative design and conventional case-control design with hospitalized controls will be used for the outcomes of severe disease, hospitalization, and non-severe disease and the key subpopulations of those with underlying health conditions, such as immunocompromising conditions, and racial and ethnic groups who are disproportionately affected by COVID-19. These VE evaluations will be designed to assess severe disease and hospitalization and non-severe disease, and they will utilize sites selected to include populations with underlying health conditions, racial and ethnic groups who have been disproportionately affected by COVID-19, and American Indian and Alaska Native (AI/AN) populations. Screening method analyses also will be conducted, which are assessments that look at vaccination coverage among a group of cases, for example cases detected through ongoing COVID-19 surveillance, and compared with vaccination coverage among the overall population from which the cases arose (e.g., people from the same state). The data analyses to be conducted will include EHRs and claims-based assessments.

Assessments are also planned to measure the vaccine impact in a population. For this, ecologic analyses are planned of the association of disease incidence and/or seroprevalence with vaccine coverage, as well as comparisons of expected vaccine impact from mathematical models with actual observed impact. Important questions include assessing VE for regimen-related questions, including use of a single dose or prolonged dosing intervals, meaning more than 3 to 4 weeks between doses or even mixed dose schedules, meaning use of more than one product in a 2-dose series. The ability to answer these questions using observational studies will depend on whether enough of these events are captured, which may occur in practice even though they may not be recommended. All of the platforms, with the exception of the NHSN will collect individual level information on dose dates and vaccine-type. Thus, they have the potential to answer these questions. However, for the early phase vaccination among HCP and residents of LTHFs, it is anticipated that there will be adherence to dosing recommendations, including the use of 2 doses of the same product, and the dosing intervals. Therefore, it is unlikely that there will be enough variation in the data from HCP and residents of LTCFs to answer these questions. Thus, the best opportunity to answer these questions may come from large prospective HER- and claims-based assessments among the general adult population.

In terms of assessing whether viral genome changes threaten VE, the prospective platforms for the general adult population will collect specimens from cases where possible for whole genome sequencing (WGS). It is important to note that this will not be performed in real time and these evaluations may not be powered for variant-specific VE assessments. Nonetheless, the hope is that these specimens can be leveraged to help answer this question. Additionally, a separate team in the Vaccine Evaluation Unit is dedicated to assessment of vaccine breakthrough cases, including investigating whether SARS-CoV-2 variants lead to breakthrough cases and have the potential to impact VE. Dr. Fleming-Dutra emphasized that this work is part of broader CDC efforts to monitor the impact of SARS-CoV-2 variants and that this would be addressed more fully in the next presentation.

In terms of assessing VE among children and pregnant women, for children a prospective test-negative design assessment is planned to evaluate VE against COVID-19 hospitalizations. This work will leverage an existing surveillance network of approximately 20 to 40 sites for pediatric COVID-19 hospitalizations, including Intensive Care Units (ICUs), step-down, and general in-patient admissions and MIS-C. Additionally, EHRs and claims database analyses will be used to estimate VE in children. For pregnant women, EHR cohort and prospective case-control VE assessments are being explored.

In conclusion, there is an urgent need for VE data to guide policy. The VE portfolio leverages multiple platforms, data sources, and methods. Early VE assessments will focus on HCP and residents of LTCFs. The portfolio will continue to evolve as more information from Phase III trials and real-world evidence become available.

Work Group Interpretation and Next Steps

Sara Oliver, MD

LCDR, U.S. Public Health Service

**Co-lead, Advisory Committee for Immunization Practices COVID-19 Vaccines WG
COVID-19 Response**

Centers for Disease Control and Prevention

Dr. Oliver presented the WG's interpretation of the data and next steps. To summarize the clinical trial data that was presented earlier from AstraZeneca, the WG reviewed the immunogenicity data for neutralizing and binding antibodies that were measured in participants after 1-dose and 2-dose series. The responses were similar to convalescent sera comparison and Th1-biased T-cell response was documented. A 5×10^{10} dose series delivered as a 2-dose series 28 days apart was selected for the US Phase III clinical trials.

The WG also reviewed safety data for the AstraZeneca. From the Phase I/II studies, local and systemic symptoms were mild to moderate in severity. Injection site pain, feeling feverish, muscle aches, and headaches were the most common symptoms reported. Reactogenicity symptoms were lower after the second dose, although small numbers of individuals received a second dose in those trials, and lower in older adults. No vaccine-related SAEs were reported. The interim results from the global Phase III trial shows similar results to the early phase clinical trials. Reactogenicity symptoms were milder and reported less frequently after the second dose and in adults 65 years of age and older. Results also were reported from the clinical hold where the study was paused due to the report of transverse myelitis in the UK. The FDA reviewed neurological events in all of the trials. After this independent review, the study was allowed to be resumed with changes, including an independent expert neurology panel.

In addition, AstraZeneca presented preliminary data from the interim global efficacy analysis. Over 11,000 participants in the UK and Brazil were included in this interim analysis. There were several dose regimens and inter-dose intervals included in this analysis. The VE estimate for the standard dose/standard dose regimen, which is what is currently being studied in the US Phase III trials was 62% of pooled VE estimates, including individuals with a lower dose as the first dose as well as a more delayed do schedule with 70%. They also discussed their plans for the US Phase III trials, which will be the primary basis the EUA application. To date, they reported over 32,000 people enrolled in the Phase III trials. The primary endpoint is symptomatic, virologically-confirmed COVID disease. The presentation earlier in the day discussed trial enrollment and diverse populations, including diversity in race and ethnicity, age, and underlying medical conditions.

Overall, the WG felt that the early Phase I/II data shows induction of binding and neutralizing antibodies as well as T-Cell responses with a favorable safety and reactogenicity profile, supporting the advance to Phase III trials. Safety pauses are expected with large clinical trials and indicate that the processes working appropriately. However, transparency around the safety pause and resolution is critical. Overall, the WG awaits the results of the US Phase III trial for an EUA application with 2 doses of the standard dose of vaccine 28 days apart.

In terms of the WG interpretation of COVID-19 in children, while the overall burden of COVID may be lower among children, preventable infections, hospitalizations, and long-term sequelae and deaths are an important public health problem. Clinical trials to evaluate safety and immunogenicity of COVID vaccines in children are essential. Given disparities noted among COVID cases in children and MIS-C, it will be crucial for pediatric clinical trials to enroll a

diverse population. The WG looks forward to reviewing data from these clinical trials as they become available.

Real-world VE studies are needed for a variety of populations, ages, and underlying medical conditions. Diverse trial designs also will be important to address a variety of questions. The WG discussed many of these that can hopefully be addressed through these studies, including VE after a single dose or a mixed series, VE in immunocompromised individuals, and duration of protection. In addition, isolates obtained through the VE platforms can help address concerns around SARS-CoV-2 variants.

For more on the SARS-CoV-2 variants, in the Fall of 2020, several SARS-CoV-2 variants emerged with changes in the receptor-binding domain of the spike protein. Preliminary studies indicate that these changes can confer increased transmissibility. Three of the concerning variants include the B.1.1.7 variant from the UK, B.1.351 from South Africa, and P.1 from Brazil. While changes in the virus over time are expected, these have been of particular concern for this specific issue. These variants have the ability to evade vaccine-induced immunity⁵².

Several pre-print studies have been made available over the past several weeks. Following vaccination, limited numbers of study participants' sera were tested in neutralization assays. Regarding the Pfizer vaccine, studies have demonstrated equivalent neutralization titers against a panel of 19 individual SARS-CoV-2 spike variants⁵³ and N501Y (variant)⁵⁴ compared to wildtype virus. Reductions to neutralization titers have been noted against the UK variant with 1.2⁵⁵ or 3.9-fold⁵⁶ reduction. One study found a modest reduction for some neutralization against certain site mutations from the South African and Brazil variants⁵⁷. However, these were tested against individual mutations. Regarding the Moderna vaccines, the same study again found modest reduction for neutralization for mutations in the South Africa and Brazil variants⁵. Another study found no significant impact on neutralization titers against the UK variant, but a 6-fold reduction for the South African variant⁵⁸. The links to each of the pre-prints are located in the footnote.

Surveillance is critical in monitoring these and possibly other future variants in the US. These surveillance efforts are detailed on the CDC website¹, but the WG wanted to highlight them here as well. The National SARS-CoV-2 Strain Surveillance (NS3) is being scaled to sample hundreds of samples per week and will allow for broad characterization of the viruses. Surveillance is also underway in partnership with national reference laboratories and universities occurring within state and local health departments and through a national consortium of around 160 laboratories called the SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology and Surveillance (SPHERES) Consortium. Additional investigations will be conducted as vaccine breakthrough cases are identified.

⁵² <https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html>

⁵³ Sahin et al. medRxiv preprint (Dec 11, 2020a); doi: <https://doi.org/10.1101/2020.12.09.20245175>

⁵⁴ Xie et al. bioRxiv preprint (Jan 07, 2021); doi: <https://doi.org/10.1101/2021.01.07.425740>

⁵⁵ Muik et al. bioRxiv preprint (Jan 19, 2021); doi: <https://doi.org/10.1101/2021.01.18.426984>

⁵⁶ Collier et al. medRxiv preprint (Jan 20, 2021); doi: <https://doi.org/10.1101/2021.01.19.21249840>

⁵⁷ Wang et al. bioRxiv preprint (Jan 15, 2021); doi: <https://doi.org/10.1101/2021.01.15.426911>

⁵⁸ Wu et al. BioRxiv preprint ((Jan 25, 2021); doi: <https://doi.org/10.1101/2021.01.25.427948>

Overall, in most of the studies reviewed, there was minimal to moderate reduction in neutralization activity for vaccine-immune sera in some persons. The implication for real-world effectiveness are unclear. Sera from mRNA vaccine recipients had higher neutralization activity than COVID convalescent human sera in the early phase clinical trials. In addition, a minimal reduction in neutralization activity may not be clinically relevant. Most of the studies mentioned previously were conducted using pseudo viruses, which are more sensitive to neutralization. Importantly, these are limited studies with small numbers. The evidence is quickly evolving, so there will need to be a continued review of the data. Studies evaluating full sets of mutation from the variants are likely more informative than studies of single mutations. Studies of vaccine breakthrough cases are planned and these may serve as an early warning. Finally, Moderna announced this week that they are in the process of developing a vaccine against the South African variant.

In terms of some recent updates to the clinical guidance around COVID vaccine dosing and schedules, the mRNA vaccines are recommended for a 2-dose series administered intramuscularly. The Pfizer vaccine doses are recommended to be given 3 weeks apart and the Moderna vaccine is recommended to be given 4 weeks apart. Persons should not be scheduled to receive the second dose earlier than the recommended intervals. Overall, the second dose should be administered as close to the recommended interval as possible. However, if it is not feasible to adhere to the recommended interval, the second dose of the Pfizer or Moderna vaccines may be scheduled for administration up to 6 weeks or 42 days after the first dose. To address discussions of alternative dosing or schedules, the currently recommended schedules and doses are from the Phase III trials where safety and high efficacy were demonstrated. If data become available for alternate schedules or doses, ACIP can review data and consider new recommendations. However, in the absence of additional data to support alternative schedules or doses, the current recommendations will remain. The mRNA vaccines are not interchangeable with each other or with other COVID vaccines. Either vaccine series may be used. ACIP does not state a product preference and every effort should be made to determine which vaccine product was received as the first dose. In exceptional situations in which the first dose of the vaccine product cannot be determined or is no longer available, any available mRNA COVID vaccine may be administered at a minimum interval of 28 days between doses. This longer interval was chosen since it is presumed that at least one of the doses may be the Moderna product⁵⁹.

While the vaccines are being used under an EUA, to allow for appropriate safety surveillance, the mRNA vaccines should be administered alone with a minimum interval of 14 days before or after administration with other vaccines. This is a reflection of the lack of data regarding co-administration and the need for careful safety surveillance, not because there are any known problems with safety or efficacy with concomitant administration. Along those lines, mRNA COVID vaccines and other vaccines may be administered within a shorter period in situations where the benefits of vaccination are deemed to outweigh the potential unknown risks of vaccine co-administration, such as Tdap after a dirty wound, Tdap during pregnancy, vaccines during an outbreak, et cetera. If mRNA vaccines are administered within 14 days of another vaccine, the doses do not need to be repeated for either vaccine.

In terms of next steps for the WG, any votes on the use of additional COVID vaccines will take place at an emergency ACIP meeting once FDA has authorized the vaccine and data are reviewed by ACIP, including safety and efficacy results from the Phase III trials. The Janssen vaccine may have results from their Phase III trial within the next several weeks based on public

⁵⁹ <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html>

statements by the company and others. This is an adenovirus 26 (Ad.26) vector vaccine. The current US Phase III trials are evaluating a single dose. To provide a very quick overview of adenovirus vector vaccines since this is where the WG and ACIP will be pivoting for future COVID-19 discussions, the Ad.26 vector in the Jansen/J&J product is a non-replicating vector. It has been used in other vaccines. J&J has Ebola vaccine that has been used in broader populations, including pregnant women and children. Unlike the mRNA platform, there will be a little more experience with this platform in various populations. However, one of the lessons learned previously through adenoviral vector vaccines is that prior exposure to the vector could possibly reduce effectiveness. The chimpanzee adenovirus vector is also non-replicating. The chimpanzee adenovirus vector can circumvent pre-existing immunity to human adenovirus vectors. The WG looks forward to providing updates from the Phase III trials of these vaccines as they become available.

Discussion Points

In terms of the variants mentioned, Dr. Ault asked whether the changes are in the antibody binding sites where the hosts would recognize the spike protein that would cause concern that vaccination is not going to protect against that.

Dr. Oliver said that the reason these particular variants are of concern is because amino acid changes have been noted in the receptor binding domain of the spike protein. That is why of all changes that the virus might make, these are the ones the WG has been talking about more frequently over the last several weeks. It is her understanding that the binding domain is the same thing that the host antibody recognizes.

Dr. Thornburg added that the answer to that is somewhat complicated because some of those mutations are in areas where neutralizing antibodies do bind in general, but everyone makes a different set of antibodies. Any one individual who is vaccinated might have an antibody binding that site or might not. They might have neutralizing antibodies that bind other residues. Also, people make a swarm of antibodies so they will make dozens of neutralizing antibodies. If one of those antibodies drops out from a mutation, the other antibodies can still be active. On a population whole an individual mutation may not truly escape, but for an individual it could.

Dr. Kimberlin (AAP Redbook) recalled that Slide 22 showed how the mRNA vaccine should be administered alone and Dr. Oliver mentioned that this was due to lack of data, which is fully understandable. As they begin to anticipate the day when these vaccines can be used in adolescents and even in younger children, it is important to remember that many children and adolescents across the country have fallen significantly behind on their immunization schedules. If there is an opportunity to catch them up on the vaccines they have missed during the pandemic and administer the COVID vaccine when they are approved to receive those vaccines, it would be highly beneficial. He inquired as to whether there would be an opportunity between now and several months from now, when hopefully there will be authorization for the use of the vaccines in children and adolescents, that some of those kinds of studies can be done in order to be better prepared for the more global health that they try to generate in patients. He emphasized that the sooner this could be done the better so that opportunities can be leveraged for catch-up on standard vaccination when patients touch the healthcare system for any reason.

Dr. Oliver said that there are ongoing discussions currently regarding additional studies that could be done in the pediatric and adolescent populations overall and then including coadministration. The current clinical considerations are for the use of mRNA vaccines in the adult population. Those considerations are being updated regularly, so when vaccines are authorized for routine use in children, there will be additional thoughts for clinical considerations in that population as well.

Public Comments

Overview

The floor was opened for public comment during the January 27, 2021 ACIP emergency meeting at 4:30 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated, selection was made randomly via a lottery. The comments made during the meeting are included here. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket No. CDC-2021-0002. Visit <http://www.regulations.gov> for access to the docket or to submit comments or read background documents and comments received.

Public Comments

Lindsay Clarke, JD
Vice President
Health Education and Advocacy
Alliance for Aging Research

Thank you so much. Good afternoon. I'm Lindsay Clarke, Vice President of Health Education and Advocacy at the Alliance for Aging Research. The Alliance is one of the convening members of the COVID-19 Vaccine Education and Equity Project, along with Healthy Women and the National Caucus & Center on Black Aging (NCBA). We are joined by more than 125 partner organizations representing patients, caregivers, families, diverse communities, health care professionals, older Americans, veterans, frontline workers, and scientists. The project is focused on promoting widespread and equitable access to COVID-19 vaccination information, particularly among those on the front lines and the communities that have been hit hardest by the pandemic. You can learn more and join us at <https://covidvaccineproject.org/>

While we are excited to see vaccine administration ramping up in recent weeks, we also need to continue to be aware of and look out for those that may be left behind. Vaccine hesitancy still exists in many communities, but as discussed earlier, the primary obstacle right now seems to be access. Older adults, Black Americans, and other vulnerable populations are more eager than ever to get vaccinated. However, in order to make vaccine appointments, they often are asked to go online, download, apps, and check back frequently for availability. Those who don't have internet access or are uncomfortable with technology or who don't have the time to devote to getting an appointment are being left out. We're glad to see the committee addressing this and encourage use of the CDC Social Vulnerability Index (SVI) to offer vaccines according to zip codes. Just because a COVID-19 vaccine clinic is set up in an underserved area does not ensure vaccine access unless appointments are limited to those residents. We also need more targeted outreach on the ground in underserved communities, as well as appointment

assistance. All of these strategies will help get vaccines into the arms of the most vulnerable in the communities that have been hit the hardest.

Even if they are able to navigate the appointment system, there are still many who are reluctant to get a vaccine. According to a survey that the Alliance recently conducted on behalf of the Vaccine Education and Equity Project, when asked about preferences on where to receive a COVID-19 vaccine, the majority of respondents (64%) indicated that they would prefer to get it at their health care provider's office, 29% prefer a pharmacy, and 20% a drive-through vaccine clinic, while only 13% would like to receive the vaccine at a grocery store pharmacy. Older adults are much more likely to cite a preference for COVID-19 vaccine administration in their health care provider's office. Those preferences seem to relate to trust and familiarity, with nearly two-thirds of respondents saying they would prefer to get vaccinated from a healthcare provider they know. While the focus is primarily on large-scale distribution sites in these early phases of administration, we encourage the ACIP and CDC to consider these barriers and preferences in future phases so that we can reduce barriers for individuals who are harder to reach or who are reluctant to actively seek out a COVID-19 vaccine. We are ready and willing to help the committee in any way, so please reach out. Thank you for the opportunity to comment.

Mark Gibbons
President/CEO
RetireSafe

Mr. Chairman. Good afternoon. My name is Mark Gibbons. I'm the President and Chief Executive Office (CEO) of an organization called RetireSafe. RetireSafe is a non-profit grassroots organization whose mission is to educate and advocate on behalf of older Americans. We address many key issues, including Social Security, Medicare, Medicaid protecting our health, and financial wellbeing by making sure the concerns as well as the wisdom of older generations are given voice. The COVID virus has impacted all of us in many unexpected and devastating ways, but the stats for those over 65 are harsh, indeed. Approximately 1 in 7 adults in the United States are over 65, but CDC reports that 6 out of every 8 COVID-related deaths have occurred in this age group. That is 6 out of 8. Older persons also have higher infection, hospitalization, and death rates from other infectious diseases, such as influenza and also pneumonia. In short, advanced age tragically also means advanced risk.

RetireSafe thanks ACIP and its advisors for their tireless work for being invited to speak today. As new vaccines for COVID and other diseases are developed, it is so important that the high-risk status of more than 50 million older Americans be addressed. We respectfully ask that ACIP consider the addition of adding a few more gerontological experts to its membership. I understand that 4 new members have been added; however, none were from this category. This is a little disappointing for my membership. I attended a meeting back in 2019, and one of the members stated that the committee's only concerns were younger children and young adults—not the aging adults. I don't think that is really what was meant to be said, but that's what was said. So, please consider adding some more doctors that handle the aging. Thank you for your time and have a good afternoon.

Dr. Justin Gregory
Division of Pediatric Endocrinology
Vanderbilt University Medical Center

Good afternoon. My name is Justin Gregory. I'm a Pediatric Endocrinologist at Vanderbilt University Medical Center (VUMC). Currently, the CDC categorization has Type 1 diabetes as a condition that *may* increase risk for severe COVID-19. In light of recent clinical evidence, I urge my colleagues on this committee to recommend revising this categorization to a condition that *does* increase risk for severe COVID-19. At present, the CDC appropriately list Type 2 diabetes as a high-risk condition. As we summarized in an article in the *Annals of Internal Medicine* published yesterday, clinical evidence unequivocally suggest that CDC should likewise categorize Type 1 diabetes as a high-risk medical condition. In our prospective cohort study of COVID-19 outcomes at Vanderbilt, originally published last month in *Diabetes Care*, we found hospitalization with COVID-19 is 4.6 times more likely to occur in patients with Type 1 diabetes than patients who do not have diabetes. By comparison, hospitalization is 3.4 times more likely to occur in patients with Type 2 diabetes than patients who do not have diabetes. Moreover, we found that even when patients with Type 1 diabetes maintain blood sugar at ideal levels, they were still 3 times more likely to be hospitalized than patients without diabetes.

Our international colleagues similarly found having Type 1 diabetes increases the risk of mortality. A recent population-wide study of England published in *Lancet Diabetes and Endocrinology* found COVID-19 mortality was 3.5 times more likely among patients with Type 1 diabetes than patients without diabetes. By comparison, COVID-19 mortality was 2 times more likely in patients with Type 2 diabetes. Fortunately, randomized clinical trials (RCTs) showed that both currently approved vaccines were just as efficacious in preventing COVID-19 complications in people with diabetes as they were in protecting the entire study cohort. Moreover, severe COVID-19 occurred only once among all of the vaccinated participants. Thus, while patients with Type 1 diabetes are at greater risk for severe COVID-19, the vaccine appears to have a profoundly protective effect against this outcome in these patients.

In conclusion, the data are clear. I join the Juvenile Diabetes Research Foundation (JDRF), the largest charitable supporter of Type 1 diabetes research to urge this committee to recommend that CDC revise its categorization of people with certain medical conditions to reflect that individuals with Type 1 diabetes are at increased risk of severe illness from the virus which causes COVID-19. As individual states will soon transition into Phase 1c of COVID-19 vaccination, this revision can play a critical role in appropriately prioritizing patients with Type 1 diabetes for immunization. Such action will allow the medical community to maximize the benefit of the vaccine by protecting over 1.6 million Americans with Type 1 diabetes through an increased risk for morbidity and mortality from this virus. Thank you.

Michaela Jackson, MS
Prevention Policy Manager
Hepatitis B Foundation

My name is Michaela Jackson. I am the Prevention Policy Manager for the Hepatitis B Foundation. On behalf of the hepatitis B and liver disease communities, I am speaking today to encourage ACIP to share available subgroup data, particularly for people living with hepatitis B and liver disease that has been presented by companies developing COVID-19 vaccines. ACIP has responded to the coronavirus pandemic swiftly and we applaud the dedication to ensuring the safety and efficacy of each vaccine. However, there remains great uncertainty and confusion among patients and providers about who should receive the vaccines. Lack of publicly available data plays a large role in this uncertainty. We are aware that people living with HepB and liver disease have been included in clinical trials, but representation matters little if the groups represented are not able to see the information relevant to them. Establishing trust in the efficacy of these vaccines is absolutely critical to ending the pandemic. While the public health community has made great strides with this endeavor, there is still a long way to go. Throughout the course of this pandemic, an increasing number of people living with HepB have approached us with questions about how effective the vaccine is for them and if they should even receive it given their health condition. Simply put, these communities have expressed an interest in getting immunized against COVID-19, but are hesitant due to a lack of information currently available to them. Presenting evidence on people living with HepB and liver disease from clinical trials will help improve access to approved vaccines and will broaden trust and acceptance as well. Too often, the medical community has neglected to listen to the concerns of under-represented groups and the consequences have been devastating. We must remember that data is one of the most powerful tools we have to build back some confidence among vulnerable populations, and it's one that we must fully utilize in order to earn the trust of consumer communities. Thank you for your time today.

Kelly Shanahan, MD
Member at Large
METAvisor

I'm Kelly Shanahan. Before my metastatic breast cancer diagnosis, I was an OB/GYN. Now, I'm an advocate on the Board of Directors of METAvisor, which raises money for metastatic breast cancer research, including the \$4.4 million dollars we awarded in the midst of this pandemic. I'm speaking for the adult cancer community as there is no such representation on ACIP. From the first paper from the COVID-19 Cancer Consortium published online in *The Lancet* last year, it has been clear that people with cancer are at increased risk of severe illness and death if infected with SARS-CoV-2. This is true whether the cancer is active or not, although people currently being treated for cancer with a metastatic diagnosis fared the worst. Work from the United Kingdom Coronavirus Cancer Monitoring Project (UKCCMP) confirmed this. Desai et al, in an article from December, performed a meta-analysis of people with cancer hospitalized with COVID-19. Thirty percent of those hospitalized died. For studies that included a mix of in- and outpatients, the mortality rate was 15%. Currently in the US, the case fatality rate of COVID-19 is 1.7%. We know that the risk of dying increases with age. Levin et al in the December *European Journal of Epidemiology* calculated an infection fatality rate of 0.4% at age 55, 1.4% at 65, and a staggering 15% at 85. What does that 15% remind us of? The 15% to 30% mortality of people with cancer who also have COVID-19. It's not just death that we need to consider. People with cancer who become ill with COVID-19 are more likely to require hospitalization at 47% according to an analysis of electronic health records (EHRs) by Wang et al published in *Jama Oncology* in December—almost double the rate of people without cancer

and almost 4 times the rate of people with cancer who did not also have COVID-19. People with cancer have increased exposure risk because staying home and skipping treatments and scans is not an option for us. If the goal is to vaccinate those at greatest risk of severe illness or death should they contract COVID-19, shouldn't people with metastatic and active cancers who die at a rate equal to and perhaps twice as high as octogenarians be vaccinated with that group? I've heard experts say that we should move to vaccinating based on age alone—that it's just too hard to prioritize by risk. They said it was too hard to go to the moon, but we did that. It's not rocket science to devise a system where people with metastatic and active cancers are vaccinated at their cancer center or oncology office. We're going for treatments and scans and follow-ups already. Our oncologists know our diagnosis. Who gets vaccinated when is all over the map. State and local public health organizations look to you for guidance. If you truly believe that the most vulnerable must be prioritized for vaccination, then that must include people who have a 15% to 30% chance of dying—the active and metastatic cancer population. Thank you.

Allison Winnike, JD
President & CEO
The Immunization Partnership

Good afternoon Chair Romero and members of the committee. My name is Alison Winnike. I'm President and CEO of the immunization partnership. Our nonprofit mission is to eradicate vaccine-preventable diseases by educating the community, advocating for evidence-based public policy, and supporting immunization best practices. Thank you for developing vaccine recommendations to keep all Americans safe and healthy. Your scientific recommendations are an important tool that states use to carry out their constitutional duty to protect the public's health. Today, I have two recommendations for the committee. First, I recommend giving greater weight to vaccine availability through the supply chain in the priority-based group recommendations. ACIP recommendations should be a solid data-driven guide for states as they implement their COVID-19 vaccine administration plans. However, it is notable that outside of the Phase 1a recommendations that were recommended by ACIP, and that were nearly universally adopted by the states, only a small minority of states are exactly following the Phase 1b and 1c recommendations. Many were frustrated by the committee's prioritization of essential workers in Phase 1b over those at high-risk for severe COVID-19 at a time when vaccine supplies were so limited and deaths were mounting in those aged 65 and older and people with high-risk medical conditions.

With nearly 425,000 deaths so far and a surge impacting our most vulnerable, states need more detailed recommendations to help them prioritize within phase groups as we struggle with such limited vaccine supply. My second recommendation is to continue your practice of transparency and deliberations for forthcoming COVID-19 vaccines. We were very fortunate that the first two vaccines authorized for emergency use demonstrated extremely high efficacy rates for the adult population, but future vaccines may not meet the efficacy levels of our current vaccines or they may have varying rates for different age groups. I am concerned that as new vaccines enter the market, people may fear they are receiving an inferior product if the efficacy rates do not meet the vaccines that are currently available. The community should take extra efforts to sufficiently explain the science behind your recommendations, both to states executing their vaccine plans and to the public. Americans are frustrated, they're scared, they're sick, and many feel forgotten if they wait their turn to be vaccinated against this novel coronavirus. Please make sure that future COVID-19 vaccine recommendations take into account the vaccine access and equity issues Americans face. Strong communications from the committee on the science may help combat the perception that future vaccines may be of lower quality or rushed through to

distribute to those with high social vulnerabilities and few resources. Thank you so much for your important work and the opportunity to share our comments.

Edward Nirenberg
Vaccine Advocate

Hello. Thank you for the opportunity and privilege you granted me today in permitting me an oral public comment. My name is Edward Nirenberg and I am a vaccine advocate who focuses primarily on debunking and pre-bunking harmful disinformation and misinformation pertaining to vaccines. I am immeasurably grateful for your labors in ensuring the safety of the American people and your transparency of these proceedings, as they have helped me personally tremendously. I'd like to call out a few issues to the attention of ACIP in this short window of time. Firstly, the Pfizer-BioNTech vaccine in preclinical and clinical data showed robust activation of CD-8 T-cells, while for Moderna's vaccine the response was undetectable. Notably, efficacy for both vaccines in the Phase III trials were very similar. Due to the exigency of our present crisis, people should absolutely take the first vaccine offered to them provided they have no contraindications. However, preclinical models in macaques implicate CD8 T-cells as important correlates of recovery from COVID-19. Epidemiological data show low CD8 T-cells are associated with poor prognosis. Many patients with certain blood as well as those with certain autoimmune diseases are placed on anti B-cell therapies such as Rituxan, Rituximab, or Ranibizumab. Operating under the assumption of a neutralizing antibody-mediated mechanism as a correlate protection, this presents many patients without protection against COVID-19. I ask that the committee consider, in light of the evidence available, a recommendation that those patients on anti-B-cell therapy should whenever possible preferentially receive the Pfizer-BioNTech vaccine over Moderna as a way to recognize of the evidence-based considerations.

Secondly, increasingly I'm seeing concerns regarding apparent functional movement issues following the receipt of COVID-19 vaccine. These have gone viral and several videos are provoking profound anxiety. The Functional Neurological Disorder Society (FNDS) has issued a statement describing the nature of these reactions. I believe it would be valuable for the committee to enhance communications regarding possible cytogenic issues related to immunization as this has been observed before with, for example, the human papillomavirus (HPV) vaccine. Lastly, the anti-vaccine movement sees the pandemic an opportunity to undermine vaccine confidence and is thus working tirelessly to correlate any adverse outcomes from anyone who receives the vaccine as a causal relationship to vaccinations. I believe it would be helpful for the committee to put out communications elucidating the inadequacy of temporal associations in establishing causality and adverse event following immunization. I have been able to rely on several excellent summaries such as one from Dr. Bob Walker showing how many adverse health outcomes can be expected in any given 2-month window for 10 million people irrespective of vaccination status. These are subject to the assumption of vaccine distribution stories with statistical average across the entire population, which as the committee is aware, would represent an underestimate with vaccine preferentially going to the elderly and those with comorbidities since such outcomes are at baseline much more likely. Thank you for your time.

Peter Matz
Director, Food & Health Policy
Food Industry Association

Good afternoon. My name is Peter Matz and I'm here representing FMI, the Food Industry Association where I'm the Director of Food and Health Policy. By way of background, as the Food Industry Association, FMI works on behalf of the entire industry from retailers who sell to consumers, to producers who supply the food, to supermarket pharmacies and beyond. The total FMI member companies operate around 3000 grocery stores and 12,000 pharmacies, touching the lives of more than 100 million US households per week and representing an industry with nearly 6 million workers. First, FMI strongly supports ACIP's recommendation to prioritize food and agriculture industry essential workers in Phase 1b. However, states and jurisdictions should be strongly encouraged to adhere to the federal recommendations. As a result of many states developing their own prioritization frameworks in the face of federal guidance, food industry essential workers are struggling to access vaccinations. For manufacturing and production employees working in close proximity, to grocery workers who have a higher contact rate with the public, to certain transportation workers and food safety auditors who ensure food, beverages, and packaged foods are safe for consumer consumption our industry's essential workforce has gone above and beyond in demonstrating their continued resilience. But to keep supply chains operating and Americans nourished until all can receive the vaccine, it is imperative that they receive vaccinations.

Furthermore, as supermarket pharmacies across the country step up in support of vaccinations plans, changes to federal prioritization guidelines across states are impeding efficiency in vaccine delivery causing confusion and undermining the national vaccination effort. With that in mind, FMI urges the Biden Administration to designate a Federal COVID-19 Vaccine Coordinator in each state and jurisdiction to coordinate at all levels of government and help ensure the deployment of vaccines among priority populations. Also, to the extent that jurisdictions have already made revisions to federal vaccine allocation guidance, FMI asks that the CDC compile and store all state plans so the information is easily accessible to all stakeholders. Separately, supermarket pharmacies administered roughly 25% of the nation's flu vaccinations this year and now they stand ready to play an expanded role in increasing access to COVID vaccines. A number of FMI pharmacy members have been providing vaccinations through the Federal Pharmacy Partnership (FPP), and a majority are enrolled as providers in the states where they operate. All of them have pharmacists prepared to administer COVID vaccinations in their stores and many pharmacists available and ready to provide vaccinations off-site as well. Many are also utilizing their parking lots and outdoor tents as COVID vaccination clinics capable of administering nearly a 1000 shots in a day. However, our members are not yet receiving vaccine supplies anywhere close to their capacity. Finally, in order for vaccine providers to fully utilize the limited supply of vaccines they do receive, they must have visibility into the expected availability of future doses. We really appreciate the opportunity and thank you to ACIP.

Claire Hannan
Executive Director
Association of Immunization Managers

Good afternoon. I'm Claire Hannan, Executive Director of the Association of Immunization Managers (AIM). AIM members are the dedicated public health immunization directors currently working to help coordinate the COVID vaccine roll out, fighting to maintain and increase other immunization rates, writing grants on both the COVID response and routine immunization, and coordinating response to state legislation, including an array of bills threatening to compromise school requirements and add barriers to vaccination. It is a critical time. I'd like to thank the committee and CDC for their dedication to thoroughly reviewing all pre-decisional data and post-authorization safety data, building public trust and vaccines. The vaccine campaign, in the use of second doses, must be driven by science. Our success in just 5 weeks of vaccinating is incredible, with more than 23 million doses administered, more than 3 million people fully vaccinated, tens of thousands of private providers enrolled and trained. But, in the context of people dying of the virus and people suffering anxiety and frustration searching for the vaccine, our accomplishments don't feel incredible. So, we will continue to address our challenges and learn from them.

Vaccination strategies are evolving as jurisdictions work to improve efficiency and reporting. Large scale, high throughput vaccination clinics are more common. Jurisdictions are benefiting from public and private partnerships, collaboration with large companies such as Starbucks, and local and chain pharmacies. In our rush to improve efficiency though, we cannot lose sight of equity. Program managers are driven to ensure this vaccine receives widespread acceptance and protects everyone in all of our communities. Listening to the discussion today, we are so pleased to hear ACIP focusing on equity as well. State and local health agencies have received funding and resources to support COVID vaccination. We are grateful, but we also see these resources as just a down payment on the needed larger investment in our future in information technology (IT) modernization, public health workforce, routine adult vaccination, and continuing the critical work of building confidence in all vaccines in all communities. The key to COVID vaccination success is increased supply, increase transparency and communication, and most importantly, increased collaboration. Federal, state, and local public health must work together, not in competition, united by the same vision and goals. Our country is in a COVID emergency, but our entire immunization infrastructure is at stake. Combating myths and dangerous legislative initiatives require all of us. Let's start with the scientific expertise of this committee and the CDC. Thank you for your continued guidance and expertise.



Certification

Upon reviewing the foregoing version of the January 27, 2021 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.

ACIP Membership Roster

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Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
December 23, 2020 – June 30, 2021**

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