

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

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



**Summary Report
February 28-March 1, 2021
Atlanta, Georgia**

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**US DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
National Center for Immunization and Respiratory Diseases**

**Advisory Committee on Immunization Practices (ACIP)
Virtual Meeting
February 28-March 1, 2021**

Statement of Purpose

The United States (US) Department of Health and Human Services (HHS), Centers for Disease Control and Prevention (CDC), National Center for Immunization and Respiratory Diseases (NCIRD) convened a virtual meeting of the Advisory Committee on Immunization Practices (ACIP). The meeting was held on February 28-March 1, 2021 beginning at 11:00 am Eastern Standard Time (EST).

The ACIP is formally chartered under the Federal Advisory Committee Act (FACA) to provide advice and recommendations to the HHS Secretary, HHS Assistant Secretary for Health, and the CDC Director regarding use of vaccines and related agents for effective control of vaccine-preventable diseases in the civilian population of the United States (US). Recommendations made by the ACIP are reviewed by the CDC Director, and if adopted, are published as official CDC/HHS recommendations in the *Morbidity and Mortality Weekly Report (MMWR)*. The CDC Director informs the Secretary, HHS, and the Assistant Secretary for Health, of immunization recommendations. Upon the licensure of any vaccine or any new indication for a vaccine, the committee shall, as appropriate, consider the use of the vaccine at its next regularly scheduled meeting. If the committee does not make a recommendation at the committee's first regularly scheduled meeting, the committee shall provide an update on the status of such committee's review.

The purpose of the February 28-March 1, 2021 ACIP emergency meeting was to review the Food and Drug Administration (FDA) Emergency Use Authorization (EUA) of the Janssen COVID-19 vaccine for individuals 18 years of age and older and consider and discuss ACIP recommendation of this vaccine. In addition, the ACIP considered and discussed implementation and clinical considerations for use of COVID-19 vaccines, COVID-19 vaccine safety, and emerging SARS-CoV-2 variants. Information for the public to attend the virtual ACIP meeting via webinar or teleconference was published in the *Federal Register* in accordance with FACA regulations and rules. All sessions of the meeting were open to the public (Attachment 1: Membership Roster).

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
AE	Adverse Event
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
APC	Antigen-Presenting Cells
APhA	American Pharmacists Association
APTR	Association for Prevention Teaching and Research
ASTHO	Association of State and Territorial Health Officers
ATSDR	Agency for Toxic Substances and Disease Registry
BARDA	Biomedical Advanced Research and Development Authority
BLA	Biologics Licensure Application
BMI	Body Mass Index
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment
CMS	Center for Medicare and Medicaid Services
CNS	Central Nervous System
COI	Conflict of Interest
COVID-19	Coronavirus Disease 2019
CSTE	Council of State and Territorial Epidemiologists
DART	Developmental and Reproductive Toxicity
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DRC	Democratic Republic of the Congo
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
DVT	Deep Vein Thrombosis
EHR	Electronic Health Record
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIH	First in Human
GBS	Guillain-Barré Syndrome
GMT	Geometric Mean Titers

GRADE	Grading of Recommendation Assessment, Development, and Evaluation
HCP	Health Care Personnel / Providers
HCW	Health Care Workers
HHS	(Department of) Health and Human Services
HRSA	Health Resources and Services Administration
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IM	Intramuscular
ISO	Immunization Safety Office
ISTM	International Society for Travel Medicine
JAMA	<i>Journal of the American Medical Association</i>
KFF	Kaiser Family Foundation
KPCO	Kaiser Permanente Colorado
LAIV	Live Attenuated Influenza Vaccine
LTCF	Long-Term Care Facilities
MAAE	Medically-Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	Multisystem Inflammatory Syndrome in Children
MMWR	<i>Morbidity and Mortality Weekly Report</i>
mRNA	Messenger Ribonucleic Acid
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
NGA	National Governors Association
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
PCP	Primary Care Physician
PCR	Polymerase Chain Reaction
PEG	Polyethylene Glycol
PHAC	Public Health Agency Canada
PhRMA [®]	Pharmaceutical Research and Manufacturers of America [®]
PI	Principal Investigator
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PP	Protocol Population

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)
RBD	Receptor-Binding Domain
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RR	Relative Risk
RSV	Respiratory Syncytial Virus
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
SGTF	S-Gene Target Failure
SHEA	Society for Healthcare Epidemiology of America
SIG	SARS-CoV-2 Interagency Group
SMEs	Subject Matter Experts
SNF	Skilled Nursing Facilities
SPHERES Consortium	SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology and Surveillance Consortium
SVI	Social Vulnerability Index
UK	United Kingdom
US	United States
USDA	US Department of Agriculture
USG	US Government
USPHS	US Public Health Service
VA	(US Department of) Veteran's Affairs
VA ADERS	VA Adverse Drug Event Reporting System
VAED	Vaccine-Associated Enhanced Disease
VAERS	Vaccine Adverse Event Reporting System
VaST	ACIP COVID-19 Vaccine Safety Technical Subgroup
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VRBPAC	Vaccines and Related Biological Products Advisory Committee Meeting
US	United States
USG	United States Government
VSD	Vaccine Safety Datalink
VTEU	Vaccine Treatment Evaluation Unit
WG	Work Group
WGS	Whole Genome Sequencing
WHO	World Health Organization

February 28-March 1, 2021: Welcome & Introductions

Amanda Cohn, MD
Executive Secretary, ACIP/CDC

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

José Romero, MD, FAAP
ACIP Chair

Dr. Cohn officially called to order the February 28-March 1, 2021 emergency meeting of the Advisory Committee on Immunization Practices (ACIP). She indicated that the slides for the meeting could be accessed on the ACIP website at the following URL:

<https://www.cdc.gov/vaccines/acip/meetings/slides-2021-02-28-03-01.html>

Additionally, the live webcast videos will be posted to the website following the meeting. Meeting minutes will be posted to the ACIP website generally within 90 to 120 days of the meeting. A short Executive Summary of the meeting will be posted within a week after the meeting.

Dr. Walensky welcomed and thanked the ACIP members, recognizing that the work they do is extraordinary and that the timing is not always ideal, during the daytime, or during work week hours. She acknowledged the many ACIP meetings that have been convened in the context of the COVID-19 pandemic, that the work has been hard and voluminous, and that the ACIP members have been making heavy and critical decisions. She indicated that she wanted to present as they embarked on this day with some very important decisions for the nation ahead of them, and to thank the members for the work they are doing. People are listening and engaged who really want to know what important information the ACIP wants to convey. From the bottom of her heart, she thanked them for their efforts. Dr. Cohn expressed appreciation for Dr. Walensky's opening comments, which she knew was much appreciated by all of the members who have been truly extraordinary over the last year.

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 meetings will be convened on June 23-24, 2021 and October 20-21, 2021. Additional meetings are likely to be scheduled to evaluate and respond to COVID vaccine issues between the regularly scheduled meetings.

Dr. Cohn explained that there would be an oral public comment session before the vote at 2:15 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-2021-0021. 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. For all COVID vaccine votes, some members may be funded by the National Institutes of Health (NIH) to work on COVID vaccine clinical trials. Because they are working on products under investigations, they will be asked to recuse themselves from COVID vaccine votes. At the beginning of each meeting, ACIP members state any COIs.

As a reminder, ACIP membership nominations are open. Applications for membership are due not later than July 21, 2021 for a 4-year term beginning July 2022. Emails will be sent out through listservs to solicit nominations.

Dr. Romero conducted the roll call on both days of the meeting. One COI was declared for this meeting by Dr. Chen, who reported that he was involved in clinical studies of COVID vaccines until October 2020. No other COIs were declared. A list of Members, *Ex Officio* Members, and Liaison Representatives is included in the appendixes at the end of the full minutes for the February 28-March 1, 2021 ACIP meeting.

Dr. Cohn announced on the second day of the meeting that Dr. Walensky, CDC Director, signed the Decision Memo approving ACIP's recommendations for use of the Janssen vaccine. A *Morbidity and Mortality Weekly Report (MMWR)* was anticipated to be published on March 2, 2021.

Coronavirus Disease 2019 (COVID-19) Vaccines: February 28, 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 reflecting on the fact that this meeting marked almost exactly one year from the first COVID-19-associated death in the United States (US). Over the course of the past year, more than half a million people in this country have lost their lives to this virus. This is the 11th emergency meeting for the ACIP on COVID-19. During this time, ACIP has made recommendations for 2 vaccines that received Emergency Use Authorization (EUA) from

the Food and Drug Administration (FDA). COVID cases and deaths are decreasing, but the pandemic is very far from over and there are still many challenges. The need for additional safe and effective vaccines remains urgent and vital to ending the pandemic.

During February, the COVID-19 WG continued to meet weekly. The topics covered during this month included an overview of adenovirus vector vaccines, the clinical development program for the Janssen Ad26.COV.2.S COVID-19 vaccine, the GRADE (Grading of Recommendation Assessment, Development and Evaluation) and EtR (Evidence to Recommendations) Framework for the Janssen COVID-19 vaccine, considerations for the use of COVID-19 vaccines, and safety updates.

The FDA issued an EUA for use of the Janssen COVID-19 vaccine on February 27, 2021 for the prevention of COVID-19 for individuals 18 years of age and older. Therefore, ACIP now needed to consider this third vaccine. With that in mind, the agenda for February 28, 2021 included the following topics:

- Overview of Janssen's Single-Dose COVID-19 Vaccine: Ad26.COV2.S
- GRADE: Janssen COVID-19 Vaccine
- EtR Framework: Janssen COVID-19 Vaccine
- Public Comment
- Discussion
- ACIP Vote: Janssen COVID-19 vaccine

Dr. Bell expressed gratitude to all of the ACIP COVID-19 WG members, liaisons, consultants, and CDC staff for all of their hard work and support in these efforts.

VRBPAC Meeting Summary

Doran Fink, MD, PhD
Deputy Director
Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

Dr. Fink provided a summary of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting convened on February 26, 2021 to discuss Janssen's request for an EUA for their COVID-19 vaccine. The meeting agenda opened with a presentation by the FDA to refresh VRBPAC on EUA and considerations specific to COVID-19 vaccines. Presentations also were heard from the CDC on the epidemiology of COVID-19 strain variants and post-marketing surveillance data from currently authorized COVID-19 vaccines, as well as a presentation from the FDA on plans for additional post-marketing surveillance. Following a public comment period, there were presentations on data from studies of the Janssen COVID-19 vaccine that were made first by representatives of Janssen and then the FDA's presentation of their comprehensive and independent review of the data submitted by Janssen in their EUA request. The meeting concluded with a discussion by the VRBPAC and a vote. The VRBPAC engaged in an in-depth discussion, following which they voted unanimously in favor of the determination that the known and potential benefits of the Janssen COVID-19 vaccine outweigh the known and potential risks in support of issuing an EUA for the vaccine.

Important questions were raised by some committee members, one of which pertained to the case definition for “moderate to severe” COVID-19 used by Janssen in their clinical trials in that it was all-encompassing of symptomatic disease and there were many cases in the trial that fell outside of that case definition. However, the FDA raised the point that the authorized indications for the COVID-19 vaccines for Janssen would be the same as for those previously authorized for Pfizer and Moderna for the prevention of COVID-19 due to SARS-CoV-2 without any specification of severity of disease. The committee also inquired about currently ongoing studies being conducted by Janssen evaluating a 2-dose regimen of their COVID-19 vaccine and asked what would happen if data from that study indicated that a 2-dose regimen was potentially more effective or offered greater benefit than the single-dose regimen for which the EUA was requested. The FDA advised the committee that if new data were to come to light supporting a 2-dose regimen, there are regulatory options either through a revision of the EUA or under a Biologics License Application (BLA) to support the use of a 2-dose regimen of the vaccine. The committee also inquired about ongoing studies to evaluate the effectiveness of the vaccine against asymptomatic infection and transmission. These studies are ongoing for the Janssen, Pfizer, and Moderna COVID-19 vaccines. Data should be available at the time BLAs are submitted if not before. The committee was very interested in further development of COVID-19 vaccines for use in pediatric populations. Those studies are either ongoing or expected to begin imminently. Finally, the FDA asked the committee to opine on efficacy in subgroups in the clinical trials specifically in adults 60 years of age and older with comorbidities. The committee members did not express serious concerns about vaccine efficacy in that population specifically, and generally were in agreement with the conclusions of Janssen and the FDA that the vaccine is highly effective against COVID-19-associated hospitalization and deaths and that apparent differences in vaccine efficacy estimates between certain subgroups are likely the result of smaller numbers of cases in those subgroups, leading to imprecision in the estimates.

In terms of the unanimous recommendation in favor of the EUA, VRBPAC members felt it was important to make sure that the public understands that this vaccine appears to be highly effective for all populations for prevention of COVID-19-related hospitalizations and deaths, and that it also is important not to compare this vaccine with other authorized vaccines because they have not been compared head-to-head and were evaluated at different times under different conditions.

Overview: Janssen’s Single-Dose COVID-19 Vaccine, Ad26.COV2.S

Macaya Douoguih, MD, MPH

Head of Clinical Development and Medical Affairs

Janssen Pharmaceuticals Companies of Johnson & Johnson

Dr. Douoguih thanked the ACIP for the opportunity to present data from Janssen’s development program as they seek ACIP’s recommendation for how the Janssen COVID-19 vaccination will be used in communities across the country. While few FDA-authorized COVID-19 vaccines are already being distributed, there remains an urgent need for effective and safe vaccines in order to vaccinate a majority of the US population, ensure protection against severe disease, and subsequently reduce the burden on the healthcare system. Now that the FDA has authorized the Janssen COVID-19 vaccine candidate (Ad26.COV2.S) for emergency use with an indication to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and above, the vaccine will be able to play a critical role in the global fight on COVID-19.

Ad26.COV2.S was studied in a large Phase 3 study in which more than 44,000 participants were enrolled. The study was conducted in multiple countries during the height of the pandemic. The vaccine offers substantial protection, especially against severe COVID-19 including hospitalization and death, irrespective of variants. It is well-tolerated and safe. It is a single-dose regimen with storage and transportation conditions that are compatible within existing distribution channels. Specifically, Janssen's vaccine has demonstrated early onset of protection against symptomatic COVID-19. Particularly important in the context of a pandemic, Janssen has observed 85% vaccine efficacy against severe COVID-19 globally and in the US at least 28 days after vaccination. For the key secondary endpoints, the effect was consistent across geographic regions. There was equally high protection in South Africa where about 95% of the strains were the emerging variant of the B.1.351 lineage.

Importantly for the primary analysis, there were no COVID-19 related hospitalizations in the vaccine group versus 16 in the placebo group. There were no COVID-19 related deaths in the Ad26 group compared to 5 in the placebo group. In the US, the vaccine showed 72% vaccine efficacy at least 28 days after vaccination. There were more than 19,000 participants in the US and particular attention was paid to ensuring that a diverse population was recruited. The primary endpoint was achieved with 66% vaccine efficacy for moderate to severe/critical COVID-19 for the overall study population after Day 28 and protection was observed as early as 2 weeks after vaccination. Consistent efficacy was seen across age, comorbidities, sex, race, and ethnicity.

These results are particularly important when considering when the vaccine was studied. The Janssen study sites were located in areas where COVID-19 incidence was highest and where variants were emerging (e.g., US, South Africa, and Brazil). Still, the vaccine efficacy against severe/critical COVID-19 was high. Based on sequencing of approximately 72% of COVID-19 cases in the study, it is evident that the prevalence of new variants was close to 70% in Brazil and greater than 90% in South Africa. Of note, Janssen did not observe the P.1 strain in the Brazil site. These efficacy rates are based on the total dataset, including non-centrally polymerase chain reaction (PCR)-confirmed cases.

The last few months have demonstrated that it is critically important to manufacture and distribute vaccines quickly and efficiently. Janssen's vaccine offers logistical and practical advantages to help simplify distribution and expand vaccine access. Each person receives a single injection of 0.5 ml. The application of a single-dose regimen offers the ability to vaccinate the population faster. Each vial contains 5 doses and no dilution is required. The vaccine can be stored for 3 months at normal refrigerator temperatures of 2° to 8° C (36° to 46° F) and has a 2-year shelf life when frozen at -25° to -15° C (-13° to 5° F). Janssen has continuously improved its manufacturing and formulation processes. Now that Janssen has received an EUA from the FDA, they are poised to begin shipping and delivering enough single doses to vaccinate 20 million Americans by the end of March. This is part of the overall commitment to supply 100 million doses to the US Government (USG) in the first half of 2021. The vaccine can be easily shipped using the existing supply chain infrastructure.

In addition to these key features, Janssen has substantial clinical experience with more than 193,000 people vaccinated with its Ad26-based vaccines. These studies were conducted across continents, including participants of various ages, races, and ethnicities and also included vaccination of pregnant and breastfeeding women within Janssen's Ebola program. Janssen's Ebola vaccine was licensed in Europe in July 2020 and is currently part of a mass vaccination program in Rwanda. Regular reviews of the safety database have shown overall good tolerability and safety. Local and systemic reactogenicity are in line with what has been

observed with other licensed vaccines. Database searches focused on adverse events of special interest (AESI) have not revealed any safety signals to date.

Regarding key studies in the comprehensive development program, Janssen has performed numerous animal studies including those in non-human primates (NHPs) to study vaccine immunogenicity and efficacy. A Phase 1/2a study, COV1001, was the first in human (FIH) study to examine safety, immunogenicity, and dose selection. A Phase 2 trial, COV2001, investigated a range of dosing regimens. An ongoing pivotal Phase 3 study, COV3001, is examining the efficacy, safety, and immunogenicity of a single-dose regimen. Data from this study were submitted to the FDA in support of Janssen's application for emergency use.

The Janssen presentation during this ACIP session provided a readout of the ongoing COV3001 study. Since the initial analyses, additional information on cases observed has become available. This will help to address some of the questions that those results could have triggered. Janssen also has a series of planned studies. The efficacy of a 2-dose regimen is being evaluated in Study COV3009 for which it is estimated that results will be available later in 2021. Several immunogenicity and safety studies will be conducted in children 0-17 years of age. The study in adolescents is anticipated to open the first week of March 2021. Janssen also anticipates starting a study in pregnant women in the second and third trimesters toward the end of March or Early April 2021. Studies also are planned to begin in immunocompromised individuals in the third quarter of 2021. Several post-authorization observational studies are also planned to assess vaccine safety and effectiveness in the real-world, which will include the development of a pregnancy exposure registry.

By design, the Janssen Ad26 vector cannot replicate in the human body. The E1 and E3 region are important in the development of Janssen's vector vaccine. By deleting E1 from the adenovirus DNA genome, the virus irreversibly loses its ability to replicate in human cells. Most of the E3 genes have been deleted as well, which creates more room for the genome for a transgene that codes for the protein that triggers the desired immune response. For the production of replication incompetent viral vectors, the well-characterized PER.C6 cell line complements for the missing E1 gene. The vector can replicate only in an E1 complementing cell line and cannot replicate in the human body. Of note, the PER.C6 cell line grows in a medium that is free of animal components. A vial of Janssen's Ad26-based vaccine contains a buffer with commonly used ingredients in vaccines. There are no adjuvants, antibiotics, or preservatives.

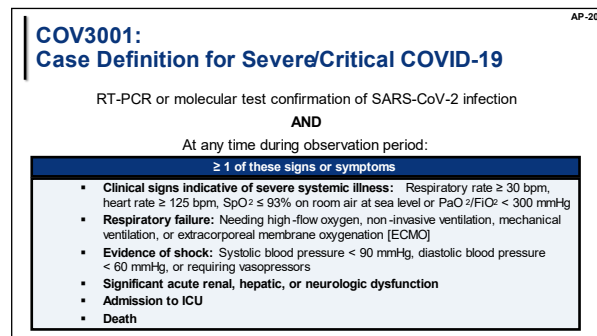
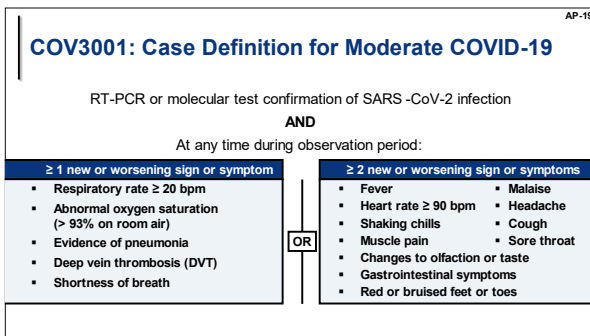
First, a single dose is injected into the muscle in order to deliver the transgene to a diversity of cells. The transgene encoded spike protein is then expressed on the surface of these cells. Innate immune responses triggered by the Ad26 vector provide the optimal microenvironment for the immune response against the spike protein. Attracted antigen-presenting cells (APCs) then pick up the spike protein and migrate to the lymph node, eliciting both humoral and cellular immune responses. The CD4+T helper cell responses are predominantly of the Th1 phenotype and stimulate B cells. Spike-specific antibodies are then produced by plasma cells. These antibodies have SARS-CoV-2 neutralizing antibodies and Fc-mediated antiviral effector functions that may place a key role in vaccine-elicited protective immunity, including protection against the new SARS-CoV-2 variants of concern. Spike-specific CD8+T cell responses are also triggered. CD8+T cell responses mature as cytotoxic effector cells with the ability to kill virus-infected cells. This is an important effector mechanism of vaccine-elicited antiviral immunity. The FDA guidelines classify adenoviral vectors as non-integrating, meaning that they do not have the propensity to modify the host genome.

In terms of preclinical data, a single dose of Ad26.COVS fully protects against SARS-CoV2 challenge in NHP. Near complete protection was observed against viral replication in the nose and full protection in the lungs. This protective efficacy was durable for at least 6 months. High-level lung viremia was seen even after vaccination with a 4-fold lower dose in the face of lower antibody titers. In addition, a single dose also gave near complete protection against viral replication in the lungs of aged NHP. To complement the NHP study, Janssen tested its vaccine in Syrian golden hamsters where it also demonstrated protective efficacy. Histopathology in animals with low-level breakthrough infections demonstrated no evidence of vaccine-associated enhanced disease (VAED).

Overall, these results satisfied the FDA guidance criteria to allow for progression into the human clinical trials. Since Janssen had an opportunity to review the previous design and results of its Phase I/II trials with ACIP, Dr. Douoguih provided a highly-level summary as a reminder. Following a single dose of Ad26.COVS, neutralizing antibody titers were elicited in 96% of adults independent of age. Titers were detected as early as 14 days post-vaccination, which increased in the following weeks and was maintained thereafter. This was irrespective of the vaccine dose used. Both CD8+ and CD4+ T cell responses were observed. The Th1 dominance of the CD4+ T cell responses in combination with the neutralizing antibody response minimizes the risk for VAED. In addition, 2 doses were tested. While both had a favorable safety profile, the lower dose had a more favorable reactogenicity profile. Therefore, the lower Ad26.COVS vaccine dose of 5×10^{10} viral particles was selected for the COV3001 Phase 3 study.

Regarding the results from the Phase 3 study known as ENSEMBLE, the primary analysis showed that the study met its primary endpoints, demonstrating the ability of a single dose of Ad26-COV2.S vaccine to protect against moderate and severe/critical COVID-19 in adults and that it has an acceptable safety and reactogenicity profile. COV3001 is a randomized, double-blind, placebo-controlled Phase 3 trial that is evaluating the efficacy, safety, and immunogenicity of a single dose of Ad26-COV2.S vaccine. Participants were randomized 1:1 to receive an injection of either vaccine or saline placebo. Randomization was stratified by site, age, and the absence or presence of comorbidities. The first part of the study consisted of a safety run-in phase. Phase 1a of the safety run-in enrolled 2000 adults 18-59 years of age without comorbidities. Following a planned safety review, enrollment was permitted to progress to Stage 1b to include participants up to 59 years of age with and without comorbidities. Stage 2a began in parallel to Stage 1a and enrolled 2000 adults ≥ 60 years of age without comorbidities. This cohort took somewhat longer to recruit. After a planned safety review in which the Data Safety Monitoring Board (DSMB) identified no safety concerns, the study progressed to Stage 2b to include adults ≥ 60 years with and without comorbidities. Given that those ≥ 60 years of age are at higher risk for severe COVID-19, the study targeted at least 30% of the total study population to be ≥ 60 years of age.

In terms of the co-primary endpoints, vaccine efficacy to prevent moderate to severe/critical COVID-19 with onset at least 14 days and at least 28 days after vaccination, the primary hypothesis is that the lower limit of the 95% confidence interval of the point estimate is $> 30\%$. This had to be met for both co-primary endpoints in order to declare success. The case definitions for moderate COVID-19 and Severe/Critical COVID-19 was as follows:



Janssen has a blinded Clinical Severity Adjudication Committee to evaluate all severe cases, as well as moderate cases that have at least 3 signs or symptoms. Classification of a case of Severe/Critical by the adjudication committee was considered definitive.

With respect to disposition and efficacy results, a total of 44,325 participants were randomized of whom 43,783 received an injection of either Ad26.COVID.S or placebo. This makes up the Full Analysis Set (FAS) and is the safety population. The per Protocol Population (PP) is the primary efficacy population and includes all participants who were seronegative at the time of injection and had no other major protocol deviations judged to possibly affect vaccine efficacy. Participants also were excluded when they had a positive PCR test result on the day of injection. The PP at-risk set includes all participants in the PP population, but excludes those with a positive PCR test between injection through Day 14 or Day 28.

No relevant differences were observed between the 2 groups in terms of the overall demographics of the global population at baseline. Efforts were in place to reach pre-defined targets for subgroups and showed good representation in terms of age, race, ethnicity, and sex. Enrolling significant numbers of participants ≥ 60 years of age was important for evaluating vaccine efficacy, with a target of 30% for the global population. The Ad26.COVID.S group includes 7331 (33%) participants ≥ 60 years of age and the placebo group had 7341 (34%). Also of note is that 20% of the FAS were frontline or essential workers or healthcare professionals. The baseline demographics for just the US participants showed no relevant differences between groups. A similar portion of participants are ≥ 60 years of age with 3761 (39%) in the vaccine group and 3777 (39%) in the placebo group. More importantly, participants are representative of the US population in terms of race and ethnicity and are reflective of the diversity of the population.

Even though people with pre-existing comorbidities are at higher risk for developing severe COVID-19, it was important to enroll participants with key risk factors. Approximately 41% of those enrolled had at least one comorbidity. The most common comorbidities across the global population with at least 2% in either group include obesity, hypertension, Type 2 diabetes, and serious heart conditions. Participants who were the most vulnerable for developing COVID-19-related symptoms were well-represented in the study overall. Looking specifically at the US subgroups, the percentages are similar to the overall trial population and are distributed between the vaccine and placebo groups.

Study COV3001 met both of its co-primary endpoints, accruing 464 primary endpoint cases between September 2020 and January 2021. The co-primary endpoint analysis includes all PCR-positive cases that were confirmed at a central laboratory. The vaccine efficacy against Moderate and Severe/Critical COVID-19 is approximately 67% (59.0, 73.4) after Day 14 and 66% (55.0, 74.8) after Day 28. The lower limit of the 95% confidence interval was well above the

FDA requirement of 30%. Over 99% of accrued cases met Moderate to Severe/Critical case definitions. Therefore, the primary endpoint is representative of nearly all symptomatic COVID-19 cases. Looking at the co-primary endpoints in the US, vaccine efficacy against moderate to severe COVID-19 is 74% (65.0, 81.6) after Day 14 and 72% (58.2, 81.7) after Day 28. The cumulative incidence curves between Moderate to Severe/Critical COVID-19 begin to separate between the Ad26.COV.S vaccine and placebo groups around 14 days after vaccination. This is suggestive of the timing of onset of protection.

Because of the rapid accumulation of cases due to high COVID-19 incidence during the conduct of the study and the time it took for central laboratory confirmation of global PCR tests, not all cases could be confirmed by the central laboratory at the time of the primary analysis. Therefore, there are two datasets. The first one consists of PCR positive COVID-19 cases confirmed by the central laboratory and is used in the co-primary and secondary efficacy analyses. However, Janssen anticipated that subgroup analyses would require a larger dataset to draw conclusions and wanted to look at all confirmed COVID-19 cases that required hospitalizations or led to deaths. Thus, they prespecified that a second dataset could be used that included all COVID-19 cases with a positive PCR of any FDA-approved test regardless of central confirmation. To justify the use of the second dataset, agreement of the positive PCR results were assessed from the central laboratory versus all other sources. These datasets were found to have high concordance. Consistency between these datasets with regard to vaccine efficacy also was assessed, which showed that there was less than a 1% difference between them for the co-primary endpoint criteria. This is true for both timepoints and therefore justified the use of the larger dataset.

There were several secondary endpoints in the study. In the interest of time, Dr. Douguilh focused only on the following key secondary endpoints during this presentation:

- Vaccine efficacy against severe/critical COVID-19
- Vaccine impact on hospitalization and prevention of death
- Vaccine impact on asymptomatic/undetected COVID-19

Overall, vaccine efficacy against confirmed Severe/Critical COVID-19 occurring after Day 14 was high at approximately 77% (54.6, 89.1) and increased to about 85% (54.2, 96.9) after Day 28. There were 14 versus 60 cases of Severe/Critical COVID-19 occurring after Day 14 in the Ad26.COV2.S vaccine group versus the placebo group, respectively. There were 5 versus 34 cases occurring after Day 28 in the Ad26.COV2.S vaccine group versus the placebo group, respectively. Looking at the Kaplan–Meier curves for confirmed Severe/Critical COVID-19 cases, vaccine efficacy starts at Day 7 or earlier indicating early onset of protection. Protection continues to increase over time, which points to the potential for longevity. After Day 48, there were no more cases in the vaccine group versus 13 in the placebo group. Looking through Day 56, an estimated increase in vaccine efficacy is seen to approximately 92% with no indication of waning thereafter. The point-wise confidence interval reflects the uncertainty around this estimate, which increases beyond the median follow-up at 58 days due to the small number of participants at those timepoints.

The data also demonstrate substantial effect of the prevention of COVID-19-related hospitalizations, with 93% vaccine efficacy for all PCR-positive cases from any source after Day 14 post-vaccination. The protective effect is even more pronounced after Day 28 with 100% vaccine efficacy. There were 19 deaths in the study overall, 3 in the Ad26.COV2.S vaccine group and 16 in the placebo group. Of the deaths in the placebo group, 5 were confirmed to be COVID-19-associated and were reported prior to the January 22, 2021 cutoff. None of the

deaths in the vaccine group were COVID-19-related. A 6th COVID-19 death occurred in a participant in the placebo group who had a positive SARS-CoV-2 PCR test at baseline. Based on the study protocol, this participant was not included in the COVID-19-related death count or efficacy analyses. The deaths after the primary analysis were assessed, with 6 more deaths identified between the initial cutoff date and February 5, 2021. Of these, 2 were in the vaccine group and 4 were in the placebo group. One of the deaths in the placebo group was confirmed to be COVID-19-associated as compared to none in the vaccine group. All COVID-19-associated deaths occurred in South Africa.

The effect of Ad26.COV2.S vaccine also was evaluated against asymptomatic, undetected SARS-CoV-2 infection to gain insight into the potential benefits of vaccination on transmission. Based on SARS-CoV-2 and IgG testing alone, 18 participants seroconverted in the Ad26.COV2.S vaccine group compared to 50 in the placebo group, resulting in vaccine efficacy of 66% (39.9, 81.1). A sensitivity analysis was performed to remove all participants with a positive serology result at Day 71 who had symptoms between Day 29 and Day 71. Seroconversion occurred in 10 of the Ad26.COV2.S vaccine group and 37 occurred in the placebo group. These findings are preliminary and while a formal analysis will occur once all participants reach 6 months post-vaccination, these data do suggest a protective effect of the vaccine on asymptomatic SARS-CoV-2 infection.

Dr. Douoguih next shared additional analyses among pre-specified subgroups and by countries with emerging variants. Vaccine efficacy against moderate to severe/critical COVID-19 is consistently observed across all pre-specified subgroups by age (18 to 59 years and ≥ 60 years), comorbidity, sex, and the largest racial and ethnic groups. A lower vaccine efficacy point estimate with wide confidence intervals was observed for the sub-group of participants ≥ 60 years of age with comorbidities compared with the overall population. However, the assessment is aligned with that of the FDA that there is an observed trend of increasing efficacy with narrower confidence intervals as numbers of cases in the analysis increased. Therefore, Janssen also aligned with the FDA that those ≥ 60 years of age are similar to any other subgroup and would benefit from vaccination with Ad26.COV2.S. Across 3 key countries, vaccine efficacy against moderate to severe/critical COVID-19 was consistently high. The majority of participants were enrolled in the US, Brazil, and South Africa. These also were the countries that contributed the most COVID-19 cases in the study. Ad26.COV2.S vaccine consistently protected against moderate to severe/critical COVID-19. Vaccine efficacy after Day 28 ranged from 64% (41.2, 78.7) to 72% (58.2, 81.7) across the 3 countries.

Vaccine efficacy against severe COVID-19 was consistently high across these countries as well. For example, South Africa had 82% (46.2, 95.4) protection after Day 28. It is important to note that 95% of the sequenced samples in South Africa were associated with the new highly transmissible variant from the B.1.351 lineage. Upon further investigation of cases in South Africa, no hospitalizations occurred in the Ad26.COV2.S vaccine group and there were 6 hospitalizations in the placebo group. There were no deaths in the Ad26.COV2.S vaccine group and 5 in the placebo group. These findings strongly suggest that Ad26.COV2.S vaccine is efficacious against this newly emerging and rapidly spreading strain.

To summarize efficacy, a single dose of Ad26.COV2.S vaccine offers substantial protection against COVID-19, including against hospitalizations and deaths. Across all countries, Study COV3001 generated high-quality and robust data at a time when the incidence of SARS-CoV-2 was increasing, and new highly transmissible variants were emerging. Janssen's vaccine demonstrated 85% efficacy against severe disease, with an early onset of protection as early as 7 days after vaccination. Importantly for the primary analysis, there were no COVID-19 related

hospitalizations in the vaccine group versus 16 in the placebo group. There were no COVID-19 related deaths in the vaccine group compared to 5 in the placebo group. Protection against moderate to severe disease was 66% across all countries, with an onset of efficacy evident as early as 14 days that increased through Day 56, especially against severe disease. In the US where study participants reflected the diversity of the overall US population, vaccine efficacy against moderate to severe COVID-19 was 72%. Protection against all symptomatic disease was consistent with the primary endpoint. High levels of protection were consistent across subgroups, countries, regions, and particular areas with high incidence of circulating variants.

Turning to the safety results, a single dose of Ad26.COV2.S vaccine is demonstrated to have an acceptable safety and reactogenicity profile. The results were consistent with the tolerability and safety of Janssen's other adenovirus-based vaccines. Severe adverse events (SAEs), medically attended adverse events (MAAEs), AEs leading to discontinuation, and deaths were collected on the 43,783 participants who make up the FAS. In addition, a safety subset was enrolled that collected solicited and unsolicited AEs in 6736 participants. The primary analysis was conducted after the FDA guideline was met for reaching a median follow-up of at least 2 months. The median follow-up after vaccination was 58 days. More than half of the participants in the full analysis had at least 2 months of follow-up. In the safety subset, nearly all of the participants (99.9%) completed the 28-day post-vaccination period.

The solicited AEs collected in the 7-day post-vaccination period were transient and more than 99% were Grade 1 or 2 in severity, and all resolved within 2 to 3 days after injection. The most frequently reported AE was injection site pain. The frequency of Grade 3 AEs was very low overall, with a higher incidence in the Ad26.COV2.S vaccine group compared to placebo. For participants in the Ad26.COV2.S group, the most frequently reported Grade 3 event was injection site pain at 0.4%. There were no Grade 4 events reported. In the Ad26.COV2.S group, the frequency of solicited local AEs was similar between those who were seropositive for SARS-CoV-2 at baseline versus those who were seronegative at baseline. The solicited systemic AEs were higher in the Ad26.COV2.S group versus placebo and most were transient and had a median duration of 1 to 2 days post-vaccination. The most frequently reported systemic symptoms in the Ad26.COV2.S group were fatigue, headache, and myalgia. Of the solicited AEs, 90% were Grade 1 or Grade 2 in severity. Grade 3 events were infrequent and were reported in about 2% of participants in the Ad26.COV2.S group. No Grade 4 events were reported for this category. Fever was reported in 9% of participants in the Ad26.COV2.S group, with 0.3% being Grade 3 among those 18 to 59 years of age and 0.1% in those ≥ 60 years of age. All fevers were reported to have started on the day of vaccination or the day after and had a median duration of 1 day. The reactogenicity profile overall was milder in the older age group compared to the younger age group.

In the safety subset at 28 days after vaccination, there were similar rates of unsolicited AEs between the Ad26.COV2.S and placebo groups. Rates also were balanced in the FAS for MAAEs, any SAE, any SAE due to non-COVID-related AEs, or any deaths. SAEs, MAAEs, and deaths were numerically higher in the placebo group. The imbalance between the Ad26.COV2.S and placebo group was driven mostly by the number of AEs associated with SARS-CoV2 infection. None of the deaths in the Ad26.COV2.S or placebo group were considered causally related to the vaccine. Janssen analyzed the occurrence of various AEs of interest identified by regulatory agencies and medical and scientific organizations, such as the Brighton Collaboration. These events include those where there is a numeric imbalance with the numbers higher in the Ad26.COV2.S group, including hypersensitivity and venous thromboembolic events. For the other events (convulsions, tinnitus, peripheral neuropathy, GBS and Bell's Palsy) no causal relation with the Janssen COVID-19 vaccine could be determined.

The assessment of causality was confounded by the presence of underlying medical conditions frequently present in individuals with these AEs of interest. All of these events are going to be included in further monitoring as part of Janssen's comprehensive pharmacovigilance plan.

Hypersensitivity events were reported in 77 (0.4%) vaccinated individuals and 65 (0.3%) individuals who received placebo. Some participants reported more than one sign or symptom. Non-serious dermatologic manifestations, particularly rash and urticaria, were the most common hypersensitivity AEs reported. Rash and urticaria, localized and more rarely generalized, were considered likely related to vaccination events reported as related by the investigator. The meantime to onset after vaccination was about 6 days and the mean resolution was approximately 13 days. The vast majority of these events were Grade 1 or 2. There were 2 SAEs in the Ad26.COVID.S group and 1 of the placebo groups. One case of hypersensitivity was reported as an SAE in a vaccine recipient, with urticaria beginning 2 days following vaccination and angioedema of the lips, but no respiratory distress. This began 4 days after vaccination. The event was likely related to the vaccine. Another SAE of angioedema that occurred 23 days after vaccination in someone who was on enalapril was considered unrelated by the investigator. Both participants recovered without sequelae. The results are similar to what has been observed with the Ad26 vaccines.

As of February 22, 2021, there have been no cases of anaphylaxis meeting the Brighton Collaboration criteria in the clinical program. However, Janssen received preliminary reports earlier in the week of 2 cases of severe allergic reaction. One of these was anaphylaxis from an open label collaborative study that Janssen has ongoing in South Africa in which approximately 70,000 healthcare workers have been enrolled. Janssen will continue to closely monitor for these events, which is outlined more specifically in the company's pharmacovigilance plan. Both arterial and venous thrombotic and thromboembolic events were similar across the Ad26.COVID.S placebo groups. An imbalance was seen for the venous thromboembolic events. Most of these participants had relevant underlying medical conditions and predisposing factors that may have contributed to these events, such as COVID-19 infection, prior history of deep vein thrombosis (DVT), new estrogen use, family history of DVT, prolonged air travel, or stopping anticoagulants. There is insufficient evidence to determine a causal relationship between these events and the Janssen COVID-19 vaccine. These events are included for further monitoring in the pharmacovigilance plan.

The safety data from the 43,783 participants in the Phase 3 study demonstrate that a single dose of Ad26.COVID.S has an acceptable safety and reactogenicity profile. Overall, reactogenicity to Ad26.COVID.S was demonstrated to be mild and transient in nature. Grade 3 events were rare. Most AEs were mild or moderate and generally resolved within 1 to 2 days post-vaccination. AEs of interest were thoroughly evaluated and Janssen will continue to monitor for these events in its comprehensive pharmacovigilance program. The safety profile is further supported by data for more than 193,000 individuals who have received at least one dose of Janssen's Ad26-based vaccines in its other clinical studies and programs.

In summary, the known and potential benefits of Ad26.COVID.S outweigh the known and potential risks. Ad26.COVID.S offers substantial protection, especially against severe COVID-19, including hospitalizations and deaths irrespective of variants. Efficacy is consistent across age, comorbidities, race, and ethnic subgroups. For safety, Janssen has shown that a single dose of Ad26.COVID.S has an acceptable safety and reactogenicity profile. Results were very much consistent with the tolerability and safety of Janssen's adenovirus-based vaccines in the platform. Plans are in place for continued safety monitoring following EUA. Now that the authorization has been received, Janssen will amend the COV3001 study protocol to facilitate

crossover of participants who have received placebo to receive 1 dose of the vaccine. This will be done as fast as operationally possible. Importantly, the vaccine is compatible within the existing distribution channels. It can be stored for 3 months at normal refrigerator temperatures and has a 2-year shelf life in regular freezers. The Janssen vaccine was specifically studied with a 1-dose regimen, which will greatly increase vaccination capacity and the ability to cover the population more quickly.

Discussion Points

Dr. Romero observed that American Indian/Alaskan Native (AI/AN) populations were not listed on Slide 39 although they comprise 10% of the total population, and asked what the VE and protection against hospitalizations and deaths were for AI/AN compared with the other groups.

Dr. Douoguih clarified that only 1% of the 10% total population overall was coming out of the US. She called upon Dr. Vandebosch from Janssen to comment on the specifics for that particular subgroup.

Dr. Vandebosch indicated that the numbers were small in that particular subgroup. As of 14 days, they observed 21 versus 41 cases corresponding to an efficacy of 49%. As of 28 days, they observed an efficacy of 32% corresponding to 18 cases in the vaccine group and 26 cases in the placebo group. As pointed out, the number of cases was relatively small with relatively widespread confidence intervals. Given that the numbers were small, they did not calculate severe disease or deaths in that population, but hospitalizations and deaths were not observed in that subgroup.

Dr. Romero asked whether the lower VE attributed to this group be related to the circulating variant in the countries from which these groups were recruited.

Dr. Douoguih said she did not think they had sufficient information to answer that question at this time. The populations coming from Latin America were spread across a number of countries. It is difficult to say, but they will continue to look at this as more cases are accumulated to determine whether in the future there will be more robust data to be able to address that question.

Ms. Bahta asked whether there is any information about participants who may have had a prior infection and their systemic or local reactions.

Dr. Douoguih indicated that they have assessed this and found that approximately 9% of the study population were seropositive at baseline and about 0.5% were PCR-positive. There was only 1 moderate case of COVID-19 in a US participant who was positive at baseline. There is really not enough information to be able to comment or draw any conclusions. While they did not have any information on systemic or local reactions for that particular participant, they did look at reactogenicity based on serostatus and found that local and systemic reactogenicity are very comparable.

Dr. Lee expressed interest in the differential timing of the separation of the curves for moderate to severe disease or just severe disease shown on Slide 29 where separation begins at Day 14 and on Slide 33 that separates at Day 7. That implied to her a moderate or perhaps good enough immune response that is sufficient against severe or critical disease, but perhaps a more robust response is needed against any symptomatic disease or moderate to severe/critical

disease. She requested further information about the differences in the two curves and whether that can be related to any correlates of immunity among the participants.

Dr. Douoguih said that they have not yet identified a correlate, but they will begin to conduct that work that certainly will help to clarify some of these important questions. It is known that traditionally, it is often easier to prevent severe disease than more mild disease in terms of prevention of infection. It is not surprising that the separation of the curve for severe disease is occurring earlier. This is also reflected in the higher VE observed compared to the moderate and severe when combined. It maybe be that more is needed to prevent milder infections. The case definition was quite broad and seems to encompass the whole spectrum, including milder cases. That may be in part why the difference is being seen.

Following up on Ms. Bahta's comment about history of infection and having information specifically on reactogenicity, Dr. Lee agreed that it would be helpful in the future to break that out in order to counsel patients accordingly if there are meaningful differences. She asked specifically whether Janssen saw lymphadenopathy as a systemic AE.

Dr. Douoguih reiterated that there was no difference in reactogenicity. They have had discussions with the WG about looking at that when they do the crossover, because there might be more people who had COVID who would get vaccinated later on. They will try to continue to capture that—hopefully in large numbers. Janssen has been evaluating 26 vaccine candidates for quite some time and lymphadenopathy has not been a prominent feature. After several years and multiple studies, they looked at the solicited AE profile traditionally thought to be associated with Ad26 and did not include lymphadenopathy because it was not seen. They had a broader set of terms, but narrowed them down based on what was specific to the viral vector. That did not include lymphadenopathy.

Dr. Poehling asked about the experience with this vaccine and adenovirus vector in terms of pregnancy. She also noted that there appeared to be about 1500 people enrolled with cancer, HIV, or immunocompromising conditions and wondered whether any data were available on those participants in terms of safety and effectiveness.

Dr. Douoguih pointed out that relatively few women became pregnant after receiving the vaccine. There were a total of 8 in this case, making it difficult to draw any conclusions. No safety issues were identified post-vaccination in terms of the reactogenicity. There have been some spontaneous and elective abortions. Only 2 continue to be pregnant, for which the outcomes will be monitored. In terms of the platform, more data are coming out of the Ebola vaccine program in addition to the standard monitoring that Janssen does for all of its studies in terms of capturing pregnancies. Approximately 1600 people were vaccinated who then became pregnant or were pregnant at the time of enrollment. They have a few studies in which they are enrolling women of all trimesters in the Democratic Republic of the Congo (DRC) and in Rwanda on the border of the DRC where there was increased risk of Ebola. Those activities started in 2020. About 1500 of the women came out of those activities. Janssen is monitoring for the outcomes. Among about 900, no safety signals have been seen to date and the birth and other important outcomes seem to be in line with the background rates at the moment. From a reactogenicity point of view, nothing has stood out based on the numbers enrolled to date. An analysis has not been performed on subgroups for safety yet, though this is the plan. There are very few cases in the HIV-positive group to date, so conclusions cannot be drawn at this time. For immunocompromised patients, overall there were 2 cases. They were encouraged by the fact that there was quite a range of subjects who participated in the trial, but the data have not yet been analyzed.

Dr. Bernstein asked what the thinking was behind choosing initially to study 1 dose rather than a 2-dose series like other vaccines.

Dr. Douoguih indicated that choosing to study 1 dose was influenced to some extent by their experience with the Ebola outbreaks many years ago. For an outbreak setting, a single dose obviously has tremendous advantage in terms of being able to rapidly roll mass vaccination, not having the complexity of follow-up, and having the ability to optimize the numbers of doses administered. While that was one of the main reasons Janssen wanted to evaluate the single dose, it also was influenced by extremely strong clinical data showing full protection after a single dose. Once they saw that, it became clear that it was a viable option. They always intended to implement a 2-dose schedule as well because based on their experience, they know that 2 doses can be more immunogenic and could lead to more durable efficacy. With a 2-month interval, that also means the results would be later. Both strategies can be utilized, but they still believe that the single dose is optimal for a pandemic setting. Should the data support SARS-CoV-2 vaccine becoming part of the routine immunization schedule in the future, it could be that a primary series for certain age groups or populations could be a 2-dose series. Janssen also is looking at boosting intervals out of their Phase 1/2a study.

Dr. Bernstein wondered why healthy adults ≥ 18 to 55 years of age and healthy adults ≥ 65 years of age and older were chosen for the early phase studies (COV1001, COV1002, and COV2001) and why there was a gap. He also noted that the multi-dose vials have 3.1ml and wondered whether Janssen anticipates that this will result in 5 or 6 doses per vial.

Dr. Douoguih indicated that the age range is typically 18 to 45 years or 18 to 50 years, but they were hoping to expand to the broadest age group possible. There were concerns about starting to evaluate the elderly initially, so they had to generate some preliminary data in the earlier age group before they could go into the older age group. In early discussions with the FDA, they asked if they could expand the age range in case there were challenges or issues with the older age group. The gap was closed in Phase 3 where all of the age ranges were included. In terms of the 3.1ml vials, the current plan is to have 5 extractable doses per vial. It would be of interest to get more out of it if possible.

Dr. Sanchez observed that one criterion in the case definition was abnormal oxygen saturation of $>93\%$ on room air, which he found confusing. For instance, would someone with a positive PCR and an oxygen saturation of 95% be considered a moderate or severe case? He also asked what the efficacy is when the mild cases are included, whether any studies have been conducted in pregnant animals and women, whether the spike protein crosses into the fetal compartment, if coadministration with other vaccines was excluded in the studies, and whether the Janssen vaccine is produced with fetal cells from aborted fetuses.

Dr. Douoguih indicated that because the FDA definition for severe/critical oxygen saturation is 93% , they wanted to make sure that those were not overlapping definition. A person with a positive PCR and oxygen saturation of 95% would not meet the case definition, but they may have other symptoms or criteria that would make them a moderate case. In terms of efficacy when the mild cases are included, only 4 cases in total were categorized as mild. Essentially, there is no difference in efficacy. Regarding pregnant women, they have conducted a reproductive toxicity study in which they have observed no AEs that would preclude evaluation in humans. There is transplacental transfer of antibody from the mom to the fetus. In terms of the case definition and whether the spike protein crosses into the fetal compartment, Dr. Douoguih called upon Drs. Sadoff and Schuitemaker to add their thoughts.

Dr. Sadoff added that they took the moderate definition word-for-word from the FDA guidance to industry, which has the peculiar wording >93. That translates into 94 being the only one that would count for moderate, because the abnormal is <95.

Dr. Schuitemaker indicated that they have not studied whether the spike protein crosses into the fetal compartment in detail. It is important to understand that the spike protein in the infection context is membrane-bound. They have tried to reduce circulation of soluble protein, but they have not studied transplacental migration of even fragments of the protein at this point.

In terms of coadministration, Dr. Douoguih indicated that the Janssen studies required spacing. The minimum was 2 weeks for inactivated vaccine and 1 month for live replicating vaccines. Coadministration studies are planned with influenza vaccine and others, but these studies have not yet begun. The Janssen vaccine does not contain any fetal tissue.

Ms. McNally asked what the impact would be on those who have received the 1-dose primary series if a 2-dose primary series is determined to be safe and effective and is ultimately recommended.

Dr. Douoguih indicated that they first would have to determine whether there is a difference in efficacy with the 2-dose schedule and they are evaluating boosting intervals following a single dose at 6 months, 1 year, and 2 years out. They should have some information that would help guide that decision-making when the time comes.

Dr. Kotton observed that on Slide 39 there appeared to be a pretty significant discrepancy between men and women with respect to efficacy and moderate to severe/critical COVID-19. It is almost 70% in men versus 60% in women. While the statistics showed some overlap, there is still a pretty dramatic difference. Women are generally smaller, so the vaccine dose might have been higher per body weight in theory. She asked whether Janssen had any thoughts about that.

Dr. Douoguih indicated that because of the overlapping confidence intervals, they did not view this as substantial. This could be evaluated in much larger numbers once the vaccine is rolled out.

Dr. Vandebosch added that from a statistical perspective, she agreed that the confidence intervals are largely overlapping. The point estimate is lower than the range of variability that can be expected with vaccine efficacy estimates of 66% overall. The difference that is observed can be due to variation and not necessarily a true difference. This aligns with the overall vaccine efficacy and natural variability.

It seemed to Dr. Long that there was a goodly number of subjects, pretty small numbers of cases, and smaller numbers of hospitalizations in the US. She asked whether that could be put into percentages of subjects in the placebo group who were moderately, mildly, or severely symptomatic. She was trying to understand the intensity of exposure, recognizing that participants probably were asked to mask and socially distance and that this could have contributed to the small number of cases. She was wondering about the intensity of exposure, density of exposure, the number of organisms and wondered if it was relatively small for the whole population if the placebo participants were not being exposed to a lot of cases in the pandemic and so forth to try to generalize the results.

Dr. Vandebosch responded that from what they have seen in the trials in terms of the placebo group, the overall incidence was actually quite large at 20% symptomatic COVID-19 disease. A fraction of that was severe disease depending upon the age group. Those 18 to 40 years of age had a lower incidence of severe disease that was more toward mild. The group above 60 years of age had a higher incidence of severe disease relatively speaking. In terms of the results in each of the different countries and specifically in the US, the trial was conducted at the height of the pandemic in the US. A trial incidence of 20% is seen in the US.

Dr. Fryhofer (AMA) indicated that as a general internist, the vast majority of her patients have multiple comorbidities and most are older. She greatly appreciates the fact that the Janssen study included about 40% of patients with comorbidities and that the target for those over 60 years of age was about 30%. She is reassured by Dr. Fink's comments and the reaction from the VRBPAC panel of experts about the smaller number of older patients with comorbidities leading to imprecision in the efficacy results. However, they are lower and she wondered whether there would be any attempt to get this information out more quickly about the subset of older, sicker patients in order to confirm that this vaccine does work. In terms of what occurs after the vaccine is injected into the body, she wondered how long vaccine fragments remain, where they go, how the body breaks them down, and if there is any concern that remaining fragments could cause other issues or problems.

Regarding the comorbidity question in older adults, Dr. Douoguih said they think this is artifact. Because of the small number of cases and the fact that this is a subgroup of a subgroup analysis, they were able to have some results only because there were so many cases. After Day 14 in that subgroup, efficacy is completely consistent and in line with the overall dataset. At the 28-day endpoint after vaccination in that subgroup is where much wider confidence intervals are seen, because the numbers are simply lower. In terms of biologic plausibility, it does not make sense. The immune responses do not drop that quickly in the vaccinees. In fact, it plateaus and efficacy increases with time after Day 29. There is no reason to believe that it does not work. Of course there will be more cases, but they also looked at hospitalization in this subgroup and there was 82% efficacy. This is still protecting in comparable ways to the overall dataset, so this is believed to be a question of small numbers after Day 28 and not in line with the rest of the dataset that fully supports protection that is comparable in that group. In terms of what occurs with the vaccine after injection into the body, Janssen has conducted a number of biodistribution studies in animals over the years. From the point of injection once the adeno is in the muscle cell, it drains to the regional lymph nodes and persists an average of about 3 months. The vector has been detected out to 6 months in a small number of animals. It is then subsequently cleared and no issues related to that have been observed.

Dr. Daley emphasized that everyone is concerned about the variants and efficacy of currently approved vaccines against these. It strikes him that they could make the most of the opportunity presented by the countries selected and by having sequencing data to look at the efficacy against variants. He is cautiously optimistic that the vaccine has high efficacy against hospitalization and severe disease, including against variants. He asked whether the 2-dose study is being conducted in sites with a high prevalence of variants so that there will be evidence about efficacy of the 2-dose schedule against variants.

Dr. Douoguih indicated that there is some overlap in terms of countries. They are enrolling a study in South Africa and the United Kingdom (UK) where B.1.117 has been circulating. Therefore, Janssen does expect to have some data once they begin assessing endpoints.

Dr. Kimberlin (AAP Redbook) requested additional information about the adolescent study that is to begin soon in terms of the start date, ages, and plans for de-escalating to younger ages down to infants.

Dr. Douoguih reported that they have 2 studies that will include pediatric populations that will begin soon. Subsequently, they may look at immunocompromised children. The COV2001 study had a different purposes but was amended because it was open in multiple countries and there was an interest expressed in adolescents. If all goes as planned, that should begin screening and enrollment would start during the second week of March. The age group is 12 to 17 years of age. The aim is to acquire data as quickly as possible on the 16 to 17 year olds such that those data potentially could be submitted for review and incorporated as part of an EUA. They will then go to the 12 to 15 year olds. Janssen estimates that approximately 660 participants will be recruited into that study. Another study comprises the whole age range of pediatrics, so there will be an age de-escalation beginning with adolescents and moving down into younger age groups. They will assess different dose levels depending on the results coming out of that study. The total data package intended for the pediatric population is anticipated to have roughly 3000 participants. The plan is for the de-escalation study to begin at the end of March or early April. They have been assessing feasibility and are almost ready to begin.

Dr. Shaw (ASTHO) noted that the FDA EUA recommends that providers follow the US CDC's guidelines on post-vaccination observation, but in the clinical trials there were no anaphylactic events and there are only 2 events pending further investigation. Among the numerous benefits of this vaccine from an operational perspective would be the potential to forgo the observation period, given that the well-known adenovirus vector does not necessarily generate that type of anaphylaxis. He asked whether any hints of anaphylaxis have been noted other than the 2 events in South Africa and if further details could be provided about those 2 events that might help state officials as they navigate the advisability of the observation period. This is important because this vaccine opens up the potential for true drive-through vaccination at the state and local levels.

Dr. Douoguih indicated that for a while, they monitored for a 60-minute period and did not see immediate reactions. In this program, the other studies, and for the safety run-in phase, people were monitored for 30 minutes. Based on seeing no immediate reactions, that was reduced to 15 minutes. In terms of the 2 cases under investigation, the 1 case that met the Brighton Collaboration criteria occurred in a 39-year old woman who developed fever, swollen tongue, and difficulty breathing a few hours after vaccination. She had hives on her limbs and upper trunk, so she was admitted to the hospital. She was treated with hydrocortisone and Phenergan. Dr. Douoguih heard that the woman is stable, but did not know if she had been discharged. The other individual did not meet the Brighton Collaboration criteria. This participant was 41 years of age. She developed fever, chills, and other systemic symptoms that were accompanied by a drop in blood pressure approximately 10 minutes after vaccination. This was deemed medically important.

Dr. Duchin (NACCHO) requested that the CDC subject matter experts (SMEs) weigh in on the recommended observation period in general and for this vaccine. In terms of Slide 34 regarding efficacy against severe/critical COVID-19 over time, he wondered why this analysis was performed with only the centrally confirmed COVID cases and whether Janssen has a similar analysis for hospitalization.

Dr. Douoguih indicated that in the interest of time, they did not show all of the analyses. In terms of hospitalizations, she called upon Dr. Vandebosch to comment on what has been explored.

Dr. Vandebosch indicated that in terms of hospitalizations, there were too few cases to assess and the imprecision gets larger. For the severe disease endpoints, the centrally confirmed cases were used to present the data. However, they also have explored the same analysis using non-centrally confirmed cases.

Dr. Fryhofer (AMA) noted in the summary provided by the FDA that one of the vaccine ingredients is polysorbate. For the mRNA vaccines, the CDC has listed handling patients with an allergy to polysorbate differently. She asked whether Janssen has thought about polysorbate as possibly being a reason for some of the skin issues and other allergic reactions that have been seen with this vaccine, and whether any of the cases with an allergic reaction were allergic to polyethylene glycol. The materials on the CDC website indicate that there could be a cross-reaction with polyethylene glycol and polysorbate.

Dr. Douoguih said it is difficult to say because they have not really seen a pattern per se. Polysorbate 80 is commonly used in vaccines and foods. At this time, Janssen is not associating a link with that ingredient. It is not clear that participants would know if they have allergies to polyethylene glycol and/or polysorbate. This is an important question that Janssen will continue to monitor.

GRADE: Janssen COVID-19 Vaccine

Julia Gargano, PhD, MS

Epidemiologist

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Dr. Gargano presented the GRADE assessment for the Janssen COVID-19 vaccine. The policy question under consideration is, “Should vaccination with Janssen COVID-19 vaccine be recommended for persons 18 years of age and older during an emergency use authorization?” In terms of the PICO (Population, Intervention, Comparison, Outcomes) question, the population under consideration is persons aged ≥ 18 years. The intervention is a single-dose of the Janssen COVID-19 vaccine Ad26.COV2.S at 5×10^{10} viral particles administered as a single-dose intramuscularly (IM). The comparison is no COVID-19 vaccine. The WG identified the following seven outcomes as the most important for the policy question:

- Symptomatic laboratory-confirmed COVID-19
- Hospitalization due to COVID-19
- All-cause death
- SARS-CoV-2 seroconversion to a non-spike protein
- Asymptomatic SARS-CoV-2 infection
- Serious Adverse Events (SAEs)
- Reactogenicity

The potential benefits included prevention of symptomatic COVID-19 and hospitalization due to COVID-19, which were both considered critical outcomes. All-cause death, SARS-CoV-2 seroconversion, and asymptomatic infection were identified as important. The potential harm of SAE was identified as a critical outcome, while reactogenicity of Grade 3 or 4 was identified as an important outcome. Hospitalization due to COVID-19 and deaths are less common and take additional time to occur and be documented after disease onset. The Phase 3 trials may not be designed or powered to evaluate the differences between treatment groups, especially at the 2-

month time point. For the outcome of seroconversion, preliminary data using antibodies to non-spike protein among asymptomatic persons are available and have been included in the evidence profile. No serial PCRs were available to assess asymptomatic infection, so this measure was not included in GRADE evidence profile.

A systematic review was conducted to identify evidence related to the policy question and additional unpublished data were sought from the trial sponsor. Published articles were identified using various databases (Medline, Embase, and Cochrane Library, written in English, restricted to 2020) and search terms (coronavirus, COVID-19, SARS-CoV-2, respiratory (symptom, disease, illness, condition), vaccine, immunization, trial, double blind, single blind, placebo, comparative study, phase 3, immunogenicity, efficacy, effective, adverse, evidence, and variations on these terms) to identify data on vaccination with the specific vaccine formulation under considerations that: 1) involved human subjects; 2) reported primary data; 3) included adults ages 18 and older at risk for SARS-CoV-2 infection; 4) included data relevant to the efficacy and safety outcomes being measured; and 5) included data on the dosage under consideration (5×10^{10} viral particles, single-dose IM). Additional resources were sought, including unpublished data from vaccine manufacturers. Nearly 4000 records were identified through database searching. There was 1 published article, 2 records were obtained directly from the sponsor, and 3 studies were included in the evidence synthesis. Additional information on the identified studies was included from FDA materials prepared for the VRBPAC.

GRADE evidence types, which assess the certainty of estimates from the available data, are shown here:

GRADE Evidence Type

- **Type 1 (high certainty):** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Type 2 (moderate certainty):** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Type 3 (low certainty):** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Type 4 (very low certainty):** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

NOTE: Evidence type is not measuring the quality of individual studies, but how much certainty we have in the estimates of effect across each outcome.

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Initial evidence type is determined by the study design. A body of evidence from a randomized controlled trial (RCT) starts with an initial evidence Type 1 indicating high certainty. A body of evidence from observational studies starts with an evidence Type 3 indicating low certainty. The evidence type can be downgraded due to risk of bias, inconsistency, indirectness, or imprecision. It is possible for other considerations (e.g., publication bias or indications of dose-

response gradient, large or very large magnitude of effect, and opposing residual confounding) to downgrade or upgrade the evidence type.¹

To review the evidence for benefits, 1 study provided data for the critical outcome of symptomatic COVID-19. This was the Janssen Phase 3 RCT. The data were obtained directly from the sponsor. The trial included persons 18 years of age and older in the United States, Argentina, Brazil, Chile, Colombia, Peru, and South Africa. The final scheduled analysis was based on data approved through January 22, 2021. The data from events recorded later have been incorporated into this analysis. A total of 44,325 adults were randomized to 1:1 to receive either vaccine or saline placebo. The numbers of persons available for analysis in the full analysis set (21,895 vaccine; 21,888 placebo) were used to assess SAEs, the per-protocol set (19,630 vaccine; 19,691 placebo) was used for most efficacy analyses, and the solicited safety subset (3,356 vaccine; 3,380 placebo) was used to assess reactogenicity.

In the Phase 3 trial, specimens from suspect COVID-19 cases had respiratory tract samples tested locally using any FDA-approved PCR assay. The protocol specified that all positive specimens would be sent to a central study laboratory at the University of Washington for molecular confirmation. This confirmation was specified to be used for primary endpoints. At the time of the interim analysis, not all local PCR tests had been tested at the central laboratory and of those tested, most were confirmed. The sponsor reported analyses using any PCR positive and centrally confirmed PCR.

The clinical trial enrollment was staggered by age group and presence of comorbidities. Those 18 to 59 years of age and those 60 years of age and older were recruited and randomized separately. In each age group, the protocol specifies that 2000 without comorbidities would be enrolled first as a safety run-in. The plan was for safety data to be reviewed by the Data Safety and Monitoring Board (DSMB) before persons with comorbidities in each age group were enrolled. The staggered enrollment resulted in variations in the median follow-up time by subgroup as follows:

- ≥60 year-olds with comorbidities: 50 days
- ≥60 year-olds without comorbidities: 54 days
- 18-59 year-olds with comorbidities: 57 days
- 18-59 year-olds without comorbidities: 64 days

For the outcome of symptomatic laboratory-confirmed COVID-19, the trial's primary outcome called "moderate to severe/critical COVID-19" was used. This was defined as persons with a positive PCR who fulfilled the system criteria listed here:

≥1 of: respiratory rate ≥ 20 breaths/min, abnormal SpO₂, pneumonia, DVT, shortness of breath/difficulty breathing

OR

≥2 of: Fever (38°C), Heart rate ≥90, shaking chills, sore throat, cough, malaise, headache, myalgia, GI symptoms (nausea, vomiting, diarrhea, abdominal pain), olfactory/taste disorder, red/bruised toes

¹ Guyatt GH, Oxman AD, Kunz R et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *J Clin Epidemiol.* 2011. DOI:10.1016/j.jclinepi.2011.04.014.

The sponsor looked at 2 different time points for their primary and co-primary outcomes of at least 14 days after vaccination and at least 28 days after vaccination. Despite the label, this case definition encompassed most systematic COVID-19 cases and mapped well to the intended outcome for GRADE. There are 4 different versions of analyses available using case ascertainment at least 14 and at least 28 days post-vaccination and using only cases that were confirmed as PCR-positive at the central laboratory or those PCR-positive from any source. The numbers of cases counted at Day 14 post-vaccination were 464 PCR-positive at the central laboratory and 682 PCR-positive from any source. At Day 28 post-vaccination, the numbers of cases counted were 259 PCR-positive at the central laboratory and 437 PCR-positive from any source. As noted earlier, confirmation of the central laboratory was incomplete at the time of the analysis. Of the samples that have been tested at the central laboratory, 90% were confirmed. Case numbers were limited at 28 days post-vaccination, especially in subgroups with shorter follow-up time. To increase the data robustness and interpretability, 14 or more days post-vaccination and any PCR-confirmed cases were selected as the outcomes to examine and evaluate for GRADE.

In terms of the efficacy estimates against symptomatic laboratory-confirmed COVID-19, using the per-protocol population for all persons at least 18 years of age, there were 173 cases among 19,514 persons in the vaccine arm and 509 cases among 19,544 persons in the placebo arm. This resulted in a vaccine efficacy estimate of 66.3% and a 95% confidence interval of 59.9% to 71.8%. The efficacy estimate was 64.7% (57.6, 70.8) for 18 to 64 year olds, 76.5% (59.1, 87.3) for 65 and older, and 89.7% (26.0, 99.8) for 75 and older. The efficacy estimate for persons with one or more comorbidities was 64.2% (52.7, 73.1). The trial is conducted in several countries. Efficacy varied geographically from a low of 52% (30%, 67%) in South Africa to a high of 74% (65%, 82%) in the US. Sequencing data on a subset of cases from South Africa, Brazil, and the US suggested that the variability in efficacy of estimates may have been related to the variants circulating in each region.

Regarding the comparison of the 4 different analyses mentioned earlier by 2 different co-primary timepoints and whether the case was confirmed in any laboratory or by the central laboratory only, the variations in case definition all yielded similar efficacy estimates ranging from 66.1% (55.0, 74.8) to 66.9% (59.0, 73.4). In a comparison of the primary outcome (no evidence of prior infection) with 2 secondary outcomes (persons with a prior infection and mild cases), the overall efficacy was 66.1% (59.7%, 71.6%) when persons with evidence of prior infection were included and 65.2% (58.7%, 70.8%) when a broader list of symptoms was used to include mild COVID-19. Note that this broader case definition including milder cases only added 15 cases overall, again indicating that the moderate to severe COVID-19 case definition captured most symptomatic cases.

In terms of the GRADE evidence table for the outcome of symptomatic COVID-19, the evidence started at Type 1 because the data were from an RCT. Regarding risk of bias, there was some concern related to blinding. Participants and study staff were blinded to assignment, but some could have received a vaccine or placebo based on reactogenicity symptoms. This was deemed unlikely to overestimate the advocacy result. Therefore, the risk of bias was considered not serious for this and subsequent outcomes. Some concern for indirectness to the outcome was noted due to the short duration of observation in the available body of evidence. The vaccine efficacy observed at a median 2-month follow-up may differ from the efficacy observed with ongoing follow-up. It is possible that with longer follow-up in the timeframe of an EUA, the efficacy estimate for symptomatic COVID-19 could fall below the FDA-defined efficacy threshold of 50%. Some concern also was acknowledged for indirectness to population because of exclusions from the clinical trial. This was judged to be not serious. There were no other serious

concerns affecting the certainty assessments. The WG assessed the level of certainty as Moderate or Type 2 for this critical outcome.

The second outcome for consideration was hospitalization due to COVID-19. The protocol included a definition of COVID-19 that resulted in medical intervention of at least hospitalization, which maps well to the PICO outcome. The protocol also used a definition of severe COVID-19 that included a COVID-19 case with ≥ 1 of following: clinical signs at rest indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit (ICU); and/or death. This did not require hospitalization. Regarding the efficacy against COVID-19 needing medical intervention assessed at least 14 days post-vaccination, there were 2 hospitalized cases in the vaccine arm and 29 hospitalized cases in the placebo arm for a VE estimate of 93% (71%, 98%). Counting only cases occurring at least 28 days post-vaccination, there were zero hospitalized cases among vaccinated and 16 hospitalized cases in placebo recipients. The protocol definition of severe COVID-19 is at least 14 and at least 28 days for which vaccine efficacy was 76% (58%, 88%) and 84% (54%, 97%), respectively. The analysis used in GRADE was the outcome of COVID-19 needing medical intervention with no evidence of prior infection at ≥ 14 days post-vaccination. It is important to point out that the efficacy for both of the more severe outcomes appears higher at least 28 days post-vaccination than after 14 days, and that no COVID-19 cases with onset at least 28 days after vaccination resulted in hospitalization.

In terms of the GRADE evidence table for hospitalization due to COVID-19, the initial evidence of Type 1 was downgraded 1 point due to serious concern over indirectness of outcomes because of the short duration of follow-up. The final certainty estimate for the outcome of hospitalization for COVID-19 is Type 2.

The next outcome of interest was all-cause death, with data obtained from the sponsor. A total of 5 deaths occurred from any cause in the vaccine arm and 20 deaths from any cause occurred in the placebo arm for a relative risk of 0.25 and a 95% confidence interval of 0.09 to 0.67, indicating a statistically significant protective effect. There were no deaths attributed to COVID-19 among vaccinated persons and a total of 7 among placebo recipients, including 1 in a participant who has PCR-positive for SARS-CoV-2 at baseline. Regarding the GRADE evidence table for all-cause death, there was no serious risk of bias identified and no serious concern of inconsistency. There was serious concern for indirectness due to the short duration of follow-up. There was no serious concern for imprecision. The relative risk of 0.25 (0.09 to 0.67) favored vaccination and the certainty estimate was Type 2.

For the outcome of interest of seroconversion to non-spike protein, preliminary data were available from the Phase 3 trial to evaluate this outcomes. As part of the routine trial procedures, blood was drawn on Days 1, 29, and 71 and then planned at Months 6, 12, 18, and 24. Asymptomatic seroconversion was defined as detecting N-binding antibody, an antibody to a non-spike protein, which can distinguish between natural infection and vaccine-induced immunity. For the seroconversion assessment, participants who had COVID-19 symptoms or who were PCR-positive prior to specimen collection were excluded. It was possible to look at preliminary data on seroconversion between 2 time points between Days 1 and 29 and between Days 29 and 71. The latter has far less data available, but the WG considered it a more relevant measure of vaccine efficacy.

In terms of the estimates for asymptomatic seroconversion between Days 1 and 29 when results were available for about 14,000 persons per group, there were 84 asymptomatic seroconversions among vaccinated persons and 108 asymptomatic seroconversions among placebo recipients for an efficacy estimate of 22.6% (-3.9%, 42.5%). The confidence interval did not exclude the null effect. Asymptomatic seroconversion based on the Day 71 serum collection was used as the outcome for GRADE based on about 7% of the population, or about 1300 persons in each arm who had data available at the time of this analysis. In the vaccine arm, 10 persons seroconverted between Days 29 and 71. In the placebo arm, 37 persons seroconverted during that time. The vaccine efficacy against seroconversion was estimated to be 74.2% (47.1%, 88.6%). This is the outcome used for GRADE.

For the GRADE evidence table for seroconversion based on the Day 71 blood draw, no serious risk of bias was identified and there was no serious concern for inconsistency. Certainty was downgraded 2 points for a very serious concern of indirectness. Efficacy against seroconversion based on Day 71 serology may not be a direct measure of efficacy over a relevant period of time for the EUA. Additionally, serology data were only available for a subset of about 7% of the per-protocol population. This likely does not represent all ages, comorbidities, geographies, and exposures to circulating variants and raises additional concern for indirectness. However, the relative risk of 0.26 favored vaccination and did not include harms and there was no serious concern for imprecision. The certainty estimate was Type 3.

In addition to the RCT already described, 2 additional studies provided data on the GRADE for harms. These included an unpublished Phase II RCT and a published Phase I/II RCT. The Phase II trial included 506 persons who received at least 1 dose of the Janssen vaccine among whom 276 received the relevant dose and 78 persons who received a placebo. Another Phase I/II trial included 323 persons who received 1 dose of the Janssen vaccine at the relevant dose and 163 who received placebo. In terms of the raw data on the critical outcome of SAEs excluding COVID-19-related SAEs and the Phase III trial for which data were collected on over 40,000 participants, there were 83 non-COVID-related SAEs in the vaccine arm and 96 non-COVID-related SAEs in the placebo arm. The FDA judged 3 events to be related or likely related to vaccination. From the Phase II trial, there was 1 SAE in the vaccine arm. In the Phase I/II trial, there was 1 SAE in the vaccine arm and 2 in the placebo arm. The non-fatal vaccine-related SAEs occurring in the Phase III trial that the FDA concluded were likely related to the study vaccines, the SAEs included hypersensitivity, injection site pain, and systemic reactogenicity. For the GRADE evidence table for SAEs, there was a balance of SAEs reported among vaccinated and placebo groups, with 0.4% in each arm and a pooled relative risk of 0.85 (0.63 to 1.13). The certainty assessment was reduced 1 point due to serious concern of indirectness of outcome due to the timing. The final certainty was Type 2.

Reactogenicity was evaluated using the same 3 studies. The Janssen RCTs used the solicited events for 7 days following vaccination and the GRADEing scales shown here:

- ☐ Local reactions (pain at injection site, redness, swelling):
 - Grade 3: pain at injection site that prevents daily activity or use of narcotic pain reliever; redness > 10 cm; and swelling > 10 cm.
 - Grade 4: hospitalization for severe pain at the injection site, necrosis (redness and swelling categories) or exfoliative dermatitis (redness category only).
- ☐ Systemic events (fever, nausea, headache, fatigue, muscle pain):
 - Grade 3: fever >38.9°C to 40.0°C, nausea, fatigue, headache, or muscle pain that prevents daily activity or use of narcotic pain reliever.

- **Grade 4:** fever >40.0°C, nausea, fatigue, headache, or muscle pain that require hospitalization or prevents basic self-care.

Regarding the numbers and proportions of Grade 3 events in the vaccine and placebo arms for the 3 trials, the proportion reporting any Grade 3 event range from 2.2% to 5% percent in the vaccinated group and from 0 to 0.7% in the placebo group. Pooling the data from the 3 trials, the relative risk estimated for any Grade 3 or 4 event was 3.42 with a 95% confidence interval from 2.20 to 5.31. There was no serious concern for risk of bias, inconsistency, indirectness, or imprecision. The final certainty was Type 1.

To summarize the GRADE assessment for the Janssen COVID-19 vaccine, in terms of benefits, the available data indicate that the vaccine is effective for preventing symptomatic COVID-19 with a evidence of Type 2. For hospitalization and death, the available evidence strongly favors the intervention and the evidence is also Type 2, The preliminary data from Day 71 indicated efficacy against asymptomatic seroconversion with Type 3 evidence. There were no data available to assess asymptomatic infection using routinely collected nasal swab specimens for PCR testing. In terms of harms, the available data indicate that SAEs were balanced between the vaccine and placebo arms with evidence of Type 2. There were 3 participants with SAEs use that the FDA judged to be related to the vaccine among over 21,000 vaccinated. Grade 3 reactogenicity was 3 times more common among vaccine recipients than among placebo groups. There were no Grade 4 reactions and Grade 3 reactions were uncommon. The evidence type for reactogenicity was Type 1.

In conclusion, the Phase 3 RCT of the Janssen COVID-19 vaccine was conducted on 3 continents during a time of high COVID-19 incidence while viral variants were emerging. The trial exceeded the target numbers of cases to meet its primary endpoint by the time the required median 2-month follow-up was complete. The vaccine efficacy estimates for the Janssen COVID-19 vaccine were 66% for symptomatic laboratory-confirmed COVID-19, 93% for hospitalization due to COVID-19, 75% for all-cause death, and 74% for asymptomatic seroconversion. No deaths due to COVID-19 were identified among vaccine recipients and 7 deaths due to COVID-19 were identified among placebo recipients. No serious safety concerns were identified in the RCTs, with balanced reports of SAEs between arms of 0.4% each. Grade 3 local or systemic reactions were more common among vaccine than placebo recipients and were reported by less than 3% of vaccinated subjects. The certainty and the estimates for all critical benefits and harms was Type 2 or moderate, with certainly impacted by concern for indirectness because of the short duration of follow-up in the available body of evidence.

Discussion Points

Dr. Lee observed that 14 days after 2 doses is different from 14 days after 1 dose. Therefore, it makes sense to assess the 28-day outcome after Dose 1 for the Janssen vaccine as it seems somewhat more equivalent in terms of understanding the impact. She found it extremely promising that a single dose of the Janssen vaccine can prevent hospitalizations and deaths and that it appears to offer protection against variants. Interestingly, the asymptomatic seroconversion efficacy of 74% between days 29 and 71 is almost equivalent to what was seen for symptomatic disease at 28 days. The potential to interrupt transmission, for which there is growing evidence, is the most promising information she has heard. The efficacy for all-cause death is substantial. She has been so focused on deaths directly due to COVID-19 that she had not thought as much about the other complications of COVID-19 infection that lead to all-cause death. The protective effect is remarkable, so she wondered if Dr. Gargano and/or others could comment on understanding what those deaths were as the benefit of COVID-19 vaccination

may be broader than preventing COVID-19 deaths. While it is not appropriate right now during the EUA, perhaps a future GRADE should examine “long-haul” COVID-19 as well as the outcomes and what the vaccine’s impact might be for the longer-term effects of COVID infection.

Dr. Gargano indicated that she did not have a slide that showed the causes of death for all of the all-cause deaths, but some were due to respiratory causes such as pneumonia determined not to be COVID and she can provide more details at a later time. She agreed that long-haul COVID would be very interesting to examine further, though not available at this time due to the 2-month follow-up.

Dr. Chen requested a reminder of whether there was a difference in the immunocompromised population studied with this vaccine. It seemed to him that there was a more restrictive definition for the so-called abnormal function of the immune system in this study. Perhaps there is a lack of efficacy information, and maybe even the safety information generated with these studies. This is a very important subpopulation of the target population in terms of vaccinating.

Dr. Gargano said that the wording of the inclusion criteria of who could be included in the immunocompromised population was somewhat different. The numbers available at this time are just too small to draw any conclusions about efficacy in that population.

Dr. Romero emphasized that the data for AI/AN are very weak as shown in the original presentation.

EtR Framework: Janssen COVID-19 vaccine

Sara Oliver, MD
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Co-lead, Advisory Committee for Immunization Practices COVID-19 Vaccines WG
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Dr. Oliver presented the EtR Framework for the Janssen COVID-19 vaccine. As a reminder, the EtR Framework is a structure to describe information considered in moving from evidence to ACIP vaccine recommendations. It also provides transparency around the impact of additional factors on deliberations when considering a recommendation. The policy question being addressed in this EtR was, “Should vaccination with the Janssen COVID-19 vaccine be recommended for persons 18 years of age and older under an Emergency Use Authorization.” In terms of the PICO question, the population is persons 18 years of age and older, the intervention is the Janssen COVID-19 vaccine, and the comparison is no vaccines. The outcomes are the same as detailed in the GRADE presentation. These are the domains for the EtR Framework discussed during this session:

Evidence to Recommendations (EtR) Framework

EtR Domain	Question
Public Health Problem	<ul style="list-style-type: none"> • Is the problem of public health importance?
Benefits and Harms	<ul style="list-style-type: none"> • How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects?
Values	<ul style="list-style-type: none"> • Does the target population feel the desirable effects are large relative to the undesirable effects? • Is there important variability in how patients value the outcomes?
Acceptability	<ul style="list-style-type: none"> • Is the intervention acceptable to key stakeholder?
Feasibility	<ul style="list-style-type: none"> • Is the intervention feasible to implement?
Resource Use	<ul style="list-style-type: none"> • Is the intervention a reasonable and efficient allocation of resources?
Equity	<ul style="list-style-type: none"> • What would be the impact of the intervention on health equity?

“The problem” = COVID-19 disease
“The vaccine” or “The intervention” = Janssen COVID-19 vaccine

As done before, updates will be made to make the questions applicable to the Janssen vaccine and to COVID-19 exercise.

The primary question for the *Public Health Problem* domain is, “Is COVID-19 disease of public health importance?” As of February 25th, there have been over 28 million cases. However, cases have been declining since late January and the 7-day moving average is now just over 67,000 cases per day. This is down from a peak of almost 250,000 cases per day in January. As of February 25th, there have been over 500,000 COVID-19 deaths reported to CDC, with a 7-day moving average at 2100 deaths per day. This is down from the peak of over 3300 deaths per day in late January. To summarize the available evidence², the cumulative hospitalization rate between March 2020 and February 20, 2021 was 452 per 100,000 population. Among those hospitalized, 25% required intensive care and 11% died. The cumulative mortality between January 2020 and February 25, 2021 with 153 per 100,000 population. As was highlighted in a report published recently, the life expectancy dropped nearly a full year for the US population using data from the first half of 2020. In addition, disparities were noted by race in that the life expectancy for the Black population declined by 2.7 years and 1.9 years for the Hispanic population. The emerging landscape of the SARS-CoV-2 variants definitely impacts the public health problem. This emerging landscape requires urgency with vaccinations to build population immunity. The WG’s judgment was that yes COVID-19 is of public health importance.

In addition to the overall GRADE presentation, the questions to determine *benefits and harms* are, “How substantial are the desirable anticipated effects, the undesirable anticipated effects, and do the desirable effects outweigh the undesirable effects?” A detailed review of the benefits and harms through GRADE was just presented, but Dr. Oliver walked through the highlights and some additional information. As a reminder, the outcomes GRADEed were 14 days post-vaccination. The clinical trial demonstrated efficacy against symptomatic laboratory-confirmed COVID-19 with an efficacy of 66.3%. This was determined to have moderate certainty relative to the policy question under the EUA. For hospitalization, 31 events occurred of which 29 were in the placebo group and 2 of which were in the vaccine group. Vaccine efficacy against hospitalizations with 93%. There also was moderate certainty in this estimate. For all-cause

² https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html; https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html; <https://www.cdc.gov/nchs/data/vsrr/VSRR10-508.pdf>

mortality, 5 deaths occurred in the vaccine group and 20 occurred in the placebo group for an estimate against all-cause mortality of 75%, again with moderate certainty in this evidence.

Preliminary data were available to assess vaccine efficacy against seroconversion between Days 29 and 71 based on the first 7% of specimens tested. The analysis was based on detection of the N-binding antibody among persons who remained asymptomatic and did not have a positive SARS-COV-2 PCR at any time in the study. Between 4 and 10 weeks after vaccination, 10 (0.7%) of vaccine recipients seroconverted compared to 37 (2.8%) of placebo recipients for a vaccine efficacy against asymptomatic seroconversion of 74%. While this data is encouraging, given the single time point only 10 weeks after vaccine receipt and that this is less than 10% of the study population, there was low certainty of this evidence. Similar efficacy was noted across age, sex, race, and ethnicity categories and those with underlying medical conditions 14 or more days post-vaccination. These estimates all coalesce around the overall efficacy endpoint of 66%. There was higher efficacy against severe outcomes than for any symptomatic COVID, with efficacy against COVID-19-associated deaths at 100%. Efficacy estimates for severe outcomes assessed at 28 days or more post-vaccination were even higher, with 83% for severe disease and 100% for hospitalization. Efficacy against severe illness remained high across world regions, suggesting protection against severe illness even with variant strains.

For a summary of possible harms, SAEs were reported in a similar proportion among recipients of vaccine and placebo. There was moderate certainty in this evidence. The reactogenicity outcome graded was severe for Grade 3 reactions. Overall, a Grade 3 or higher reaction was reported by 2.5% of those receiving the vaccine and 0.7% for placebo. This is graded with a high certainty of evidence. Local reactions occurring within 7 days were common. Pain at the injection site was the most common. Systemic reactions within 7 days were common as well, with headache, fatigue, and myalgias as the most common symptoms reported. Most symptoms resolved after 1 to 2 days. Including local and systemic AEs by age group, reactogenicity was higher among vaccine compared to placebo recipients and in younger compared to older adults. Overall Grade 3 reactions were rare in the range of 1% to 2% percent of participants and again more common in the younger age. As was done with other COVID vaccines, there will be a website summarizing reactogenicity data on the CDC and ACIP websites to help inform providers and patients about symptoms post-vaccination seen in the clinical trials.

There were several AE imbalances of note. Urticaria events that FDA determined could possibly be related to the vaccine, tinnitus, and thromboembolic for which FDA stated there was insufficient data to determine a causal relationship. In addition for thromboembolic events, many of the participants had predisposing conditions. However, FDA recommends surveillance for further evaluation of thromboembolic events.

As this is the third COVID vaccine with an EUA, the WG wanted to provide one slide with thoughts on how this vaccines is in the overall program. There were no trials that compared efficacy between vaccines in the same study at the same time. All Phase 3 trials differed by calendar time and geography. This is important because it means that the vaccines were tested against different circulating variants and in settings with different background incidence. This limits the ability to draw specific comparisons with each of the Phase 3 trials. All authorized COVID vaccines have demonstrated efficacy against symptomatic laboratory-confirmed COVID ranging from 65% to 95%. All authorized COVID vaccines have demonstrated high efficacy against COVID severe enough to require hospitalization at 89% or higher. In the vaccine trials, no participants who received a COVID-19 died from COVID. The Moderna and Janssen trials each had COVID deaths in the placebo arm.

This table shows a summary of GRADE from earlier, with each evidence type listed:

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
Symptomatic laboratory-confirmed COVID-19	Critical	RCT (1)	Janssen COVID-19 vaccine is effective in preventing symptomatic COVID-19	2
Hospitalization due to COVID-19	Critical	RCT (1)	Janssen COVID-19 vaccine prevents COVID-19-resulting in hospitalization	2
All-cause Death	Important	RCT (1)	Janssen COVID-19 vaccine is associated with a lower risk of both all-cause death and death due to COVID-19	2
SARS-CoV-2 seroconversion	Important	RCT (1)	Data from day 71 serology indicates that Janssen COVID-19 vaccine prevents seroconversion during the available follow-up period; data support an effect on prevention of asymptomatic infection	3
Asymptomatic SARS-CoV-2 infection	Important	No Studies	No systematically collected PCR data are available to develop an estimate for this outcome	ND
Harms				
Serious adverse events	Critical	RCT (3)	SAEs were balanced between vaccine and placebo arms. 3 participants had SAEs judged by FDA as likely related to vaccination	2
Reactogenicity	Important	RCT (3)	Severe reactions were about 3 times more common in vaccinated vs. placebo; any grade ≥ 3 reaction was reported by 2.5% of vaccinated	1

Evidence type: 1=high; 2=moderate; 3=low; 4=very low; ND, no data

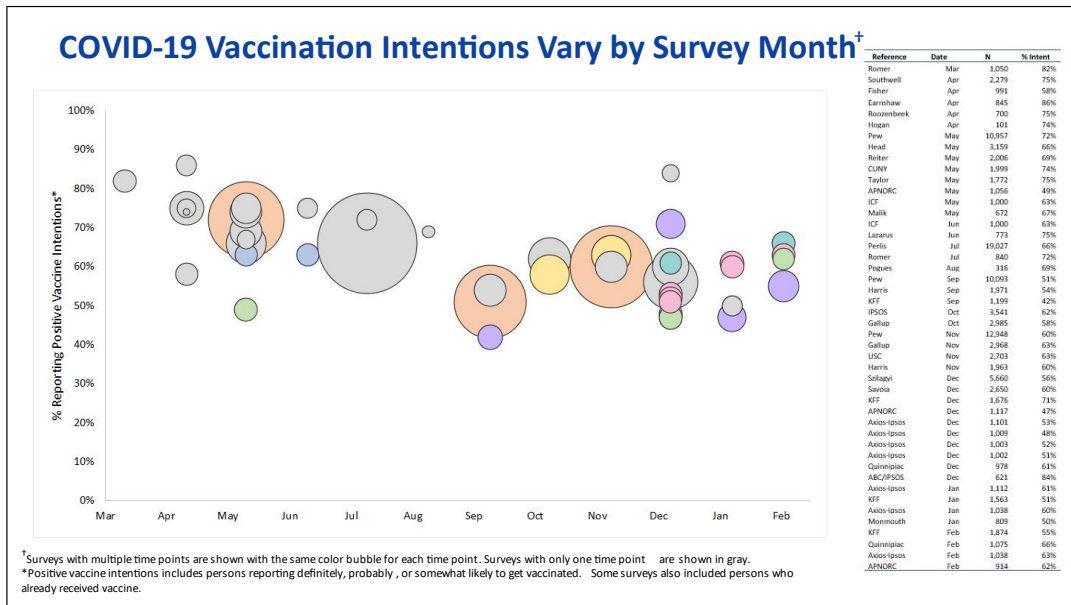
In summary, the WG felt that the desirable anticipated effects were large and that the undesirable anticipated effects were small. Based on this, the WG felt that when considering how the desirable effects balance with undesirable effects, it favors the intervention—the Janssen COVID-19 vaccine.

The questions for the *values* domain are, “Does the target population feel that the desirable effects are large relative to undesirable effects?” and “Is there important uncertainty about, or variability in, how much people value the main outcome?” As detailed previously, a review was conducted of the scientific literature, media, and reports updated through February 26, 2021. The overall acceptability of a COVID vaccine was moderate,³ with the proportion intending to receive the vaccine ranging from 42% to 86%. A recent survey in February showed that 46% would receive the vaccine as soon as possible, 27% plan to wait and see, and 18% said they would not receive it.⁴ Another recent survey detailed the populations with the highest estimates for people who do not intend to receive a COVID vaccine, particularly younger adults, women, non-Hispanic Black adults, adults living in non-metropolitan areas, and those with less education and income and without health insurance.⁵ This graphic combines the data from now 45 surveys, with the proportion reporting positive vaccine intent by month of data collection, with bubbles proportional to the survey sample size:

³ APNORC; Harris; Fisher *Ann Intern Med.*; ICF; Kreps *JAMA Netw Open.*; Lazarus *Nature Med.*; Malik *EClinicalMedicine.*; Pogue *Vaccines.*; Reiter *Vaccine.*; Thunstrom *SSRN.* Szilagyi *JAMA.* Axios-IPSOS. Pew. KFF. ABC News-IPSOS. Quinnipiac. Monmouth.

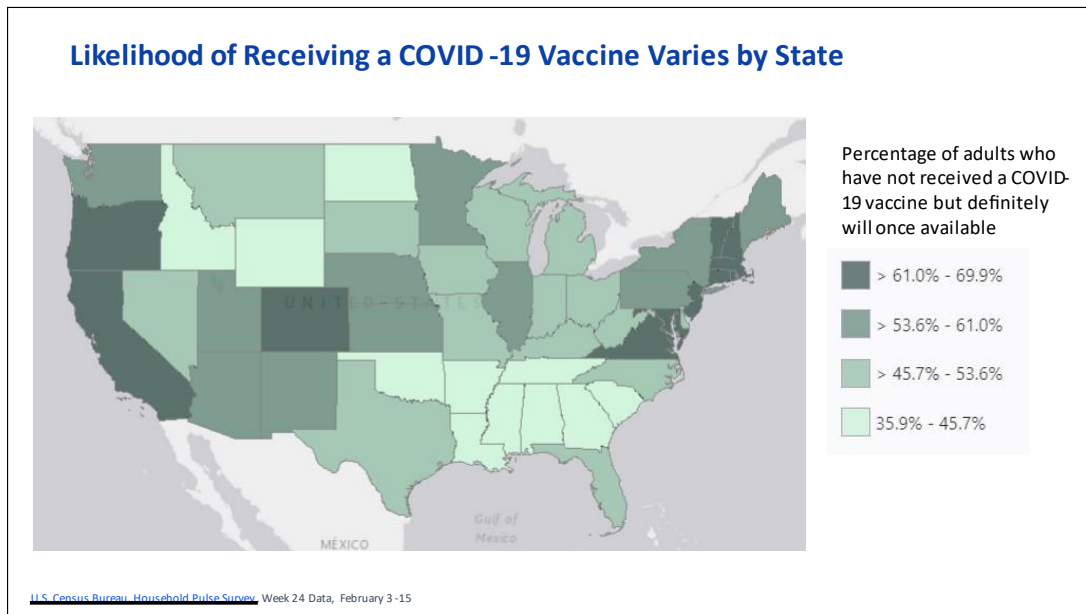
⁴ KFF COVID-19 Vaccine Monitor: February 2021. February 26, 2021. <https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-february-2021/>

⁵ Nguyen KH, Srivastav A, Razzaghi H, et al. COVID-19 Vaccination Intent, Perceptions, and Reasons for Not Vaccinating Among Groups Prioritized for Early Vaccination — United States, September and December 2020. *MMWR Morb Mortal Wkly Rep* 2021;70:217–222. DOI: <http://dx.doi.org/10.15585/mmwr.mm7006e3>



In addition, surveys with multiple time points are shown with the same color. From March to September, vaccine intention slowly declined. However, since the winter when there were tangible data on safety and effectiveness of vaccines, it appears intent has increased slightly and leveled out around 60%.

This map shows the percentage of adults who have not yet received a COVID vaccine but definitely will once available, with the darker shade of green representing higher intent to vaccinate using data from early February and showing that the likelihood of receiving a COVID-19 varies by state and region of the country:



Intent to receive a vaccine by race and ethnicity come from data from surveys around theoretical vaccines when the questions were asked before data was known on any specific vaccine. Two of the surveys were conducted in January or February 2021 when information was known around specific vaccines.⁶ Overall, vaccination intention varied substantially by race, ethnicity, and socioeconomic status. Common reasons for positive intentions included protecting self, family, and community from COVID; belief that vaccines are safe; and the ability to resume social activities. Common concerns included vaccine side effects and uncertainty around vaccine safety. Most of the data presented so far were for overall COVID vaccines. However, one recent survey addressed a situation that could be related to this specific vaccine. This survey asked about a 2-dose vaccine with high efficacy compared to a 1-dose vaccine with a moderate efficacy estimate. Over half would choose the 2-dose vaccine with higher efficacy, 7% would choose the 1-dose vaccine, and 21% would take either. There wasn't a follow-up question. There was a follow-up question that asked of those who stated that they would choose the 2-dose vaccine would wait a month to receive that 2-dose vaccine or would receive the 1-dose vaccine now. Of those who initially said that they would want the 2-dose vaccine, 28% said they would get the 1-dose vaccine now instead of waiting.⁷ Limitations for the data include that most surveys are conducted prior to the availability of information on the Janssen vaccine and convenience samples may not be representative.

The WG interpretation of the first question was that yes, the desirable effects are large relative to undesirable effects. However, they also felt that there was probably important uncertainty or variability in how much people value the main outcomes.

The question addressed for the *acceptability* domain was, "Is the Janssen COVID-19 vaccine acceptable to key stakeholders?" A review of the literature was conducted as well as other relevant information, including news media. There are still no published provider knowledge, attitude, and practices surveys. Previously, the WG presented a survey of State Health Officers⁸ demonstrating concern with vaccine hesitancy, safety, and communications. They were recently made aware of concern from jurisdictions regarding vaccine supply and unmet demand in a letter to the President from the National Governors Association (NGA) Executive Committee.⁹

The logistics of this particular vaccine may make it more acceptable to a wide variety of stakeholders. This is a single-dose vaccine with more convenient storage and does not require dilution. In addition, COVID vaccination programs have been implemented in a variety of settings, including state and local health departments, health care sites and hospitals, mass vaccination clinics, long-term care facilities (LTCF), and retail pharmacies. As of February 27, 2021, over 72 million doses have been administered. Over 48 million people have initiated the series, over 23 million have completed 2-dose series, and over 7 million doses have been given in LTCF.¹⁰ Addressing the main question for this domain, the WG felt that the Janssen COVID-19 vaccine was acceptable to key stakeholders.

⁶ Szilagyi PG, Thomas K, Shah MD, et al. National Trends in the US Public's Likelihood of Getting a COVID-19 Vaccine—April 1 to December 8, 2020. *JAMA*. 2021;325(4):396–398. doi:10.1001/jama.2020.26419

⁷ NORC AmeriSpeak, Feb 11-15, 2021. CDC unpublished data.

⁸ CDC COVID-19 Response Team.

⁹ National Governors Association. Executive Committee Letter To President Regarding Vaccine Distribution Process. <https://www.nga.org/advocacy-communications/executive-committee-letter-to-president-regarding-vaccine-distribution-process/>

¹⁰ COVID Data Tracker. <https://covid.cdc.gov/covid-data-tracker/#vaccinations>.

The question for the *feasibility* domain was, “Is the Janssen COVID-19 vaccine feasible to implement?” The specific characteristics of this vaccine likely make it more feasible to implement. Vaccine shipment and storage is at refrigerator temperatures and is a single-dose series. To address possible financial barriers, COVID-19 vaccines are provided free of charge. However, as discussed previously, health systems or health department could incur cost for vaccine implementations and clinics. There is also concern for personal investments in time and travel to obtain the vaccine that may be a barrier for some groups. However, for the Janssen product, these costs related to implementation or vaccine receipt would presumably be less for a 1-dose compared to a 2-dose schedule. For complexity of recommendations, 1 adenoviral vector vaccine and 2 mRNA vaccines under an EUA with a different number of doses, dosing intervals, and storage and handling requirements may make vaccine recommendations more complex. In addition, there is the potential for emerging challenges related to managing choice or preference for providers and consumers for different products.

In terms of access to vaccines, adding a third vaccine will increase access in terms of total vaccine doses available. However, access to vaccines still could be limited for people who are underserved or live in rural or other hard-to-reach areas. Jurisdictions need to consider differential access when planning vaccination locations, communicating vaccination information, and scheduling appointments.¹¹ A variety of programs are coming on board including the Federal Retail Pharmacy Program¹², Federally Qualified Health Center Program¹³, and the FEMA Community Vaccination Centers¹⁴ which should further expand access. Finally, a vaccine without freezer requirements could be used in individual provider offices once supply allows. Based on these considerations, the WG felt that yes, COVID-19 vaccine is feasible to implement.

The question for the *resource use* domain was, “Is the Janssen COVID-19 vaccine a reasonable and efficient allocation of resources?” As has been discussed previously, health-related costs have been estimated at \$8.5 trillion.¹⁵ It is worth noting that this estimate was provided before the December/January surge in cases, so it is likely even higher at this point. The US Government (USG) has committed over \$10 billion to provision of vaccines¹⁶ and is committed to purchasing hundreds of millions of doses of vaccines over the next several months. A recent study estimated the cost per quality adjusted life year (QALY) for a hypothetical vaccine. This vaccine was not provided under the current situation, is not provided free-of-charge, and modeling did not consider societal costs associated with the pandemic. However, even with these limitations, there were many circumstances where the vaccine was cost-saving depending on the target population.¹⁷ Finally, one modeling study concluded that there are only limited situations that would favor foregoing currently available vaccines for higher efficacy vaccines

¹¹ COVID-19 Vaccination Program Interim Playbook for Jurisdiction Operations. October 29, 2020: <https://www.cdc.gov/vaccines/covid-19/covid19-vaccination-guidance.html>

¹² CDC. Understanding the Federal Retail Pharmacy Program for COVID-19 Vaccination. <https://www.cdc.gov/vaccines/covid-19/retail-pharmacy-program/index.html>

¹³ CDC. Ensuring Equity in COVID-19 Vaccine Distribution. <https://www.cdc.gov/vaccines/covid-19/planning/health-center-program.html>

¹⁴ FEMA. <https://www.fema.gov/press-release/20210216/fema-supports-vaccine-distribution-amid-winter-weather-response>

¹⁵ 1 Cutler and Summers. 2020. JAMA. “The COVID-19 pandemic and the \$16 trillion virus.”

¹⁶ Source: <https://www.hhs.gov/about/news/2020/05/15/trump-administration-announces-framework-and-leadership-for-operation-warp-speed.html>

¹⁷ Kohli M, Maschio M, Becker D, Weinstein M. “The Potential Public Health and Economic Value of a Hypothetical COVID-19 Vaccine in the United States: Use of Cost-Effectiveness Modeling to Inform Vaccination Prioritization.” *Vaccine* 2021 Feb 12; 39(7): 1157–1164.

available later in the pandemic. These situations were only for a vaccine with efficacy lower than the current FDA threshold for an EUA.¹⁸

The precise cost-effectiveness analysis and economic impact of vaccination depends on a number of factors that are currently unknown, including real-world vaccine effectiveness and duration of protection, vaccination coverage levels and speed of vaccination, implementation costs associated with large vaccination program, and the overall course of the pandemic. The WG again concluded the cost-effectiveness may not be a primary driver for decision-making during the pandemic and for vaccine use under an EUA. This will need to be reassessed in the future as more becomes known about the variables discussed here. However, during the pandemic, the data show that the best utilization of resources is to employ all available vaccines with acceptable vaccine efficacy. This will save cost and lives. Based on the current situation, the WG felt that yes, the Janssen COVID-19 vaccine is a reasonable and efficient allocation of resources.

The question for the *health equity* domain was, “What would be the impact of the Janssen COVID-19 vaccine on health equity?” A number of groups have experienced increased COVID-19 disease or decreased uptake of COVID-19 vaccine, including the following:

- Racial and ethnic minority populations and tribal communities
- People living in poverty or with high social vulnerability
- Essential workers:
 - Almost one quarter live in low-income families¹⁹
 - Some racial/ethnic minority populations disproportionately represented in subsets of essential workers, e.g., public transit, building cleaning services, construction, food and agriculture^{19, 20, 21}
- Residents in congregate settings, such as long-term care facilities, correctional/detention facilities, homeless shelters, and group homes
- People with disabilities
- People with substance abuse disorders
- Sexual and gender minorities (social or structural inequities leading to health disparities)

Based on states’ initial vaccine allocation plans, only 19 (38%) states used a Social Vulnerability Index (SVI) to deliver vaccines more equitably.²² There was a national survey in early January 2021 that showed that Black persons were 52% less likely than White persons to be vaccinated or plan to get vaccinated.²³ As of February 26, 2021, there is a lower proportion of Black and Hispanic persons who have received the vaccine compared to the demographics of the overall population.²⁴

¹⁸ Bartsch SM, O’Shea KJ, Wedlock PT, et al. The Benefits of Vaccinating With the First Available COVID-19 Coronavirus Vaccine. *American Journal of Preventive Medicine*. 2021 Jan 19.

¹⁹ 1Rho HJ, Brown H, Fremstad S. A basic demographic profile of workers in frontline industries. April 2020. Washington, DC: Center for Economic and Policy Research;2020. <https://cepr.net/a-basic-demographic-profile-of-workers-in-frontline-industries>

²⁰ 2Bui DP, McCaffrey K, Friedrichs M, et al. Racial and ethnic disparities among COVID-19 Cases in workplace outbreaks by industry sector — Utah, March 6–June 5, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1133–8. DOI: <http://dx.doi.org/10.15585/mmwr.mm6933e3>

²¹ 3Waltenburg MA, Rose CE, Victoroff T, et al. Coronavirus disease among workers in food processing, food manufacturing, and agriculture workplaces *Emerg Infect Dis*. 2021 Jan. https://wwwnc.cdc.gov/eid/article/27/1/20-3821_article

²² Schmidt et al. Equitable Allocation of COVID-19 Vaccines. 2020: <https://scholarship.law.georgetown.edu/facpub/2333/>

²³ Kim et al. <https://www.medrxiv.org/content/10.1101/2021.02.16.21251769v1>

²⁴ CDC. <https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic> as of Feb 17 2021, and US Census Bureau 10-year July 2019 National Population Estimates

There are specific characteristics of the Janssen COVID-19 vaccine that could impact health equity. In terms of storage, handling, and administration requirements, this refrigerator-stable vaccine will facilitate the ability of the vaccine to get into most community settings and mobile sites once supply allows. A single-dose schedule could be an advantage to equity, particularly in settings or populations where follow-up for a second dose would be challenging. It also would allow for increased vaccine options and more doses available. This vaccine could make it easier to reach some disproportionately affected groups, such as persons experiencing homelessness, rural resident, justice-involved persons, disabled persons, homebound persons, or persons with limited access to health care. Community engagement and education will be important as new vaccines are utilized. Finally, equity and vaccine program implementations are closely linked. Advancing health equity requires community engagement and focused efforts to identify and reduce vaccine access and confidence-related²⁵ barriers to vaccination among groups who experience a disproportionate COVID-19-related morbidity. In addition, wherever possible when setting and supply allow, consideration should be given to extending choices for COVID-19 vaccines.

The WG felt that the impact of the Janssen COVID-19 vaccine would be to increase health equity. The feasibility of the Janssen COVID vaccine to be implemented in a wider variety of settings is an opportunity to improve equitable access to an effective COVID-19 vaccine.

This table summarizes the EtR domains, questions, and WG judgments from everything that was just presented:

EtR Domain	Question	Work Group Judgments
Public Health Problem	Is COVID-19 disease of public health importance?	Yes
Benefits and Harms	How substantial are the desirable anticipated effects?	Large
	How substantial are the undesirable anticipated effects?	Small
	Do the desirable effects outweigh the undesirable effects?	Favors Janssen COVID-19 vaccine
	What is the overall certainty of the evidence for the critical outcomes?	2 (moderate) for prevention of symptomatic COVID-19 2 (moderate) for hospitalization 2 (moderate) for safety
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	Yes
	Is there important variability in how patients value the outcomes?	Probably important variability
Acceptability	Is the Janssen COVID -19 vaccine acceptable to key stakeholders?	Yes
Feasibility	Is the Janssen COVID -19 vaccine feasible to implement?	Yes
Resource Use	Is the Janssen COVID -19 vaccine a reasonable and efficient allocation of resources?	Yes
Equity	What would be the impact of the intervention on health equity?	Increased

²⁵ CDC. COVID-19 Vaccination Program Interim Playbook for Jurisdictions Operations Annex: Considerations for Increasing COVID-19 Vaccination, Reaching and Increasing Uptake in Priority Populations (January 2021 Version 1.0). <https://www.cdc.gov/vaccines/covid-19/downloads/COVID-19-vaccination-program-playbook-annex.pdf>

After reviewing the data, the WG provides a judgment on the balance of consequences based on the following categories:

- Undesirable consequences *clearly outweigh* desirable consequences in most settings
- Undesirable consequences *probably outweigh* desirable consequences in most settings
- The balance between desirable and undesirable consequences is *closely balanced* or *uncertain*
- Desirable consequences *probably outweigh* undesirable consequences in most settings
- Desirable consequences *clearly outweigh* undesirable consequences in most settings
- There is insufficient evidence to determine the balance of consequences

The WG felt that the desirable consequences clearly outweigh undesirable consequences in most settings. In addition, after reviewing the totality of information presented in the EtR Framework, the WG discussed the type of recommendation proposed to ACIP. The options are:

- We do not recommend the intervention
- We recommend the intervention for individuals based on shared clinical decision-making
- We recommend the intervention

Based on the totality of data presented, the WG has proposed to recommend the intervention to the ACIP.

Discussion Points

Dr. Whitley-Williams (NMA) found it more reassuring to see 13% African American and 14% Hispanic or LatinX participation in the US and asked whether there are data on the AEs by race/ethnicity. She understood that the total SAEs are small in numbers to begin with. Given the requirement that all participants are encouraged to remain in the study up to 2 years to assess efficacy, safety, immunogenicity, she wondered if any information was available about how many of the URM participants have remained in the study and if those in the placebo group were offered vaccine and also are being followed in the 2-year follow-up study.

Dr. Goldman (ACP) said that if this vaccine is approved for recommendation by ACIP, it will be important to be very clear on the messaging regarding the lack of comparison of the vaccine, but that in and of itself, this appears to be a very safe and effective vaccine based on good data. They must ensure that the public understands that the best vaccine is the one to which they can get access. He encouraged Governors and jurisdictions to adhere to the ethical framework in order to get the vaccine out to the most people possible. As a primary care physician (PCP), he emphasized that many PCPs are eager to be able to vaccinate their populations. This vaccine may be very helpful in achieving that goal with the refrigerator-stable storage. He inquired as to whether Dr. Oliver could provide more details about the thromboembolic events that were reported.

Dr. Oliver called upon representatives from Janssen and the FDA to provide an overview of the thromboembolic events.

Dr. Douoguih indicated that Janssen has observed a slight imbalance in thromboembolic events, although there is not a big difference between groups. As mentioned during her presentation, a large proportion of participants who have had these events had predisposing factors, underlying medical conditions, that plausibly could have contributed to these events. Right now, they do not believe there is a causal association with the vaccine. However, they

have committed to monitor this post-authorization beginning immediately. As the vaccine is rolled out, it is Janssen's intent to examine these events closely—keeping in mind that COVID-19 is also an underlying factor that will have to be included in the assessment.

Dr. Long expressed appreciation that the WG's judgement that the level of confidence in prevention of asymptomatic infection is tempered by low numbers. This is important to remember, because it would be the opposite of every instance that is known in terms of efforts to prevent severe disease with basically IgG antibody that is derived from an IM injection. It prevents more invasive and more severe disease better than it does upper respiratory tract or asymptomatic disease. It would be great news if this vaccine prevents some asymptomatic infection, especially transmission from that. She appreciated that the WG concluded that the confidence in that is not high. To discuss these vaccines one against the other or one compared with another and nuances of recommendations, she was especially appreciative of some of the public comments as she has been thinking about some of these issues, age groups, and the difficulty in reaching some populations. She asked whether the plan was to focus the first day of the meeting on the recommendation and put off other nuances until the next day.

Dr. Romero indicated that ACIP's mandate was to make recommendations regarding this specific vaccine and each specific vaccine as it comes forward. At this time, they were not tasked with comparing the vaccines to one another and making specific recommendations for each one independent of the other. They could discuss this further during the second day of the meeting, but at this moment that was not a decision they were ready to make.

Dr. Duchin (NACCHO) expressed appreciation for the presenters for highlighting that it is inappropriate to try to compare the 3 available vaccines directly with respect to effectiveness. It is clear that they all provide a high level of protection against what is more important, which is severe illness, hospitalizations, and deaths. However, it seemed to him that they may be able to compare the reactogenicity and particularly the severe and Grade 3 systemic reactions among the available vaccines. It appeared to him that the Janssen vaccine has significantly fewer such severe reactions. He wondered whether someone would care to comment on that aspect of the vaccines.

Dr. Oliver said she thought they also would caution against event comparing reactogenicity across the trials, given that this very much depends upon how it was asked in the trials and the number and type of symptoms that were asked. These vaccines will be closely monitored as they are rolled out and there will be post-authorization safety data that the WG will present to ACIP as it becomes available.

Dr. Eckert (ACOG) stated that on behalf of the American College of Obstetricians and Gynecologists, she was very happy that Janssen has data for this vaccine being used in pregnancy with the Ebola platform. While acknowledging that this information is present in the VRBPAC materials and is available publicly, she wondered when the results from the Ebola pregnancy trials would be published. Pregnant women are very interested in safety data about this vaccine as is everyone else.

Dr. Douoguih indicated that these studies are ongoing. One of the studies that she mentioned earlier that is ongoing in Rwanda will randomize 2000 individuals. It is in the early phases of enrollment, so it will be some time before infant outcomes are available. Of course, they are very much committed to publishing as soon as they can. Within the context of the COVID-19 program, they will make every effort to publish data, perhaps even in the interim. They will be conducting open label studies.

Dr. Romero pointed out that while he agrees with the acceptability as stated for key stakeholders, it is still important to have Indian Health Services (IHS) and other stakeholders from that group and their advisors weigh in on the acceptability of this vaccine for AI/AN.

Dr. Weiser (IHS) responded that he believes there is a place for this vaccine. Many people already have mentioned cases and times where this vaccine would be more acceptable in terms of mass vaccination campaigns and logistics around easy distribution and administration in offices and clinics. Therefore, the IHS feels that this vaccine would be used and anticipates using this vaccine in accordance with the other ACIP authorized vaccines.

Public Comment Overview

The floor was opened for public comment during the February 28-March 1, 2021 ACIP meeting at 2:30 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-2021-0021. Visit <http://www.regulations.gov> for access to the docket to submit comments or read background documents and comments received.

Dorit Reiss, PhD, LLB
Professor of Law
University of California
Hastings College of Law

Thank you for the opportunity to comment. My name is Dorit Reiss. I'm a Professor of Law at the University of California Hastings College of Law. I'm grateful to the committee for all its work. I have three topics I want to address. First, your safety update today is about Johnson & Johnson. I'm looking forward to a more general one. These have been incredibly helpful. As you know, there are anti-vaccine activists online misrepresenting the data about COVID-19 vaccine to create or increase vaccine hesitancy. I know some of you also respond to that online. I want to thank the committee members personally for their measured, informed responses. We really appreciate that. Among other things, anti-vaccine activists are misusing Vaccine Adverse Event Reporting System (VAERS) reports in multiple ways and amplifying any harm after COVID-19, even if it's unfounded and even if it's against the facts. We can't stop them from doing that, but you can help in responding to this. For example, when you provided the numbers on the benefits of influenza vaccine, even with limited effectiveness, it was a powerful and helpful counter to claims that it is useless. Short materials setting out, for example, death report numbers in context, background race, causes, and why you conclude that there is no link to vaccines for most of them would be helpful. Short material summaries on the complex safety data by Johnson & Johnson that you covered would be extremely helpful. Short materials about VAERS reports and what they mean would be helpful. Although this is not the committee, if there is a way to add to every VAERS table generated explaining the reason that mentions the limits, that would also be helpful. My other two comments are about allocation. First, I hope you will consider the point made during your February 24-25 meeting about the need to prioritize incarcerated people. Up to this point, this population is being disproportionately impacted by COVID-19, is at high risk, and may be mistreated in distribution. When you incarcerate people, you take responsibility for their needs. ACIP discussed these people early on with long-term care facilities (LTCFs), but it is not reflected in the guidance. Maybe it's time to revisit and redefine long-term care facilities to cover incarcerated people, for example, by redefining priority institutions as residential institutions for those who have limited ability to leave. They deserve an

opportunity to get vaccines if they want them. Finally, as mentioned in the last presentation, we're seeing strong inequities in access to the vaccine. That is not on you. That is not your recommendation, but maybe it's time to remind states that they need to prioritize high need populations and bring vaccines to where people are, including people who have less access to the internet-dependent channel or less mobility. That should be a priority. We need to protect everyone to end the pandemic. Thank you for your time.

Ms. Karen Ernst, MA, BA
Executive Director
Voices for Vaccines

Thank you. Hello ACIP members. My name is Karen Ernst and I am the Director of Voices for Vaccines. A year ago, I attended ACIP in person where Dr. Messonnier delivered an update on the SARS-CoV-2 and its spread overseas. At the time, there were 80,413 cases worldwide. Today, you are discussing the third vaccine approved by the Food and Drug Administration (FDA) under Emergency Use Authorization (EUA) to fight this virus. Thank you and thank everybody who worked to get us here today. This single dose vaccine elicits a lot of hope. We all know that many people who need COVID vaccines the most are often having difficulty getting them. Some of this is simple supply and demand, some of it is distribution, and some of it is people gaming the system. My own parents were frustrated for weeks working within the system as we witnessed younger, healthier people cross state lines to access vaccine likely meant for others. An entire Vaccine Hunters Facebook group locally to me has 18,000 members and 190 posts today and works on the premise of finding vaccines via connections and rumors. We all know that these scenarios exacerbate health inequities. A single dose vaccine that can be stored in regular vaccine refrigerators has the potential to get more vaccines to Black, Indigenous, and People of Color (BIPOC); rural; and poor communities. I would get the Janssen vaccine in a heartbeat, but it has been billed as a less effective vaccine in the media already. If we put the single dose vaccine on a bus and drive it to places where people have had access issues with other vaccines, we risk the perception that the inferior vaccine is being saved for poor people, BIPOC communities, or rural folks. We need some real, plain language, clear public education on the difference between clinical trial efficacy and real-world effectiveness. We need people to understand that the efficacy numbers put out were not on the same scale, like a standardized test, and we need people to have at the absolute best medicine and the best vaccines available to everyone in an equitable way. Without this work, we risk increasing not only vaccine hesitancy, but also distrust in healthcare for years to come. Thank you very much.

Ms. Amy Pisani, MS
Executive Director
Vaccinate Your Family

Good afternoon. My name is Amy Pisani and I'm honored to serve as the Executive Director of Vaccinate Your Family (VYF). Our organization was formed on the heels of a measles epidemic of '89/'90 as Every Child By Two (ECBT). Our co-founders, former first lady Rosalynn Carter and Mrs. Betty Bumpers, knew that even 150 lives lost to a vaccine-preventable disease were too many and so they dedicated their lives to vaccine advocacy. We are proud to have been a part of the solutions that have resulted in a massive decline in vaccination disparities among children, although we recognize that we must continue to be vigilant and focus on ensuring that every child has access to life-saving vaccines. Thirty years later, we are renamed Vaccinate Your Family and are a part of the fight against a worldwide pandemic. On behalf of all of us, I wish to thank the committee and all of the staff at CDC for your unyielding commitment to stopping this deadly virus. I agree with the previous public comments with regard to the critical

importance of transparency in the review of the safety data for COVID-19 vaccines, both pre- and post-authorization. This intense review and the sharing of safety data is of paramount importance to help advocacy organizations like ours as we prepare resources that may help increase not only confidence in vaccinations, but also COVID-19 vaccine readiness, particularly among minority communities. I also wish to thank the members of the National Academy of Medicine (NAM) and the ACIP Work Group for the diligent work you conducted to not only research disproportionate burden of coronavirus on various communities and ethnic populations, but also to develop the prioritization plans. Not all states chose to follow the plans. I can tell you that based on the calls that flooded into our organization on phone and email lines, particularly in the early weeks, that the overwhelming majority of calls were received from seniors desperately searching for COVID-19 vaccinations came from states that failed to follow your prioritization scheme. Confusion and chaos in those states was real and we hope that when the pandemic is behind us, government agencies and legislators will conduct a postpartum analysis to determine which prioritization plans resulted in reduced cases and overall public health functionality. Here at Vaccinate Your Family, we paid close attention not only to the morbidity and mortality data, but also to the plan and we redoubled our efforts to eliminate immunization disparities, particularly among communities of color. In December, we proudly announce our partnership with the National Council of Negro Women (NCCW) to create the Good Health Women's Immunizations Network (Good Health WINs), which will begin in 10 states where we will create a network of African-American women who will become COVID vaccine allies, encouraging their local communities to vaccinate against this deadly disease. We have also set our sights on developing new culturally competent resources and videos featuring experts in many languages and we're translating our website into Spanish. We are also translating a large portion of our resources into over 6 languages. We wish to thank you so very much for everything you're doing. We know that everyone on this committee is committed to our shared mission to save lives. We look forward to working with you now and into the future.

Jeffrey Silberzweig, MD
Chief Medical Officer
The Rogosin Institute

Good afternoon. Thank you for the opportunity to address ACIP today. I am Jeffrey Silberzweig, Chief Medical Officer of the Rogosin Institute in New York City (NYC). We are a non-profit provider of kidney care, including dialysis to some 1500 patients. I speak today on behalf of my colleagues, the 21,000 members of the American Society of Nephrology (ASN), whose COVID-19 Response Team I have Co-Chaired for the past year, and dialysis providers large and small for-profit and non-profit across the United States. Most importantly, I speak on behalf of the 500,000 Americans with chronic kidney disease (CKD) who depend on life-sustaining dialysis treatments. By virtue of their primary condition and the invasive nature of their ongoing regular care, these individuals when infected with SARS-CoV-2, are at higher risk of serious COVID requiring hospitalization and of more mortality than age-matched Medicare beneficiaries. Dialysis patients must go out into the community 3 times weekly for 4 to 6 hours in each time. They do not have the option of sheltering at home, increasing their risk and the risk of those in their family and community. Patients with chronic kidney disease are disproportionately African-American, Hispanic, and Native American. They experience the effects of lifelong health disparities, heightening their susceptibility. Data show that they have a higher risk of acquiring COVID and of more severe complications from it due to their multiple comorbid medical conditions. In the US and around the world, mortality rates of dialysis patients with COVID range from 20% to 40%. The dialysis community has committed to working together to ensure that patients and staff get vaccinated if vaccines are allocated. Because our patients are treated 3 times weekly, administration of the second dose is less problematic than in most patients.

Because of the long-standing trusted relationship between dialysis patients in the staff who care for them, we have consistently had high rates of vaccination against infectious diseases, like influenza and hepatitis B. Our patients are less likely to be able to register online for vaccine appointments because of their medical and socio-economic conditions, and are less likely to be able to wait in line for vaccinations. I do not envy the responsibility you carry in recommending who merits priority for vaccination, but I ask that you consider that dialysis patients are like daytime congregate care facility patients with similar mortality and should be prioritized like residents of long-term care facilities. They are among the highest risk groups of dying from COVID. I beseech you to provide an allocation of 500,000 doses of vaccine to allow dialysis providers to protect these mostly Black and Brown patients. Thank you for your time today.

Albert Faro, MD
Vice President, Clinical Affairs
Cystic Fibrosis Foundation

Good afternoon. My name is Dr. Albert Faro and I'm the Vice President of Clinical Affairs at the Cystic Fibrosis Foundation (CF Foundation). On behalf of the foundation and the more than 30,000 people with CF in the United States, I would like to thank the committee for the opportunity to provide comments regarding development and allocation of COVID-19 vaccines. The CF Foundation is a national organization actively engaged in research and development of new therapies for CF, a rare life-threatening genetic disease characterized by thick, sticky mucus in the lungs resulting in frequent acute and chronic respiratory infections. These chronic airway infections are punctuated by pulmonary exacerbations—events often triggered by respiratory viral infections that are a risk factor for an irreversible decline of lung function and associated with morbidity and mortality. Continued progression of the disease can result in advanced lung disease so severe that lung transplantation may be the only life-extending option. COVID-19 represents a serious threat for people with CF. The CF Foundation Patient Registry collects information on the health status of people with cystic fibrosis who receive care in CF Foundation-accredited care centers. The data underscores the threat this infection poses to people with CF. A published global analysis of 181 COVID-19 cases among people with CF demonstrated that CF patients with advanced lung disease and those who are post-lung transplant are at increased risk of severe outcomes, including death. We recognize that to date, the ACIP included those with high-risk conditions as a prioritized group in the committee's COVID-19 vaccine allocation recommendations, and we are pleased that these recommendations are accompanied by language from the CDC about using individuals clinical judgment to identify patients whose risk factors warrant priority vaccine access. However, we are deeply concerned about the wide range of interpretations of ACIP's recommendations among states and localities, in some cases not including rare diseases like CF on lists of prioritized populations and in other cases, opting to use age-based criteria alone. The desire for simplicity must not come at the expense of those who are most vulnerable to the consequences of this infection. People with CF and others with high-risk conditions must be prioritized for early access. Some current state and local practices run counter to ACIP's intent of prioritizing those at highest risk of morbidity and mortality and are placing people with CF and other underlying medical conditions at greater risk, solely for the sake of expediency. We urge the ACIP to provide clarifying language on Phase 1c recommendations for rare disease populations to ensure that high-risk patients with diseases like CF are able to gain early Access to COVID-19 vaccines. Thank you again for your attention and consideration of people with CF as you tackle these critical issues.

Jonathan Brand, JD
President
Cornell College

Thank you. My name is Jonathan Brand. I am President of Cornell College in Mount Vernon, Iowa. I'd like to offer an idea of using the 1 shot Janssen vaccine right now to target a population that as a group moves around the most—the 53 million 18 to 29 year old population, which includes college and university students. In fact, at over 30 million, 18 to 24 year olds are also a group highly likely to live in congregate settings, residence halls, and apartments—an environment that greatly increases spread. A strategy that relies on colleges and universities to vaccinate all 18 to 29 year olds, not just our students, could jumpstart a second front against COVID. Vaccinating those ages 18 to 29, some of our biggest spreaders, will dramatically accelerate reaching herd immunity. In addition, colleges and universities can be set up as mass vaccination sites, inoculating thousands of individuals in this cohort in short order rather than further taxing current mass vaccination sites. We have the gyms, the arenas, the field houses, the parking lots. Because schools of higher education are located all over the country in urban, suburban, and rural settings, we can increase access. We are everywhere. Fortunately, the Janssen vaccine does not need special cold storage. Because it's a 1 shot deal, this vaccine resolves a logistical challenge we'll soon confront—a group that tends to relocate throughout the country in May or June and won't be able to easily return to the same location or state for a second shot. Finally, because about 45% of those ages 18 to 24 work in retail and leisure hospitality industries where we've been concerned with COVID transmission and the harmful economic impact of COVID, this vaccination strategy can only help to jumpstart those sectors as we return to normalcy. Some believe my idea would encourage reckless behavior post-vaccination. I don't believe that. I'm not seeing 20 year olds at bars and restaurants any more than older populations. At Cornell, we currently have a 0% student positivity rate and cumulatively 1.6% because our students, like so many others, are willing to sacrifice. I am confident that this will continue until you tell us we can relax our protocols. States should continue their current phases with Pfizer and Moderna, but they should plan to concurrently mass vaccinate all 18 to 29 year olds with the Janssen vaccine. Higher education can help get this done now. Thank you.

Mr. Eugene Jackson, III
NxStage

My name is Eugene Jackson and I am currently a dialysis patient in Waco, Texas. I want to thank you for giving me the opportunity to give my voice. I am an African American male and I work in the African American community as well as the dialysis community. We now understand that African-Americans and Hispanics are disproportionately being affected by COVID-19. African Americans are 1.9% more likely to have COVID-19 and Hispanics are 2.3% more likely to be affected by COVID-19. Our communities have been ravaged by this dreaded disease and the only way to receive protection is by vaccination. I appreciate the effort to be vaccinated, but also it seems to me that we seem to be further down the line to be vaccinated. If we are such a high risk, it would seem to me that we should be more likely to be one of the first ones to be vaccinated. I understand that it's up to each state to disseminate the vaccinations as you see fit, but I just wanted to get an understanding of why it is that those who have such morbidity conditions seem to be so far down the line. If we know that we are so disproportionately affected by this dreaded disease, why are we so haphazardly down the line to be vaccinated? I appreciate the effort that has come about from the CDC and the ACIP to get the vaccines out, but I just hope that in the future, these people become more of a priority. Thank you.

Michelle Fiscus, MD, FAAP
Board Certified Pediatrician
Medical Director
Vaccine-Preventable Diseases and Immunization Program
Tennessee Department of Health

Good afternoon. I'm Dr. Michelle Fiscus. I am the Medical Director of Tennessee's Vaccine-Preventable Diseases and Immunization Program. I'm also a Board Certified Pediatrician. I'd like to thank the committee for all its work during this challenging time. The work you do has never been more important to the health of this nation. We all owe you a debt of gratitude for sacrificing your time to ensure that the COVID-19 vaccines that have been granted emergency use authorization are administered based upon sound research and science. It's easy to lose sight of the tremendous magnitude of this pandemic, which is far and away the most significant infectious event ever to impact the world in more than a century. It has justifiably impacted every aspect of our lives. More than half a million Americans are dead—41 times the number of lives lost during the 2009 H1N1 pandemic. More than 28 million, nearly 1 in 11 of us, have been affected by the SARS-CoV-2 virus with 13% of the cases in children. That amounts to 1 out of every 25 children in the United States having been infected with this virus, the long-term outcomes of which are still unknown. It is likely reasonable to assume that the more than 2000 children who have gone on to develop multi-system inflammatory syndrome children, or MIS-C, will have their lives shortened by this disease. Early studies have indicated that more than half of these children suffer heart damage, 70% suffer acute kidney injury, and many require dialysis. While it's true that children tend not to die from acute COVID-19, how many more children will suffer the chronic effects of this disease? Yet, children will be the last to be vaccinated, in part due to their lower risk of acute morbidity and mortality, but most importantly due to the lack of an authorized vaccine. It is critically important that the vaccine manufacturers make progress in pediatric COVID-19 vaccine trials as quickly as possible not only to prevent infections, but to achieve herd immunity. As children comprise nearly a quarter of the US population, being able to vaccinate children against SARS-CoV-2 is crucial to our ability to achieve herd immunity in this country. In the meantime, we need every qualified individual to say "yes" when offered a COVID-19 vaccine, no matter the vaccine, and do their part to end this pandemic. We need to work tirelessly to earn the trust of those who are hesitant, especially our Black and Hispanic brothers and sisters, so that these populations that have been disproportionately impacted by COVID-19 will also accept this truly remarkable opportunity to protect themselves, their loved ones, and their communities against this terrible infection. Thank you again for your dedication to this work.

Mr. Ben D'Avanzo, MPA
Senior Health Policy Analyst
National Immigration Law Center

Thank you. My name is Ben D'Avanzo. I appreciate the committee members for your service. I am the Senior Health Policy Analyst with the National Immigration Law Center (NILC). We are the primary advocacy organization working on behalf of low-income immigrants, particularly engaging on health and benefits issues. We have a long history of working to protect the health rights of immigrants, including through a network of community legal advocacy organizations. There are over 22 million non-citizens living in the US and they've been disproportionately serving on the front lines of this pandemic. The ACIP and CDC have worked hard to prioritize different populations based on risk factors, such as being frontline workers. Yet, being eligible for vaccine is not much use if you face deep barriers to accessing it. We have seen from our partners and media reporting that many immigrants face numerous barriers to accessing the

vaccine. Because many communities of color have high rates of foreign-born individuals, we cannot address racial equity without addressing immigrants. I want to address a few of those barriers that this committee can play a role in addressing. First, we did send comments to the committee. In your December meeting, there were concerns immigrant-heavy industries like food and agriculture production may be left out of state definitions of essential workers. These can be isolating places to work that have seen many outbreaks, like meat packing plants, and also has workers in congregate settings. Workers may be unaware of their eligibility for vaccine, even if they are technically included in that definition. We are also very concerned about attempts to ask that immigrants bring in identification documents. Many immigrants, particularly low-income ones, lack such documents. Well-intentioned efforts that require proof of residency, place of work, or medical status may exclude those communities. Asking for an email harms those who are less educated or have low technology literacy, and asking for Social Security Numbers (SSNs) for the uninsured deters many from getting the vaccine. If the goal is to get as many shots in arms and to as many higher risk populations as possible, we should not be creating barriers. We need clear standards to vaccine-providing entities and states that they cannot prioritize anyone based on their immigration status, which we have seen both political leaders declare intentions to do and providers denying people because they are undocumented. These events are spread by social media and by the news and can overpower important messages coming from public health officials about the vaccine to communities. We must provide clear information in as many languages as possible to immigrants about the availability of the vaccine, the fact that their immigration status does not preclude them from getting it, and the fact that their data is safe. Thank you very much.

Vote: Janssen COVID-19 vaccine

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 reminded everyone that the policy question considered by the WG was, “Should vaccination with the Janssen COVID-19 vaccine (1-dose, IM) be recommended for persons 18 years of age and older under an emergency use authorization?” The WG interpretation was that the desirable consequences clearly outweigh undesirable consequences in most settings. Therefore, the WG recommended the vaccine and proposed the following interim recommendation language:

“The Janssen COVID-19 vaccine is recommended for persons 18 years of age and older in the U.S. population under the FDA’s Emergency Use Authorization.”

Motion/Vote: Janssen COVID-19 Vaccine

Dr. Poehling made a motion to accept the proposed language for an ACIP vote on the interim recommendation for use of the Janssen vaccine as presented, “The Janssen COVID-19 vaccine is recommended for persons 18 years of age and older in the U.S. population under the FDA’s Emergency Use Authorization.” Dr. Lee seconded the motion. Dr. Chen recused himself from the vote due to a potential COI. The motion carried with 12 affirmative votes, 0 negative votes, and 1 abstentions. The disposition of the vote was as follows:

12 Favored: Bahta, Bell, Bernstein, Daley, Kotton, Lee, Long, McNally, Poehling, Romero, Sanchez, Talbot
0 Opposed: N/A
1 Abstained: Chen
2 Absent: Ault, Frey

Discussion Points

Ms. McNally inquired as to whether V-SAFE would be adapted to accommodate the Janssen vaccine.

Dr. Cohn indicated that recipients of the Janssen vaccine could enroll in V-SAFE the same as for the other two recommended vaccines.

Reflecting on Dr. Bell’s introductory comments and the scope of the tragedy, Dr. Daley stressed that in the midst of this tragedy, there was some reason for optimism. A very common greeting in the world has been, “Have you eaten today?” That is reflecting a fundamental human need. Now the most common greeting is, “Have you gotten vaccinated?” People are intensely concerned about where they are on the prioritization list, and that has been very complicated. People want to get vaccinated as soon as possible to protect themselves and their families. In many ways this may be an obvious point, but he said he wanted to state explicitly how very grateful he is that there are now 3 safe and highly effective vaccines and remind everyone that if they use all supplies of all 3 vaccines, then everyone essentially moves up on whatever prioritization list they are on. For that, he thought everyone should be very grateful.

Dr. Lee expressed appreciation for Dr. Daley’s comments and reiterated that the life expectancy overall has decreased by 1 full year. However, life expectancy has decreased disproportionately for Black populations by 2.7 years and Hispanic populations 1.9 years. In parallel, there continue to be challenges with regard to equity, access, and the substantial variability that continues to occur by state and county. Those numbers mean to her that it is imperative to continue to ensure that equity is at the forefront of how vaccines are implemented and that this must be done systematically. The disproportionate difference in life expectancy is not specific by age. It really reflects the overall burden of disease in the population. She recognized all of the implementation challenges that occur, but emphasized that it would behoove them all at the national, state, local, and practice levels to continue to be vigilant in trying to keep equity at the forefront.

Dr. Romero thanked all of the members of the ACIP COVID-19 Vaccine WG for the work that they engaged in to bring forward this vote, as well as the voting members and liaisons for giving up all of their time on the weekend. He recognized that this is a very heavy and intense schedule that cuts into personal time and time with everyone's families.

Coronavirus Disease 2019 (COVID-19) Vaccines: March 1, 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, indicating that the agenda for the day would include presentations on the following topics:

- Implementation Considerations for COVID-19 Vaccines
- Clinical Considerations for Use of COVID-19 Vaccines
- Vaccine Safety Technical Subgroup (VaST) Introduction
- COVID-19 Vaccine Safety Update
- VaST Assessment of Safety Data
- Emerging SARS-CoV-2 variants

Implementation Considerations for COVID-19 Vaccines

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

Dr. Dooling presented on implementation considerations for the Janssen COVID-19 vaccine specifically, COVID-19 vaccine prioritization, and dosing intervals for mRNA vaccines. In a unanimous vote to recommend the Janssen COVID-19 vaccine on February 28, 2021, ACIP stated no preference for any of the 3 authorized vaccines. The vaccines were not studied in head-to-head trials. Therefore, the results of the Janssen Phase III trial are not directly comparable with the messenger ribonucleic acid (mRNA) vaccines. Janssen's COVID-19 vaccine was studied at a different calendar time and under different geographical circumstances, which led to difference in the circulating SARS-CoV-2 variants and a higher background incidence during their study. The Janssen vaccine demonstrates strong protection against severe COVID-19, with 93% VE against hospitalizations with 2 cases in the vaccinated compared with 29 cases in the placebo. Moreover, there were no COVID-associated deaths in vaccinated group versus 7 in the placebo group.

Given that the Janssen COVID-19 vaccine has been authorized for emergency use by the FDA and recommended by the ACIP, consideration can be given to how this vaccine best fits into the national COVID vaccination program. The characteristics of this vaccine are that it is a 1-dose regimen and may be transported and stored at 2° to 8°C for up to 3 months. It requires no diluent or reconstitution at the point of use. In terms of where the Janssen COVID-19 vaccine

may best fit into a vaccination program, jurisdictions may consider use in places such as mobile or pop-up clinics, newly established vaccine administration sites, and sites that do not have freezer capacity such as in most adult healthcare provider (HCP) offices. It should be noted that the type of vaccine available at any given appointment should be transparent to the consumer. Recipients of this vaccine might include people who want to be fully vaccinated quickly, people who do not want to return or cannot return for a second dose, and mobile populations or homebound populations.

Ultimately, the WG thought that during a pandemic and under an EUA, offering Janssen COVID-19 vaccine to persons 18 years of age and older, according to established allocation and eligibility recommendations in a given jurisdiction, is an effective implementation strategy. This approach allows for jurisdictional flexibility, supports rapid vaccination and increases in population immunity, does not single out any particular group, and allows individuals to be vaccinated with the earliest vaccine available.

Regarding vaccine prioritization, the original goals of the COVID-19 Vaccine Program were to: 1) ensure the safety and effectiveness of COVID-19 vaccines; 2) reduce transmission, morbidity, and mortality of COVID-19 disease; 3) help minimize disruption to society and the economy, including maintaining healthcare capacity; and 4) ensure equity in vaccine allocation and distribution. As of February 27, 2021, more than 72 million doses of COVID-19 vaccine have been administered in the US. However, jurisdictions continue to face constrained supplies and continued reliance on large vaccination centers. Most jurisdictions are in Phase 1b or expanding into Phase 1c, and most states have made modifications to the ACIP prioritization framework²⁶. These modifications include either sub-prioritization or delayed vaccination of essential workers, adding eligibility age bands for people younger than 65 years of age, and sub-prioritization of high-risk medical conditions or requiring ≥ 2 conditions. Looking forward toward the next several weeks, vaccine manufacturers have made specific commitments by the end of March 2021²⁷. Pfizer has indicated that they will produce 120 million doses, Moderna committed to 100 million doses, and Janssen committed to 20 million doses. The fulfillment of these commitments will result in a significant increase in available vaccines compared to prior months.

Even with increased vaccine supply, a number of implementation challenges remain. There are a number of responses jurisdictions may consider to meet those challenges. First, adjudicating eligibility in large vaccination centers, particularly on the basis of essential worker status or high-risk medical conditions, can be difficult and time-consuming. It should be noted that verification of eligibility should not hamper throughput at large vaccination clinics. Medical care homes or PCPs may be better able to assess eligibility on the basis of underlying medical conditions. Another challenge is implementing the list of high-risk conditions. The CDC list relies on published studies and is not exhaustive. Certain conditions on the list encompass a wide range of severity. Therefore, clinical judgement may determine if rare conditions not on the list confer increased risk of severe COVID-19.

Another challenge is that the size of the eligible groups in Phase 1c may exceed vaccine supply. Jurisdictions may consider the addition of eligibility age bands for people younger than 65 years of age (e.g., 60-64 or 55-64 or 50-64) as supply permits. This may be particularly helpful in large vaccination settings. Jurisdictions also may consider prioritizing people with ≥ 2 high-risk conditions. Transmission in congregate settings (e.g., prisons, homeless shelters, or LTCFs)

²⁶ <https://energycommerce.house.gov/committee-activity/hearings/hearing-on-pathway-to-protection-expanding-availability-of-covid-19>

²⁷ <https://www.kff.org/other/state-indicator/state-covid-19-vaccine-priority-populations>

continues to be a challenge. Jurisdictions may consider offering vaccine to all unvaccinated staff and residents at the same time without waiting for eligibility of each individual group.

Another major challenge is promoting health equity while ensuring efficient vaccine distribution and administration. Some strategies jurisdictions can use to improve equitable vaccine distribution include: 1) using a SVI or other needs-based indexes to place vaccine clinics; 2) partnering with FQHCs such that they can be vaccination hubs and help to register eligible community members for vaccination; or 3) offering the Janssen COVID-19 vaccine as an option for populations for whom returning for a second dose would be difficult. Of course, community engagement and education will be important as new COVID-19 vaccines are authorized and recommended for use.

In terms of dosing intervals for mRNA vaccines, there are two issues. The first issue regards the potential risks and benefits of delaying the second dose of an mRNA vaccine. The second issue arises around the potential for a single dose of an mRNA vaccine for individuals with confirmed prior SARS-CoV-2 infection. As background for the issue of delaying the second dose, extended inter-dose intervals have been adopted by other national vaccine advisory groups and proposed by individuals in the US as a strategy to increase 1-dose coverage during a time when demand exceeds supply. Note that the current CDC guidance is that, "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 Pfizer-BioNTech and Moderna COVID-19 vaccines may be scheduled for administration up to 6 weeks (42 days) after the first dose."²⁸

With respect to delaying the second dose, in Phase I/II clinical trials, neutralizing antibodies did not show large increases until after receipt of the second dose. In Phase III trials, about 97% to 98% of recipients received both doses on schedule, which makes the study of prolonged intervals almost impossible with these data. The 1-dose VE estimates from those trials are between 50% to 90% and are higher when the follow-up time considered is that which happens at least 2 weeks after the first dose, thereby making the follow-up under study very short. There have been a number of early studies of real-world effectiveness of 1 dose of the vaccine. A matched case-control study in Israel²⁹ found effectiveness of a single dose preventing hospitalization to be 78% between 21 to 27 days post-dose 1. A prospective cohort study in Scotland³⁰ also found 1 dose to prevent hospitalization and found that VE reached a high of 85% 28 to 34 days post-dose 1, followed by a slight decline after that. It should be noted that the group with longer follow-up in that study had a higher proportion of older people.

In terms of the pros and cons of delaying the second dose, the pros are that this strategy could provide 1 dose protection to a larger number of people over the next several months. If 1 dose protection is high and persists, this could prevent more infections and deaths³¹. Most experts expect that boosting from the second dose is still likely to be effective, even at a longer interval. As for cons, lower neutralization antibodies could be protective against "wild-type" COVID-19,

²⁸ <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html>

²⁹ Dagan N, et al. NEJM, 2021

³⁰ Vasileiou E, et al. Lancet, preprint 2021

³¹ Accelerate COVID-19 Vaccine Rollout by Delaying the Second Dose of mRNA Vaccines <https://doi.org/10.1093/cid/ciab068>; The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence | medRxiv

but not novel variants³²⁻³³⁻³⁴. 1-dose vaccination could leave individuals susceptible to variants, providing selective pressure and increased transmission of variants³⁵. The estimates of effect for a single dose are imprecise and duration of protection after the first dose is unknown. Additionally, a prolonged interval would contradict FDA's EUA for a vaccine platform for which there is minimal experience.

In summary, the majority of WG members thought that there currently are insufficient data to increase recommended intervals and that there is important uncertainty regarding protection from the variants following 1 dose of mRNA COVID-19 vaccines. The next steps on this issue are to continue to monitor post-authorization effectiveness studies. Any updates to vaccine recommendations will be evidence-based, discussed publicly, and made in collaboration with the FDA.

Moving on to the question of a single dose of mRNA vaccine for individuals with confirmed prior SARS-CoV-2 infection, by way of background, there have been anecdotal reports of increased reactogenicity following vaccination among people with prior COVID-19. Additionally, recent published reports suggest high antibody response after 1 dose for individuals with prior SARS-CoV-2 infection. The current CDC guidance³⁶ states, "...while vaccine supply remains limited, persons with recent documented acute SARS-CoV-2 infection may choose to temporarily delay vaccination, if desired, recognizing that the risk of reinfection, and therefore the need for vaccination, might increase with time following initial infection."

Immunogenicity following vaccination among persons with prior SARS-CoV-2 infection was evaluated in 2 studies published in pre-print. Both studies assessed antibody titers after 1 dose in seropositive compared to seronegative individuals. Both studies showed higher antibody titers in seropositive individuals compared to seronegative individuals after 1 dose^{37, 38}. One available pre-print study evaluated reactogenicity following mRNA vaccination in seropositive and seronegative persons³⁹. This study found that localized injection site symptoms occurred with similar frequency between the two groups; however, systemic side effects occurred at higher frequency among individuals with pre-existing immunity. The reactogenicity was similar to symptoms reported for the second dose for people who did not have pre-existing immunity in the Phase 3 trials.

To summarize the pros and cons for the question of a single dose of mRNA vaccine for individuals with confirmed prior SARS-CoV-2 infection, the pros are that this strategy could free up second doses from seropositive persons to be provided to seronegative persons and that seropositive persons would not receive 2 doses of reactogenic vaccine. The cons are that current studies included individuals with confirmed antibodies to SARS-CoV-2. Not everyone with prior infection still has detectable antibodies and performing large-scale antibody screening prior to vaccination is not feasible. Also, correlates of protection are currently unknown.

³² Increased resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7 to antibody neutralization. 2021.01.25.428137v2.full.pdf (biorxiv.org)

³³ SARS-CoV-2 variant B.1.17 is susceptible to neutralizing antibodies elicited by ancestral Spike vaccines Microsoft Word - Shen_B117_ver10.docx (biorxiv.org)

³⁴ The E484K mutation in the SARS-CoV-2 spike protein reduces but does not abolish neutralizing activity of human convalescent and post-vaccination sera | medRxiv

³⁵ Epidemiological and evolutionary considerations of SARS-CoV-2 vaccine dosing regimens
<https://doi.org/10.1101/2021.02.01.21250944>

³⁶ <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html>

³⁷ Robust spike antibody responses and increased reactogenicity in seropositive individuals after a single dose of SARS-CoV-2 mRNA vaccine | medRxiv

³⁸ Single Dose Vaccination in Healthcare Workers Previously Infected with SARS-CoV-2 | medRxiv

³⁹ Robust spike antibody responses and increased reactogenicity in seropositive individuals after a single dose of SARS-CoV-2 mRNA vaccine | medRxiv

Therefore, it is not possible to extrapolate antibody studies directly to VE. In addition, there are currently only limited data and small studies and a single dose would contradict the FDA's evidence-based EUA for a vaccine platform for which there is minimal experience.

In summary, the majority of WG members thought that there are currently insufficient data to support changes to guidance or recommendations. The WG did feel that this is an important area to pursue further data in the coming weeks and months, and that jurisdictions could consider promotion of the existing guidance that those with prior infection may choose to temporarily delay vaccination for several months. The next steps are to collect and review further data on safety and reactogenicity, as well as immunogenicity and effectiveness of COVID-19 vaccines among individuals with prior infection. Any updates to the vaccine recommendations will be evidence-based, discussed publicly, and made in collaboration with the FDA.

In closing, Dr. Dooling posed the following questions for ACIP consideration and deliberation during the discussion period:

Janssen COVID-19 Vaccine

- Do you agree that offering Janssen COVID-19 vaccine to persons 18 years and older, according to established allocation and eligibility recommendations, is an effective implementation strategy?

Vaccination Prioritization

- What are the key challenges and opportunities of implementation guidance options for:
 1. Additional age eligibility brackets <65 years
 2. Eligibility based on 2 or more high risk conditions

mRNA Vaccine Dosing

- What additional data are needed to inform:
 1. Delay the second dose?
 2. Single dose of mRNA vaccine for individuals with confirmed prior SARS-CoV-2 infection?

Discussion Points

Janssen COVID-19 Vaccine: Do you agree that offering Janssen COVID-19 vaccine to persons 18 years and older, according to established allocation and eligibility recommendations, is an effective implementation strategy?

In terms of whether the Janssen COVID-19 vaccine is an effective strategy, Dr. Bernstein inquired as to whether there are data on the effectiveness of the implementation strategy with the two mRNA vaccines. When the phases were developed, there were 3 million LTCF residents and that discussion included giving the vaccine to the staff in the LTCFs. It was mentioned the previous day that although there are 3 million LTCF residents, 7 million doses have been administered in LTCFs.

Dr. Dooling indicated that evaluation of the implementation strategies is currently ongoing in a number of ways. Slide 30 includes more details on at least the procedural outcomes of how many doses have been delivered. More than 48 million people have been vaccinated with 1 or more doses, which accounts for approximately 19% of the US adult population 18 years of age

and older. Of the 7 million doses administered in LTCF, which were considered a priority in Phase 1a, over 1.5 million doses have been administered to LTCF staff.

Dr. Messonnier added that this is perhaps a larger topic than the time allotted during this meeting and that it is important to assess the safety and effectiveness of both the vaccines and vaccine strategies. There are a variety and series of studies that they can come back to the ACIP with that are evaluating the short-term effectiveness and duration of protection. Specifically, there is work now within CDC looking at the impact of the vaccine in LTCFs in which they are trying to disentangle the effect of vaccination and the effect of other mitigation measures. Similarly, there are studies ongoing to assess the effectiveness of the strategies among healthcare workers (HCW).

Dr. Kotton said that in thinking about where the new Janssen vaccine would be used, she would encourage enrichment and enhancement of the comorbidity list. It appeared that the list was suggesting that this could be determined by physicians, but she did not think this would be a realistic aspect. It would be helpful to have better guidance regarding the comorbidities, given that many states are relying on this list.

Dr. Messonnier acknowledged that this is a valid point that is under active discussion. There are many issues on which ACIP could provide helpful input, but in the limited time available they would like the members to focus on the Janssen vaccine and how to specifically alter, modify, or target Janssen's vaccine.

When discussing eligibility for the Janssen vaccine, Ms. Stinchfield (NAPNAP) suggested also mentioning those for whom the vaccine would be contraindicated.

Dr. Dooling indicated that CDC is not aware of any contraindications and the FDA information does not include any specific contraindication outside of an allergic reaction to any of the vaccine components.

Dr. Long agreed with the WG's interpretation that this is not an inferior vaccine and instead of talking about who should not receive it, they should talk about how to further the desire to immunize all people by particularly discussing targeting the use of this vaccine. It could and should be prioritized to what are perceived to be difficult-to-reach populations (e.g., homeless, those without access to transportation, people who cannot take off of work for 2 doses without losing income, those who do not have easy access to the internet to get appointments easily) and how to best do this without causing more unworkable recommendations. They should give guidance to further the goal to increase more people and decrease inequity. She is convinced by the data shown that this vaccine is comparable to the others and this one can be given in 1 dose.

Dr. Daley felt that there were some negatives to separating the Janssen vaccine out (e.g., less value, would give local jurisdictions less flexibility, would be less efficient as a delivery strategy, and is less evidence-based). He agreed with and supported the statement that "offering Janssen COVID-19 vaccine to persons 18 years and older, according to established allocation and eligibility recommendations, is an effective implementation strategy."

Dr. Hahn (CSTE) indicated that the National Governors Association (NGA) and Kaiser Family Foundation (KFF) both have updated tables state-by-state:

- https://www.nga.org/wp-content/uploads/2021/02/State-Phased-Vaccine-Distribution_2.17.pdf
- KFF, updated as of 2/22: <https://www.kff.org/report-section/state-covid-19-data-and-policy-actions-policy-actions/>

In terms of implementation guidance, Dr. Sonja Hutchins expressed concern that if ACIP/CDC state that the Janssen vaccine should be used in mobile clinics, for certain populations or communities considered hard-to-reach, this may introduce a level of mistrust because it is a single dose vaccine and might lead to increased hesitancy. Therefore, she did not support targeting mobile clinics. Those who have run mobile clinics for vaccination know that they can return to those communities to give another dose. They must be very careful to understand what might be some of the unintended consequences of targeting communities of color, who some may think are hard-to-reach when they are reachable.

Dr. Fryhofer (AMA) said that speaking as a practicing general internist, she has a lot of immunocompromised patients. They do not recommend live attenuated influenza vaccine (LAIV) as a first line for these patients. In terms of thinking about who to give this vaccine to now that there are two different platforms, she wondered whether additional thought should be given to immunocompromised patients. There is good experience using the Janssen platform and the company shared the previous day that they have given this vaccine platform to over 193,000 people, including pregnant women, children, and infants. However, when ACIP asked about the specifics of giving this vaccine during pregnancy, the manufacturer indicated that these data have not been published. She wondered at this time whether they felt totally comfortable giving a viral vaccine to immunocompromised patients.

Dr. Dooling reiterated that being immunocompromised is not a contraindication to this vaccine. The vaccine itself is not considered live as it is not capable of replication, which differentiates it from live vaccines.

Ms. Bahta indicated that she is very much in support of moving forward using the established allocation and eligibility recommendations for the Janssen vaccine. She believes that states and local jurisdictions appreciate the nimbleness that this vaccine provides and it really should not have preference of one over another, given the potential for unintended consequences or sending an indirect message that it is not equivalent. It is a very nimble vaccine that is very helpful for the response.

Dr. Lee stated her agreement that for Question 1, the Janssen vaccine should be offered as an equivalent to other available vaccines to protect against COVID. In terms of clarifying questions, there is extreme variability in the way allocations are done state-by-state and sometimes county-by-county. She called upon the American College of Obstetricians and Gynecologists (ACOG) to comment on whether there are any difference in the ability to offer vaccine, particularly the Janssen vaccine, to pregnant women who wish to be vaccinated if, for example, an mRNA vaccine is not available.

Dr. Eckert (ACOG) indicated that ACOG does not have a preference about the vaccines. They felt that moving ahead with using the Janssen is appropriate in pregnant patients.

Dr. Drees (SHEA) agreed with others that the Janssen vaccine should be offered similar to the other two available vaccines to everyone who is eligible. HCWs have had access to the mRNA vaccine from the beginning, but many remain unvaccinated. Anyone who remains unvaccinated should have access to the Janssen vaccine as well. Some people may have a preference for a single dose, uncertainty about the mRNA technology, or other reasons why they might want the Janssen vaccine instead. It sends a good message that they are comfortable giving this vaccine to HCW and not just other eligible people.

Dr. Goldman (ACP) said that from the ACP perspective, he certainly thinks the ethical framework and allocation strategy that has been previously recommended is well thought out and favors maintaining the current strategy. They should look at all of the vaccines as somewhat interchangeable in the sense of getting the vaccine to as many people as possible. His concern with chronic conditions is that many jurisdictions are requiring physicians to certify patients' health conditions, putting them in the precarious situation of making the patient have to disclose protected health information, patients not receiving vaccination who do not have access to healthcare, and/or the physicians having to certify health conditions. He also expressed concern with preferentially going to certain jurisdictions and making it seem that this vaccine is being reserved for certain areas, minorities, and people of color. This may have the unintended consequence of making it seem like an inferior vaccine. It must be messaged correctly that this vaccine is effective, everyone should get it, it needs to go out to as many people as possible just as the other vaccines do, and it is important to respect minorities and people of color to make sure that the frontline gets it. This is why age-based strategies offer him great pause and concern in terms of ethics and equity.

Dr. Sanchez noted that based on what Janssen presented the previous day and in agreement with what ACOG said, from a neonatologist standpoint, he does not see any concerns about contraindications in pregnancy from a fetal standpoint to be vaccinated.

Dr. Howell (AIM) indicated that AIM surveyed its 64 awardees charged with allocating COVID-19 vaccine and found that almost 60% are waiting for ACIP's recommendations in terms of how to allocate the Janssen vaccine. AIM would appreciate any guidance that could be provided. It is likely that this vaccine will have to be allocated toward certain HCP in order to prevent providers from having multiple types of vaccine on hand, which could cause administration errors. It is likely that they would allocate toward public health or pharmacies in order for it to be allocated easier logistically and to prevent vaccine administration errors by having multiple vaccines on hand.

Dr. Poehling agreed with the first question that the Janssen COVID-19 vaccine is 93% protective against hospitalizations and deaths. It is known that there is far more demand than supply for vaccines. Giving jurisdictions flexibility makes sense to her. They also need to address the fact that there is a decrease in the lifespan among Black and Brown communities of 1.9 and 2.7 respectively in the last year.

Dr. Romero said he thought the Janssen vaccine could be used widely across groups. ACIP is at a disadvantage in that initial reports on this vaccine focused on the differences of vaccine efficacy compared to the previous 2 vaccines. Messaging must go to all recipients that this vaccine is effective in prevention of hospitalizations and deaths. This is what he has been stressing to the constituents in his state.

Vaccination Prioritization: What are the key challenges and opportunities of implementation guidance options for: 1) Additional age eligibility brackets <65 years; and 2) Eligibility based on 2 or more high risk conditions.

Referring to the list of high-risk conditions that currently appear on the CDC website, Dr. Poehling expressed concern that the more frequent it is, the more likely it is going to show up. For example, thinking mechanistically, Type 1 and Type 2 diabetes are more similar than different and they both cause many problems. However, Type 1 diabetes is not on the list because it is less frequent. She suggested that perhaps they could adopt the influenza recommendations for high-risk conditions so that less common conditions are not excluded.

Dr. Romero indicated that individual states already are modifying the definition of diabetes to include Type 1.

Dr. Hayes (ACNM) asked whether there are any data on the variety of the guidelines from state-to-state in terms of how each state has made its own decisions about who are the priorities for the vaccines, and whether this might be useful moving forward.

Dr. Romero indicated that this information does exist from a number of sources, including CDC.

As a reminder, Dr. Dooling showed a schematic (Slide 31) of how prioritization was laid out when the ACIP voted on this matter in December 2020. Phase 1a included LTCF and HCP; Phase 1b included persons 75 and older and frontline essential workers; and Phase 1c included persons 65 to 74 years of age, other essential workers, and persons 60 to 64 years of age with high-risk medical conditions. She also showed the number of unique individuals estimated to be in each of those categories (Slide 32). A lot has happened since the time that the ACIP last voted. Many jurisdictions have adapted the guideline to their local needs and have moved to include all persons 65 and older earlier in their prioritizations, which has expanded Phase 1b.

Regarding vaccination prioritization, Dr. Lee said that she felt very challenged by ensuring that they continue to stress equity as a focus for implementation of the COVID Vaccination Program. Having information about age, race, and ethnicity in terms of severe disease, hospitalizations, and deaths would be incredibly helpful to know in terms of what the intended and unintended consequences might be. It also will be helpful to understand how comorbidities layer in. She worries about having additional age eligibility brackets, decrementing by 5 years at a time, because that functionally delays the ability to potentially effectively reduce deaths, particularly where there has been a disproportionate share of infection and severe disease in minority populations. She challenged them to think about implementation efforts in this space. Age alone does not tell the story clearly. The question about comorbidities has come up in terms of whether there are additional comorbidities in these age groups. The risk is not even across age groups. Someone who has multiple comorbidities and is 30 or 40 years of age might carry a different risk of mortality and hospitalization than somebody who is 50 years of age and perfectly healthy. She expressed her hope that they would continue to bring this back into view for those on the frontline who are trying to figure out how to best vaccinate given the resources they have.

Referring to Slides 40 and 41, Dr. Dooling highlighted data on deaths in 2020 that were associated with COVID-19. This basically tells them that for minority groups, a higher proportion of deaths occurred among younger age groups. For White, non-Hispanic groups as has come to be expected, as the older age groups take up a higher and higher proportion of the deaths among that particular race/ethnicity group. The opposite trend is occurring in other minority

groups, whereby the highest proportions of deaths are happening among people in their 30s, 40s, and 50s.

Dr. Romero emphasized that he is not in favor of eligibility brackets under 65 years of age, which is being implemented in some states. While it is an easier way to distribute vaccine among large populations in the US, it will lead to inequity. Dr. Dooling presented data earlier that clearly showed this. In the rush to administer vaccine, equity cannot be sacrificed. That has been a primary principle of the ACIP in developing these guidelines and they need to stand by that. Dr. Lee agreed completely.

Dr. Poehling also agreed with Dr. Romero's statement and the rationale behind it for eligibility. She does think that the high-risk conditions are concerning. Dr. Goldman explained earlier that he is personally being asked to sign off on conditions. She encouraged ACIP to think about simplifying the high-risk conditions to something like those for influenza vaccine, because they seem to be very similar. She worries that saying 2 or more conditions will create administrative barriers.

Dr. Dooling called upon the SME who is working on the list of high-risk conditions, Dr. Naeemah Logan to speak to future directions.

Dr. Logan responded that in attempting to answer this question, it may be helpful first to provide some context to clarify. The primary purpose of the list on the consumer webpage is and always was to inform individuals about risks, but the list is not exhaustive and does not include every condition that may increase one's risk of getting COVID-19. This is clearly stated on the current webpage. They understand that ACIP provides a framework for decision-making regarding prioritization and realize the challenges everyone is facing. They hope that HCP and jurisdictions will consider additional conditions as consideration for vaccination.

Dr. Daley reminded everyone that he raised two issues about age bands on a COVID-19 Vaccines Workgroup call, in part because he was asked by local public health who said they were struggling to figure out how to implement that at mass vaccination clinics. While he appreciates the challenges that local public health is facing with implementation, the solution is not to abandon the strategy that has been taken for exactly the reasons Dr. Romero outlined, given that it is more likely to increase inequality.

Dr. Long said she found this issue to be somewhat more difficult, not because of the principle but in thinking about how unnamable the current recommendations are. Some states and jurisdictions where HCP are currently giving vaccine to their patients who are much younger. She is also concerned that multigenerational families are not eligible thus far, most of which have younger people who are taking care of older individuals. Although this is being done because of principle and equity, the translation of guidance has resulted in inequity in some situations. Those who have good follow-up in healthcare systems who do not have underlying conditions may be getting vaccinated, while those who do not have a medical home, are less well-cared-for, or are less informed about ways to get on lists are not getting vaccinated. She expressed her hope that ACIP could clarify at least the risk conditions to make that manageable and that this recommendation does not stand for longer than 30 to 60 days.

Dr. Talbot noted that her other daytime job is collecting information on people who are hospitalized with COVID-19 and agreed that the most common conditions in the US are the ones that come up first and the rare ones do not. Simplifying the high-risk conditions as they did for influenza would have great impact. However, she would not use 2 or more high-risk conditions because there could be a well-controlled diabetic and well-controlled hypertensive who get in line before someone who has poorly controlled diabetes. She also did not think they should start trying to make hierarchies of whose disease is more severe than others. The impact of certain diseases compared to others is not known with regard to one's risk for COVID-19. The goal is to vaccinate everyone with a high-risk condition and ultimately everyone in the US. They have to stress to people that they are working their way to getting everyone vaccinated and to please be patient. She also emphasized that they should not expect anyone to police this. There are going to be people who will try to cheat the system. It is not worth wasting time arguing about that. She supported continuing with the recommendations as designed and simplify and be more inclusive for people with high-risk conditions.

Dr. Bell stressed that the ACIP wants to be as helpful as possible at any juncture to further the goals as Dr. Dooling laid them out. ACIP is providing guidance or advice to CDC. Dr. Messonnier asked them earlier to tell CDC what ACIP thinks about the Janssen vaccine, for which they provided feedback. Now they were on the issue of the list and, as everyone could hear and as she has been hearing as the Chair of the WG for quite some time, there is a lot of anxiety and displeasure with this list. While she recognizes that they are at a certain juncture, she was hopeful that within a month they would not have to worry about this list. The list is currently a problem and barrier for many on the frontline in many states. Therefore, there is a need to address this list in some way. They heard from Logan at CDC that what they are doing in terms of the list is not actually going to address the concerns raised by the committee. One could make the case that the reality is that ACIP has used this list and cannot rewrite history. She felt that it would be very difficult for the ACIP to do anything other than state what they think the objectives of improving the list should be. They heard that there are some concerns about complexity, so she expressed hope that CDC address these concerns that they were hearing loud and clear about current status of this list.

Dr. Sanchez agreed that it is a difficult decision to go to less than 65 years of age. He thinks using the age strata in terms of who receives the vaccine is the easiest route because at least there is something concrete upon which to decide. Among the states that have vaccinated those over 65 years of age, it is because that is where the majority of deaths are occurring. He understands the need for equity, but also understands high-risk conditions that put some individuals at higher risk are essential to consider. He also agreed that documentation would not be feasible. In addition, he agreed that they must start including contacts of individuals who are high-risk themselves, particularly the elderly. Those who care for elderly individuals or other compromised individuals at home should be prioritized.

Dr. Bernstein noted that based on the phased allocation, the number of unique persons in each group for Phases 1a, 1b, and 1c is 202 million. With 72 million doses already administered and 240 additional anticipated within a month from the 3 manufacturers, he thought that broadening this to reach as many people as possible might be appropriate at this point in order to include those in different age groups and with high-risk conditions without documentation from any provider.

Dr. Poehling add that 160 to 170 million doses were expected to be distributed by the end of March, so a lot more people should be able to be vaccinated. She also expressed concern about requiring 2 or more high-risk conditions, given the difficulty in trying to judge who that is and the potential to create health inequities. She wondered whether the *MMWR* update would offer an opportunity to provide an update on high-risk conditions as well.

Dr. Cohn clarified that the *MMWR* would discuss only the Janssen recommendation made the previous day, and that CDC was discussing a separate web-based implementation guidance document that is nimble and can be updated frequently. This would address how to think through the list, which already was in the process of being updated as described earlier.

Dr. Lee agreed that they should not state 2 or more high-risk conditions, given that there is not enough information to compare high-risk conditions. While that information is needed, trying to implement based on that makes an assumption about the science and data that are simply not available. Among the proportion of people hospitalized in pediatric and young adult populations, the most common condition is obesity. That does not necessarily mean that they have other comorbid conditions. It is important to be inclusive in the ability to vaccinate the younger adult and older teen populations, particularly for younger populations who may not have multiple comorbidities. That also includes an example of pregnancy, which is a high-risk medical condition for which requiring 2 conditions makes no sense as that would exclude the majority of pregnant women. She strongly stated that she did not support moving toward 2 or more high-risk conditions for implementation. For the record, she said she thought that families of individuals who cannot get vaccinated but are at the highest risk should be prioritized above the general population, such as stem cell transplant patient. She emphasized that at this stage in the vaccination program, they must move away from a punitive approach to an improvement mindset in thinking about vaccine implementation. Many facilities are extremely worried about getting it exactly right, it is actually inhibiting access except for those who are the strongest advocates. The more restrictions they place on things, the more likely it will continue to inadvertently create a disincentive for enhanced outreach. Given that the intent is to vaccinate everyone anyway, other than in the most egregious of situations, access should be provided and states and jurisdictions should move toward a more positive mindset.

Dr. Hutchins (NMA) expressed gratitude for sharing the slide of the higher proportion of deaths among younger age groups among populations of color compared with non-Hispanic White populations. She asked whether CDC had a slide of current age-specific risk of severe COVID-19 disease (hospitalization and death) by race and ethnicity?

mRNA Vaccine Dosing: What additional data are needed to inform: 1) delay the second dose; and 2) a single dose of mRNA vaccine for individuals with confirmed prior SARS-CoV-2 infection?

Dr. Sanchez asked whether the study showing reactogenicity after the first dose was for both the Pfizer and BioNTech mRNA vaccines.

Dr. Oliver indicated that the pre-print article refers to a single dose of mRNA and does not specify between the Pfizer and BioNTech mRNA vaccines. CDC does not have reason to think that there would be substantial difference between the two.

Dr. Sanchez wondered about the current guidance in terms of the second vaccine dose to 6 weeks only and where that comes in, given that it will have issues with respect to later doses.

Dr. Dooling clarified that the current guidance is to adhere to the 3- to 4-week interval as closely as possible, but that a 6-week interval may be used for the purpose of scheduling in extenuating circumstances where that is not possible. The 42-day interval was used as the analytic interval in the Moderna and Pfizer analyses, with very few doses were given out that far.

Dr. Sanchez disagreed with delaying the second dose of the mRNA vaccine at this time and emphasized that they need to follow the science from the RCTs showing optimal efficacy in order to bring this pandemic under control. Eliminating and delaying a second dose at this time has the potential to raise questions about whether the vaccine is needed at all. Therefore, they should abide by the current recommendations and guidance that are supported by what the evidence has shown thus far. Whether a single dose is sufficient for those with confirmed prior infection is an intriguing and important question. Gathering additional information on this will be extremely beneficial, because it is possible that these individuals may not require a second dose if one infection turns out to develop an anamnestic response such that the vaccine would act as a booster dose.

Dr. Talbot did not feel the need for more data on the second question as they know there is a prime boost with the first dose, and the data they were shown are sufficient to make a decision rather than waiting on the second part of the question.

Ms. Bahta agreed with Dr. Sanchez said about the second dose. More information is needed, especially in light of variance development. For the second question, it made sense to her from a priming and boosting standpoint that only a single dose may be necessary. However, she would like to know more about the behavior of coronaviruses and how the vaccination might compare to the reoccurrence of diseases.

Dr. Lee agreed that there are not sufficient data to delay the second dose beyond what is currently recommended of up to 6 weeks. If there are large differences identified, they can be dynamic about their decision-making process. She also agreed with Dr. Talbot in part because she does feel that the infection is the prime and the vaccine is the boost. She did not see any advantage to giving a second dose either from an immunogenicity standpoint or from a safety standpoint. She feels like the second dose is not necessary and felt that she had sufficient evidence for that now.

Dr. Long agreed with everything stated thus far for all of the reasons presented. Delaying a second dose would be very confusing. Regarding the second question, she would like to see more data on harm or systemic reactions among people who previously had coronavirus disease and were then vaccinated in terms of whether they needed a second dose. Over time with more data, they may even learn that perhaps people who had coronavirus disease do not need a first dose. Her own brother who lives in Alaska where there was no coronavirus in March became severely ill, recovered fully, and had a central nervous system (CNS) vasculopathy 8 to 9 months later for no explicable reason other than perhaps related to coronavirus and from which he recovered. He got his first vaccine and had a recrudescence of the CNS symptoms. Whether that was from coronavirus is unknown. It may have been from an inflammatory response. It is important to know whether the first dose confers enough benefit to be worth the risk of harm. For her, it seems that the second dose would have much more likelihood of harm than benefit that perhaps this should remain a relative contraindication until more is known.

Dr. Romero agreed with the theory and science already presented, but it is important to remember that the data available on the boosting after the first dose in individuals previously infected are in individuals who already have adequate or high titers of antibody to SARS-CoV-2. The question in his mind regards what happens to individuals with no antibody or very low

antibody at the time of being sampled. While he agreed that an anamnestic response is most likely to occur, it is not clear whether people have enough memory B cells available to boost to levels that would be protective. Those are the studies that he thinks will need to come forward.

Ms. Stinchfield (NAPNAP) agreed with Dr. Romero that they need to understand the longevity of protection. She has not been a fan of the recommendation to delay the second dose due to concerns about variants. Reflecting on the good science/ethics/implementation triangle, most scheduling systems are developed for the 2 doses and the first and second appointments are made at the same visit. To change that would be a significant lift on the ground.

Dr. Bernstein agreed that for the first question, they should go where the science leads them and should stay where they are at the moment. He also agreed with Dr. Romero and others regarding the second questions, given that more data are needed about correlates of protection, duration of immunity, and how the current mRNA vaccines fit with the variants that are increasing in the community. With that in mind, he was not enthusiastic about a single dose in those with confirmed prior SARS-CoV-2 infection.

Dr. Bell agreed with others on Question 2, including on making this a priority in terms of obtaining additional data. They certainly do not want to do harm. She was not comfortable making a recommendation because it makes immunologic sense. Insufficient information is known about the unintended consequence. There is also the issue about knowing who has antibodies and who does not and what happens with a single dose for those who do not have antibody. In terms of what ACIP can do, it would be very useful for the committee to send a strong message that this needs to be a priority for study. It may not be that difficult logistically to obtain this additional data in order to make evidence-based recommendations on this topic. The current recommendation about how long after SARS-CoV-2 infection a person should wait to get vaccinated is to consider waiting for 90 days. Her understanding anecdotally is that a lot of people rushed to get a vaccine after infection. She wondered whether people had an opinion about whether it would be useful to clarify or strengthen the guidance about waiting for a while after a confirmed infection even to get a single dose.

Dr. Sanchez emphasized that those who have had symptomatic disease very likely will have an immunologic response, which raised concerns for him about having the first dose. He also thinks guidance is needed in terms of the 6-week delay after the first dose, as well as those who are beyond the 6-week delay for the second dose.

Dr. Fink (FDA) supported the statements made by Drs. Romero, Bell, and others. They all want to make the best recommendations possible to cover the universe of potential circumstances. He acknowledged that the ACIP has the difficult task of developing recommendations to cover situations and circumstances not covered in the FDA labeling and even on occasion makes recommendations that are off-label for approved products when this makes sense and is backed by data. The fact is that at this time, these COVID-19 vaccines remain unapproved products that are available under EUA. The label used under EUA is based on data that are sufficient to support that use, but are rapidly evolving and that FDA continues to gather. He agreed that gathering more data to inform use in previously infected individuals and to inform potential changes to dosing intervals should be priority. At this time, they certainly do not have data to support any of the types of proposals being discussed in terms of the labeling of these unapproved products that are made available under EUA.

Dr. Kotton said that she was comfortable with the immunologic data for Question 2 in terms of a single dose for confirmed infection. There may be a need for boosters in the future, which will be an interesting area for which they do not have significant information. Hopefully, more information will be available about correlates of protection that will help ACIP make good decisions. While a single dose of mRNA vaccine would be acceptable for healthy people who have had COVID-19 infection, but it probably would not be adequate for immunocompromised populations. It will be challenging to create a guideline that would fit everybody and would probably require distinguishing between different at-risk cohorts.

Referring to Slide 23 in Dr. Dooling's presentation, Ms. McNally noted that the third bullet under next steps said that any update would be made in collaboration with FDA. She wondered whether this involves a formal collaboration process or if these are ongoing discussions and how the public becomes aware the discussions. In terms of reactogenicity among persons with prior infection, she wondered how they would be made aware.

Dr. Dooling responded that there are numerous mechanisms for FDA and CDC collaboration, including informally as agencies within the HHS structure and additionally through the collaborations with ACIP, with Dr. Doran Fink being the *ex officio* member who represents FDA at the ACIP table and also sits on the COVID Workgroup of the ACIP to name a couple of mechanisms. Regarding reactogenicity, there are no current mechanisms to state that there is any difference in reactogenicity for persons who may have had prior infection.

Dr. Cohn added that CDC is currently assessing its data sources and ability to examine whether there is increased reactogenicity or AEs among people who previously have had infection, and should soon have an update for the ACIP.

Clinical Considerations for Use of COVID-19 Vaccines

Jessica MacNeil

National Center for Immunization and Respiratory Diseases Centers for Disease Control and Prevention

Ms. MacNeil reviewed CDC's clinical considerations for the use of COVID-19 vaccines in the US. CDC's clinical considerations for mRNA COVID-19 vaccines were presented to ACIP in December 2020 and are published on the CDC website. During this session, she presented proposed updates to the clinical considerations to include information on the newly authorized Janssen viral vector COVID-19 vaccine. In addition, she highlighted other key updates that have been raised as clinical considerations since the December 2020 ACIP meeting. These considerations will continue to be updated as additional information becomes available or if additional vaccine products are authorized. She also noted that people can sign up on the CDC website to receive email updates when the clinical considerations are updated.⁴⁰

Beginning with vaccine administration, COVID-19 vaccines are administered intramuscularly as either a 2-dose series or as a single dose. One valid vaccination series should be administered, meaning either a 2-dose mRNA COVID-19 vaccine series or a single dose of Janssen COVID-19 vaccine. Individuals are not recommended to receive more than one complete COVID-19 vaccination series at this time. The vaccines' authorized age groups, dose volumes, number of doses in the vaccine series, and the interval between doses are shown in this table which is also included in the clinical considerations document:

⁴⁰ <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html>

Vaccine	Dose	Dose Volume	Number Doses/Series	Interval Between Doses
Pfizer-BioNTech	30 µg	0.3 ml	2	3 weeks (21 days)
Moderna	100 µg	0.5 ml	2	1 month (28 days)
Janssen	5×10 ¹⁰ viral particles	0.5 ml	1	N/A

Any of the currently authorized COVID-19 vaccines can be used when indicated. The ACIP does not state a product preference. However, the COVID-19 vaccines are not interchangeable and the safety and efficacy of a mixed product series has not been evaluated. In exceptional situations where the first dose of an mRNA COVID-19 vaccine was received but the patient is unable to complete series with either the same or different mRNA COVID-19 vaccine (e.g., contraindication), a single dose of Janssen COVID-19 vaccine may be administered at minimum interval of 28 days from the mRNA COVID-19 vaccine dose. However, these patients should be considered to have received a valid, single-dose Janssen vaccination, not a mixed mRNA/viral vector series. The currently authorized COVID-19 vaccines are all inactivated vaccines. COVID-19 vaccine should be administered alone with a minimum interval of 14 days before or after administration with any of the other vaccines. However, a shorter interval may be used in certain situations where the benefits of vaccination are deemed to outweigh the potential unknown risks of vaccine co-administration (e.g., tetanus toxoid vaccine for wound management, rabies vaccination for post-exposure prophylaxis, or measles or hepatitis A vaccination during an outbreak) or to avoid barriers or delays to COVID-19 vaccination (e.g., LTCF residents or HCP who received influenza or other vaccinations prior to admission or onboarding).

Regarding the considerations for vaccination among people with prior or current SARS-CoV-2 infection, persons with prior SARS-CoV-2 infection should be offered vaccination regardless of history of prior symptomatic or asymptomatic SARS-CoV-2 infection. Data from clinical trials suggest that the currently authorized COVID-19 vaccines can safely be administered to persons with evidence of a prior SARS-CoV-2 infection. Viral testing for current infection or serologic testing for prior infection is not recommended for the purpose of vaccine decision-making. Vaccination among persons with known current SARS-CoV-2 infection should be deferred until the person has recovered from acute illness if person had symptoms *and* criteria have been met to discontinue isolation. While there is no recommended minimal interval between infection and vaccination, current evidence suggests that reinfection is uncommon in the months after initial infection. While vaccine supply remains limited, persons with recent documented SARS-CoV-2 infection may choose to temporarily delay vaccination if desired, recognizing that the risk of reinfection and therefore the need for vaccination might increase with time following initial infection.⁴¹

There are currently no data on the safety and efficacy of COVID-19 vaccines in persons who received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment. Based on the estimated half-life of such therapies and evidence suggesting that reinfection is uncommon in the 90 days after initial infection, vaccination should be deferred for at least 90 days. This is a precautionary measure until additional information becomes available to avoid potential interference of the passive antibody therapy with vaccine-induced immune responses. This recommendation does not apply to persons receiving antibody therapies not specific to COVID-19 treatment. There is currently no recommended minimum interval between antibody therapies not specific to COVID-19 treatment and COVID-19 vaccination.⁴²

⁴¹ <https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html>; <https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html>

⁴² <https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html>

In terms of COVID-19 vaccinations in special populations, COVID-19 vaccines can be administered to persons with underlying medical conditions who have no contraindications to vaccination. The clinical considerations document includes information for vaccination of immunocompromised persons; those with autoimmune conditions; and people with a history of Guillain-Barré syndrome (GBS), Bell's palsy, and dermal filler use. Clinical trials have demonstrated similar safety and efficacy profiles in persons with underlying medical conditions, including those that place them at increased risk for severe COVID-19 compared to persons without comorbidities.⁴³

Persons with HIV infection, other immunocompromising conditions, or who take immunosuppressive medications or therapies might be at increased risk for severe COVID-19. Immunocompromised individuals may receive COVID-19 vaccine if they have no contraindications for vaccination, but should be counseled about the unknown vaccine safety profile and effectiveness in immunocompromised populations, as well as the potential for reduced immune responses and the need to continue to follow current guidance to protect themselves against COVID-19.⁴⁴

Observational data have demonstrated that pregnant people with COVID-19 have an increased risk of severe illness, though the absolute risk is low. Additionally, they may be at increased risk for adverse pregnancy outcomes. There are currently limited data on the safety of COVID-19 vaccines in pregnant people. No safety concerns were demonstrated in animal developmental and reproductive toxicity (DART) studies in any of the animals that received any of the 3 authorized COVID-19 vaccines. In addition, the adenovirus vector platform used in the Janssen COVID-19 vaccines has been used for other vaccine development programs that included pregnant people vaccinated during any trimester, including a large-scale Ebola vaccination trial. No adverse pregnancy-related outcomes, including infant outcomes, were determined to be related to the vaccines in these trials. Based on current knowledge, experts believe that COVID-19 vaccines are unlikely to pose a risk to the pregnant person or fetus, because the currently authorized COVID-19 vaccines are all inactivated vaccines. However, the potential risks of COVID-19 to the pregnant person and fetus are unknown because these vaccines have not been studied in pregnant people. Clinical trials to evaluate safety and efficacy of COVID-19 vaccines in pregnant people are planned or underway. The vaccine manufacturers are following outcomes in people in clinical trials who became pregnant.⁴⁵

Pregnant people may choose to receive a COVID-19 vaccine when eligible. A conversation between the patient and their clinical team may assist with the decision about the use of COVID-19 vaccine, though a conversation with a HCP is not required prior to vaccination. When making a decision, pregnant people and their HCP should consider the level of COVID-19 community transmission, the patient's personal risk of contracting COVID-19, the risks of COVID-19 to the patient and the potential risks to the fetus, the efficacy and side effects of the vaccine, and the limited data about use of the vaccine during pregnancy.

⁴³ <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>

⁴⁴ <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>;
<https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html#phrecs>

⁴⁵ <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnancy-breastfeeding.html>;
<https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/special-situations.html>

Recommendations for contraindications and precautions for COVID-19 vaccines are summarized in this table:

Contraindications and precautions for COVID-19 vaccines		
CONTRAINDICATION TO VACCINATION	PRECAUTION TO VACCINATION	MAY PROCEED WITH VACCINATION
<p>History of the following:</p> <ul style="list-style-type: none"> Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to component of the vaccine¹ Immediate allergic reaction² of any severity after a previous dose or known (diagnosed) allergy to a component of the vaccine¹ <p>Actions:</p> <ul style="list-style-type: none"> Do not vaccinate. Consider referral to allergist-immunologist. Consider other vaccine alternative.¹ 	<p>Among persons without a contraindication, a history of:</p> <ul style="list-style-type: none"> Any immediate allergic reaction² to other vaccines or injectable therapies¹ <p>Note: persons with a contraindication to mRNA COVID-19 vaccines have a precaution to Janssen COVID-19 vaccine, and vice versa³</p> <p>Actions:</p> <ul style="list-style-type: none"> Risk assessment Consider referral to allergist-immunologist 30-minute observation period if vaccinated 	<p>Among persons without a contraindication or precaution, a history of:</p> <ul style="list-style-type: none"> Allergy to oral medications (including the oral equivalent of an injectable medication) History of food, pet, insect, venom, environmental, latex, etc., allergies Family history of allergies <p>Actions:</p> <ul style="list-style-type: none"> 30-minute observation period: persons with history of anaphylaxis (due to any cause) 15-minute observation period: all other persons

¹ See Appendix C for a list of ingredients. Persons with a contraindication to one of the mRNA COVID-19 vaccines should not receive doses of either of the mRNA vaccines (Pfizer-BioNTech or Moderna).
² Immediate allergic reaction to a vaccine or medication is defined as any hypersensitivity-related signs or symptoms consistent with urticaria, angioedema, respiratory distress (e.g., wheezing, stridor), or anaphylaxis that occur within four hours following administration.
³ Includes persons with a reaction to a vaccine or injectable therapy that contains multiple components, one of which is a vaccine component, but in whom it is unknown which component elicited the immediate allergic reaction.
⁴ Polyethylene glycol (PEG) is an ingredient in both mRNA COVID-19 vaccines, and polysorbate 80 is an ingredient in Janssen COVID-19 vaccine. PEG and polysorbate are structurally related, and cross-reactive hypersensitivity between these compounds may occur. Persons with a contraindication to mRNA COVID-19 vaccines (including due to a known [diagnosed] allergy to PEG) have a precaution to Janssen COVID-19 vaccine. Among persons who received one mRNA COVID-19 dose but for whom the second dose is contraindicated, consideration may be given to vaccination with Janssen COVID-19 vaccine (administered at least 28 days after the mRNA COVID-19 dose). Persons with a contraindication to Janssen COVID-19 vaccine (including due to a known [diagnosed] allergy to polysorbate) have a precaution to mRNA COVID-19 vaccines. In patients with these precautions, vaccination should be undertaken in an appropriate setting under the supervision of a health care provider experienced in the management of severe allergic reactions. Consider referral to allergist-immunologist.

This table summarizes information related to the contraindications and precautions by vaccine type:

Information by vaccine type				
<table border="1"> <thead> <tr> <th>mRNA COVID-19 vaccines</th> <th>Janssen COVID-19 vaccine</th> </tr> </thead> <tbody> <tr> <td> <ul style="list-style-type: none"> Persons with contraindication to one mRNA vaccine should not receive doses of either vaccine (Pfizer BioNTech or Moderna) Persons with a contraindication to mRNA COVID-19 vaccines (including due to a known allergy to PEG) have a precaution to Janssen COVID-19 vaccine.* In persons who received one mRNA COVID-19 dose but are contraindicated to receive the 2nd dose, consideration may be given to vaccination with Janssen COVID-19 vaccine (at least 28 days after mRNA dose).* </td> <td> <ul style="list-style-type: none"> Persons with a contraindication to Janssen COVID-19 vaccine (including due to a known allergy to polysorbate) have a precaution to mRNA COVID-19 vaccines.* </td> </tr> </tbody> </table> <p><small>*In patients with these precautions, vaccination should be undertaken in an appropriate setting under the supervision of a health care provider experienced in the management of severe allergic reactions. Consider referral to allergist-immunologist. Note: Polyethylene glycol (PEG) is an ingredient in both mRNA COVID-19 vaccines, and polysorbate 80 is an ingredient in Janssen COVID-19 vaccine. PEG and polysorbate are structurally related, and cross-reactive hypersensitivity between these compounds may occur.</small></p>	mRNA COVID-19 vaccines	Janssen COVID-19 vaccine	<ul style="list-style-type: none"> Persons with contraindication to one mRNA vaccine should not receive doses of either vaccine (Pfizer BioNTech or Moderna) Persons with a contraindication to mRNA COVID-19 vaccines (including due to a known allergy to PEG) have a precaution to Janssen COVID-19 vaccine.* In persons who received one mRNA COVID-19 dose but are contraindicated to receive the 2nd dose, consideration may be given to vaccination with Janssen COVID-19 vaccine (at least 28 days after mRNA dose).* 	<ul style="list-style-type: none"> Persons with a contraindication to Janssen COVID-19 vaccine (including due to a known allergy to polysorbate) have a precaution to mRNA COVID-19 vaccines.*
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In closing, Ms. MacNeil posed the following discussion questions for ACIP consideration and discussion:

- Does ACIP agree with the proposed clinical considerations related to vaccination?
- Are there any sections of the clinical considerations that ACIP would like to discuss?

Discussion Points

Dr. Romero noted that current guidelines state that 14 days after receipt of the second dose of an mRNA vaccine, an individual who has been fully vaccinated does not have to enter into quarantine and wondered whether the same would apply to the Janssen vaccine product.

Ms. MacNeil indicated that the current version of the clinical consideration does include a public health recommendation for vaccinated people. It has been updated to state 2 weeks following receipt of 1-dose of Janssen vaccine. This section of the guidance likely will be updated in the

next week or so with additional recommendations pertaining to quarantine for vaccinated individuals.

Dr. Drees (SHEA) recalled that Ms. MacNeil indicated that someone who received the first dose of an mRNA but was unable to receive a second dose due to a contraindication could get a single dose of the Janssen vaccine, but that some of the ingredients are similar such as polysorbate or polyethylene glycol (PEG). She asked whether patients who had a possible allergic reaction to the first vaccine should be advised to get the Janssen vaccine to complete their series.

Ms. MacNeil clarified that the way the considerations are written currently, persons who had a contraindication or anaphylactic reaction with either mRNA or Janssen vaccine will be considered to have a precaution against vaccination with the other type of vaccine. If they are vaccinated, it should be done in a setting where any reactions could be managed and have a 30-minute observation period.

Dr. Drees observed that the risk of anaphylaxis for the Pfizer and Moderna vaccines is very low at 2 to 5 cases per million doses given, which is similar to other vaccines for which 15 minutes of monitoring is not required. As she recalled, the majority of cases were among people with a history of severe allergy of some type and she wondered if there had been any consideration for dropping the 15-minute monitoring recommendation for people who do not have that allergy history.

Ms. MacNeil indicated that the usual recommendation for any vaccine is to monitor the recipient for 15 minutes following vaccination. In terms of the 30-minute window following vaccination for people who have had anaphylactic reactions, people are still feeling relatively conservative and that is why the 30-minute window was maintained. She is fine with the 30-minute window for high-risk people. From an implementation standpoint, there are large mass vaccination influenza clinics all of the time and the majority do not monitor for 15 minutes. Therefore, this feels very different from other vaccines.

Dr. Mbaeyi added that they have been thinking through this and conducting analyses of the anaphylaxis cases that have been reported so far in terms of trying to understand the incremental benefits of a 30-minute wait period for high-risk patients. They would like to review more data before making a decision.

Dr. Poehling emphasized that because anaphylaxis to the two mRNA is very rare, she was still struggling with where the information was coming from regarding 28 days later with the Janssen vaccine it is not needed.

Ms. MacNeil indicated that the 28-day interval came from the interval that is being used between mRNA doses if one product is unknown. This was carried forward for this recommendation as well.

Dr. Mbaeyi added that they wanted to provide an interval and for it to be an appropriate interval not only for reactogenicity considerations, but also to ensure a good boost if it is going to be given as a dose after a previous mRNA dose. The 28-day window seemed most reasonable because the interval for the authorized Pfizer mRNA vaccine is 21 days and Moderna mRNA vaccine is 28 days.

Dr. Daley noted that he was staffing a large vaccination clinic a couple of weeks previously and was amazed at the number of true precautions that arose and the number of things that were not precautions but were perceived as such. The individual risk balance was still strongly in favor of vaccination that day and these were individuals who may have had significantly increased risk of COVID disease. Waiting because of a precaution puts them at risk of COVID. Therefore, he wondered whether there is a place to clarify that the vast majority of cases with a precaution for vaccination should be vaccinated that day after a conversation with whomever is there and perhaps just be observed for longer.

Ms. MacNeil indicated that they will review the language to ensure that it is clear.

Dr. Sanchez recalled that the previous day when he asked about concomitant vaccinations with the Janssen product, it was indicated that other vaccines should not be given for 1 to 2 months and he wondered whether that was part of the 28-day window as well. He is very much in favor of having a more lenient approach to other vaccinations with any of these 3 vaccines.

Ms. MacNeil pointed out that all of the studies handled this issue differently. In terms of concomitant administration with other vaccines, the guidance states that there should be 14 days between the administration of COVID vaccine and any other vaccines unless there is an urgency to receive the vaccine such as tetanus for wound prophylaxis.

Dr. Cohn added that they are looking very closely at concomitant administration and the 14-day interval. They plan to review the safety data to evaluate whether there is an ability to relax that guidance in the near future.

Referring to Slide 9, Dr. Lee stressed that increasing younger population will begin to be vaccinated in the coming months. She worries about late complications of COVID-19 such as Multisystem Inflammatory Syndrome in Children (MIS-C) or Multisystem Inflammatory Syndrome in Adults (MIS-A). Even though there is a minimum interval between infection and vaccination other than the quarantine restrictions, she would say that advocating for waiting 4 to 6 weeks makes sense from a clinical standpoint to ensure that they are not conflating late complications of COVID-19 infections versus AEs to the vaccine. Many considerations may be important in terms of the timing.

Ms. Stinchfield (NAPNAP) said she was glad that the professional societies are supporting vaccination of pregnant women with all of the products available, but fever in a pregnant woman should be avoided for the fetus. She wondered if the Janssen product would be preferable for that reason, given that the risk of fever is reduced because of just one dose.

Dr. Meaney-Delman indicated that CDC did discuss this with their colleagues at ACOG and others and decided that they did not want to limit the opportunity for any vaccine. Whatever vaccine a pregnant woman has in front of her, she should receive. The guidance does include that acetaminophen can be given if temperature rises, which they think will address the issue.

Dr. Kotton found the considerations presented to be excellent overall, but highlighted a phrase in the middle of Slide 13 reading, "all currently authorized vaccines are inactivated vaccines." She suggested considering a different word than "inactivated" in that this implies that they have been active and were rendered inactive. For clarity and uptake, the Janssen vaccine is a non-replicating viral vector and mRNA vaccines were never active in any way.

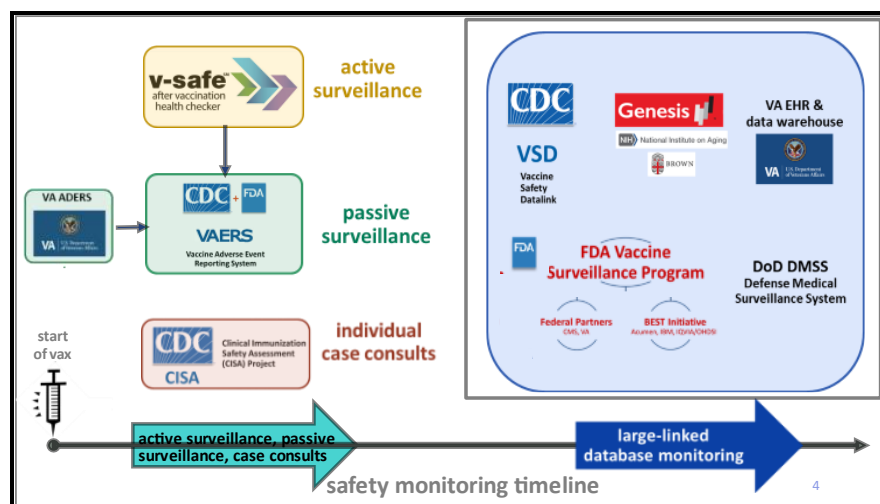
Ms. MacNeil indicated that they would revisit this wording.

VaST Introduction

Grace M. Lee, MD MPH
Chair, ACIP COVID-19 Vaccine Safety Technical Subgroup
Associate CMO, Stanford Children's Health
Professor of Pediatrics, Stanford University School of Medicine

Dr. Lee provided an overview of the COVID-19 vaccine safety activities on behalf of the VaST Subgroup. 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; and 4) provide updates to the ACIP COVID-19 Vaccines Work Group (WG) and the ACIP on COVID-19 vaccine safety.

VaST has met 24 times since June 2020 and 10 times specifically since December 21, 2020 to review the post-approval vaccine safety data. The Janssen vaccine that was approved on February 28, 2021 has now been added. As a reminder, this graphic illustrates the vaccine safety surveillance systems engaged in the VaST meetings and as mentioned in prior ACIP meetings, vaccine safety monitoring has relied on v-safeSM, the VA Adverse Drug Event Reporting System (VA ADERS), the Vaccine Adverse Event Reporting System (VAERS), and Clinical Immunization Safety Assessment (CISA) early in the US vaccination program as early detection systems for safety:



Dr. Lee expressed gratitude to federal colleagues and their investigator teams who have been collecting and reviewing these data each week for presentation to the VaST Subgroup. It takes a tremendous amount of effort each week for the teams to do this work and it requires them to be nimble, patient, and responsive to the VaST Subgroup's many questions.

In terms of the VaST Subgroup's procedures, the group engages in a weekly review of available data on vaccine administration and adverse events of special interest (AESI). All members, federal partners, and SMEs are present for presentation of data. VaST members discuss these findings independently after the meetings. A summary and interpretation of aggregate data are

provided to the ACIP Secretariat on a regular basis. Since the last ACIP meeting, VaST has covered the following topics:

- ❑ Reviewed routine data from VAERS, v-safeSM, VA ADERS, VSD, and CMS
- ❑ Reviewed special topics including:
 - Background rates for AESI
 - Maternal immunization
 - Thrombocytopenia
 - Multisystem Inflammatory Syndrome (MIS)
 - Vaccination of persons with prior infection
- ❑ Initiated monthly sessions with additional experts to review data on vaccine safety in pregnancy

This session included a COVID-19 vaccine safety update overall and with a special focus on maternal immunization at the request of ACIP members during the last meeting, as well as the COVID-19 VaST Subgroup's discussion and interpretation of those data.

COVID-19 Vaccine Safety Update

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Vaccine Safety Team
CDC COVID-19 Vaccine Planning Unit (VPU)
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Shimabukuro provided an update on v-safeSM, VAERS, VSD, CISA, and COVID-19 vaccine safety in pregnancy. As a reminder, v-safeSM is CDC's smartphone-based active surveillance system that uses text messaging with links to web-based surveys to help conduct check-ins on individuals after vaccinations. These check-ins occur daily the first week after vaccination, weekly through 6 weeks, and then at 3, 6, and 12 months. This process basically resets when a person has a second dose. The daily check-ins during the first week post-vaccination solicit responses on local and systemic reactions. Local and systemic reactions are not asked about after that. On all check-ins, there is a health impact assessment. If an individual reports that they received medical care, that information is transmitted to a VAERS call center, the person is contacted, and a VAERS report is taken if appropriate. There are also questions on the surveys to capture information on pregnancy status. An effort is made to enroll people who were pregnant at the time of vaccination or became pregnant after vaccination in the v-safeSM pregnancy registry through a separate process.

Based on an analysis of v-safeSM data as of February 16, 2021, approximately 55 million people had received 1 or more doses of COVID vaccine in the US and roughly 3.9 million v-safeSM registrants had completed at least 1 health check-in. Of these, there were just over 30,000 self-reported pregnancies in v-safeSM. It is known from reviewing the data that the highest amount of reactogenicity is reported on Day 1. Based on a fairly recent publication in the *MMWR* on the initial safety findings for mRNA COVID-19 vaccines, comparing Dose 1/Day 1 (the day after vaccination) of the Pfizer-BioNTech and Moderna vaccines, the safety profiles are quite similar and consistent. The takeaway is that a substantial amount of reactogenicity is reported and these vaccines are known to be reactogenic. In terms of Day1/Dose 1 compared to Day 1/Dose 2 of the Pfizer-BioNTech vaccine, striking is that the reported systemic reactions are substantially more following Dose 2. In some cases, they are 3- to 4-fold higher. Therefore, the

reactogenicity profiles based on v-safeSM are consistent with what was observed in the clinical trials in terms of reactogenicity in general and the observation that there is more systemic reactogenicity after Dose 2. At the time of this analysis, CDC did not have information on Dose 2 of the Moderna vaccine. They now have those data and will be updating this analysis in the future.⁴⁶

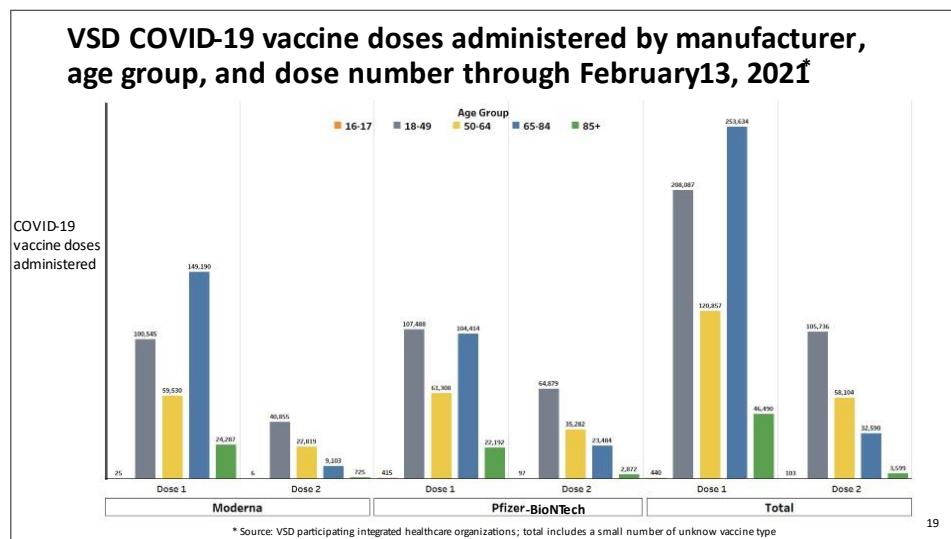
VAERS is the nation's early warning system for vaccine safety. It is a spontaneous reporting or passive surveillance system that is co-managed by CDC and FDA. The strengths of VAERS are that it is national data of essentially the entire US population who is eligible to receive a vaccine. Because of the size and breadth of VAERS, it can rapidly detect safety signals and rare AEs. The main limitation is that VAERS is not designed to assess causality. VAERS accepts all reports from everyone 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. As of February 16, 2021, there were just over 104,000 reports to VAERS of which 94% are non-serious and 6% are serious. That breakdown of serious and non-serious is similar to what is observed for other vaccines administered to adults such as influenza vaccines. Comparing the most commonly reported AEs to VAERS after COVID-19 vaccines, systemic reactions are most commonly reported and local reactions are commonly reported for both the Pfizer-BioNTech and Moderna vaccines. The safety profiles for these two vaccines look remarkably similar. Importantly, no empirical Bayesian data mining alerts were detected for any adverse event-COVID-19 vaccine pairs. The takeaway message from the v-safeSM and VAERS data is that the initial safety profiles of these vaccines are consistent with what was observed in the clinical trials and are generally reassuring. In terms of anaphylaxis follow mRNA COVID-19 vaccines from a fairly recent publication in the *Journal of the American Medical Association (JAMA)*⁴⁷, after additional data were accumulated from the last time ACIP was briefed, there are updated reporting rates. For the Pfizer-BioNTech it is 4.7 cases per million doses administered and for Moderna it is 2.5 cases per million doses administered.

The VSD is a CDC collaboration with 9 participating integrated healthcare organizations data on over 12 million persons per year. The VSD has electronic health record data and administrative data to include information on immunizations, encounters with the healthcare system, birth and death certificate information, and demographics that are all linked by unique study identifications (IDs). The VSD also has rapid access to charts and electronic health records to go in and review cases. The VSD is conducting near real-time sequential monitoring called Rapid Cycle Analysis (RCA) for COVID-19 vaccines. In RCA, the data are refreshed weekly. The outcomes that are monitored are pre-specified (i.e., identified in advance). It includes methods to adjust for sequential testing when sequential testing is performed. RCA is a surveillance activity, which is not the same as an epidemiologic study. It is designed to detect statistically significant associations and statistical signals, which are values above specified statistical thresholds. Not all statistical signals indicate a safety problem and need to be assessed further. When a statistically significant association or signal occurs, assessment involves a series of checks and evaluations. Chart-confirmation of a diagnoses to confirm or exclude cases as true incident cases is a key part of statistical signal assessment.

⁴⁶ Gee J, Marquez P, Su J, et al. First Month of COVID-19 Vaccine Safety Monitoring — United States, December 14, 2020–January 13, 2021. *MMWR Morb Mortal Wkly Rep*. ePub: 19 February 2021. DOI: <http://dx.doi.org/10.15585/mmwr.mm7008e3>

⁴⁷ Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US—December 14, 2020-January 18, 2021. *JAMA*. 2021;325(11):1101–1102. doi:10.1001/jama.2021.1967

The VSD RCA planned for COVID-19 vaccines include unvaccinated concurrent comparators (currently being conducted), vaccinated concurrent comparators (currently being conducted), self-controlled risk interval (planned), and historical comparators (planned). The combined total of VSD COVID-19 vaccine doses administered by February 12, 2021 was roughly 630,000 Dose 1 doses and just over 200,000 Dose 2 doses. These doses are broken down by manufacturer, age group, and dose number through February 13, 2021 in the following table, with the blue bar (ages 65-84) having increased as time has gone on, likely indicating expansion of the vaccination program more toward the general population:



The VSD unvaccinated concurrent comparator analysis for COVID-19 vaccine safety after either dose of any mRNA vaccine through February 13, 2021 allowed CDC to get data most quickly on the following 21 pre-specified outcomes that are being monitored:

- Acute disseminated encephalomyelitis
- Acute myocardial infarction
- Acute respiratory distress syndrome
- Anaphylaxis
- Appendicitis
- Bell's palsy
- Convulsions/seizures
- Disseminated intravascular coagulation
- Encephalitis/myelitis/encephalomyelitis
- Guillain-Barré syndrome
- Thrombotic thrombocytopenic purpura
- Immune thrombocytopenia
- Kawasaki disease
- MIS-C and MIS-A
- Myocarditis/pericarditis
- Narcolepsy and cataplexy
- Stroke, hemorrhagic
- Stroke, ischemic
- Transverse myelitis
- Venous thromboembolism
- Pulmonary embolism (subset of VTE)

The concurrent comparator analysis is basically an assessment of vaccinated individuals compared to unvaccinated individuals matched on certain characteristics. It does not require maturation of vaccinated individuals into the control window, so it can provide information as soon as individuals begin to get vaccinated and events begin to accrue. No statistically significant increased risks were detected in this analysis for any of the prespecified outcomes in the unvaccinated concurrent comparator analysis. No statistical signals were detected in the preliminary results of the VSD sequential vaccinated concurrent comparator analysis for COVID-19 vaccine safety after either dose of any mRNA vaccine as of February 13, 2021. The next steps for the VSD RCA include dose-specific analyses, product-specific analyses, analyses for two risk intervals (1-21 and 1-42 days), and a historical comparator analysis.

The CISA project is a collaboration between CDC and 7 participating medical research centers. The CISA project, COVID-vax, is an extension of CDC's CISA⁴⁸ Project's clinical consultation service for US healthcare providers and health departments for complex COVID-19 vaccine safety questions/issues that are⁴⁹ about individual patients residing in the US that are not readily addressed by CDC or ACIP guidelines⁵⁰. The CISA team and its partners include individuals with vaccine safety subject matter expertise in multiple 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 webform⁵¹ and indicating the request is for a "CDC CISA" consult (no patient identifiers).

CISA has responded to 331 clinical inquiries or consultation requests about COVID-19 vaccine safety during the period from December 14, 2020 through February 10, 2021. These requests were received from 43 states, with over 90% from healthcare provider or health departments. The most common topics include anaphylaxis/allergic reactions and nervous system disorders. This includes inquiries about AEs and for clinical guidance without AEs. The CISA project also has assisted state health departments with evaluation of complex medical issues pertaining to COVID-19 vaccine safety. The CISA Project also established a WG with allergy and immunology specialists to provide expert input on anaphylaxis and other allergic reactions to inform clinical considerations for use of COVID-19 vaccines. The WG is engaged in ongoing work to investigate a possible mechanism for anaphylaxis after COVID-19 vaccine in collaboration with FDA, NIH, and other partners.

Moving into COVID-19 vaccine safety in pregnancy, there have been just over 30,000 self-reported pregnancies reported during v-safeSM health check-ins as of February 16, 2021 as noted earlier. Looking at local reactions for Doses 1 and 2 post-vaccination for Pfizer-BioNTech recipients and Dose 1 for Moderna recipients, no substantial differences have been observed in local reactions in pregnant and non-pregnant women 16-54 years of age. In fact, there appear to be less reported reactions in pregnant women compared to non-pregnant women, although the numbers are small. The same is observed with systemic reactions in pregnant compared to non-pregnant women. In fact, there may be more self-reported systemic symptoms in non-pregnant women. Substantially more systemic symptoms were reported after Dose 2 compared

⁴⁸ <https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html>

⁴⁹ Advice from CDC and CISA is meant to assist in decision-making, rather than provide direct patient management

⁵⁰ <https://www.cdc.gov/vaccines/acip/recommendations.html>

⁵¹ <https://wwwn.cdc.gov/dcs/ContactUs/Form>

to Dose 1 for the Pfizer BioNTech vaccine, but there were no concerning patterns that differed among pregnant versus non-pregnant women.⁵²

In terms of the v-safeSM pregnancy registry, participants who report pregnancy following COVID-19 vaccination are actively contacted to enroll in the pregnancy registry. Participants are contacted once per trimester, after delivery, and when the infant is 3 months old. The outcomes of interest include miscarriage and still birth, pregnancy complications, maternal ICU admission, adverse birth outcomes, neonatal death, infant hospitalizations, and birth defects. As of February 19, 2021, there were 1815 pregnant women have been enrolled in the v-safeSM pregnancy registry. In the enrolled population, there have been 275 completed pregnancies, including 232 live births. Other outcomes have included miscarriage, stillbirth, ectopic/tubal pregnancies, and other. In terms of v-safeSM pregnancy registry outcomes of interest in COVID-19 vaccinated pregnant women as of February 18, 2021 compared to background rates based on the published literature, no concerning patterns have been observed.

Regarding characteristics of COVID-19 vaccine pregnancy reports to VAERS through February 16, 2021, of which there have been 154, the median maternal age is 33 years (16–51) and the median gestational age is 13 weeks (2–38). Just over half of the reports involved pregnancies during the first trimester (60/118; 51%), about a third during the second trimester (36/118; 31%), and the remainder were in the third trimester (22/118; 19%). The vaccines received included 97 (63%) Pfizer-BioNTech, 56 (36%) Moderna, and 1 (0.6%) unreported. About 73% of the 154 reports involved non-pregnancy-specific AEs that would be expected in the general population that typically are systemic and local reactions as shown in this table:

Adverse Events	N (%)
Pregnancy/Neonatal Specific Conditions	42 (27)
Spontaneous abortion/miscarriage [†]	29
Premature rupture of membranes	3
Fetal hydrops	2
Neonatal death in 22-week preterm birth	1
Premature delivery	1
Gestational diabetes	1
Vaginal bleeding	1
Stillbirth	1
Shortened cervix	1
Leakage amniotic fluid	1
Calcified placenta	1
Non-Pregnancy Specific Adverse Events (top 10)	112 (73)
Headache (31), fatigue (29), chills (21), pain in extremity (17), nausea (15), dizziness (14), pain (14), pyrexia (13), injection site pain (13), injection site erythema (10)	

To put the 29 reports of miscarriage into perspective, the frequency of clinically recognized early pregnancy loss for women 20 to 30 years of age is estimated to be between 9% to 17%, at age 30 it is 20%, at age 40 it is 40%, and at age 45 it is 80%.⁵³

There are other ongoing CDC COVID-19 maternal vaccination safety activities. In the VSD, there is a COVID-19 vaccination coverage project in pregnant women; a study on the risk of miscarriage and stillbirth following COVID-19 vaccination; and a safety in pregnancy study focused on acute AEs in pregnancy, longer-term safety assessment of acute AEs, pregnancy complications and birth outcomes, and infant follow-up for the first year of life. In the CISA

⁵² CDC unpublished v-safe data through January 13, 2021

⁵³ ACOG Practice Bulletin No. 200: Early Pregnancy Loss. Obstet Gynecol. 2018;132(5): e197-e207

Project, a prospective observational cohort study is planned to examine adverse pregnancy and birth outcomes, SAEs, local and systemic reactogenicity, and infant health outcomes for the first 3 months of life.

To summarize maternal vaccination safety, pregnant women were not specifically included in pre-authorization clinical trials of COVID-19 vaccines. Post-authorization safety monitoring and research are the primary ways to obtain safety data on COVID-19 vaccination during pregnancy. Substantial numbers of self-reported pregnant persons (>30,000) have registered in v-safeSM. The reactogenicity profile and AEs observed among pregnant women in v-safeSM did not indicate any safety problems. Most (73%) reports to VAERS among pregnant women involved non-pregnancy-specific AEs (e.g., local and systemic reactions). Miscarriage was the most frequently reported pregnancy-specific AE to VAERS. The numbers are within the known background rates based on presumed COVID-19 vaccine doses administered to pregnant women.

Closing thoughts on COVID-19 vaccine safety are that 75 million COVID-19 vaccine doses have been administered in the US through February 28, 2021. Reactogenicity profiles of mRNA vaccines in v-safeSM monitoring are consistent with what was observed in clinical trials, and systemic and local reactions are most commonly reported to VAERS. Anaphylaxis following both vaccines has been reported to VAERS, though rarely. No other safety signals for SAEs have been detected in VAERS. No safety concerns have been identified among VSD RCA prespecified outcomes as of February 13, 2021. No unexpected pregnancy or infant outcomes have been observed related to COVID-19 vaccination during pregnancy. Safety monitoring in pregnant women is ongoing and planned in v-safeSM, VAERS, VSD, and CISA.

VaST Assessment of the Safety Data

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Dr. Lee provided VaST's discussion and interpretation of the safety data. Well-established vaccine safety surveillance systems remain the cornerstone for monitoring the safety of approved COVID-19 vaccines in the US. Enhanced approaches to surveillance have enriched the understanding of COVID-19 vaccine safety in the early phases of vaccine deployment. VaST continues to meet weekly to review all available data and to ensure a coordinated approach across multiple safety surveillance systems.

Local and systemic reactions continue to be the most commonly reported AEs following vaccination in v-safeSM, VAERS, and VA-ADERS. Anaphylaxis reporting rates range from 2.5 to 4.7 cases per million doses administered and is the most common reason for CISA consultations. Allergy and immunology specialists provide expert input on clinical considerations. The VSD RCA uses multiple methods for surveillance depending on the phase of the vaccination program. Dr. Lee anticipates that into the future, VaST will continue to dive deeper into those VSD data. Pre-specified outcomes are actively being monitored and no statistical signals have been detected to date. VaST also has reviewed the CMS RCA descriptive analyses and the sequential analyses are to begin soon.

A large number of pregnant women have chosen to receive COVID-19 vaccines in the US. A novel pregnancy registry was established in v-safeSM to monitor pregnancy and birth outcomes. VaST is greatly appreciative of CDC being nimble enough to establish such a registry. It was not anticipated that so many pregnant women would be interested in vaccination, so this is a great opportunity to have a better understanding of the safety and outcomes. Similar to non-pregnant adults, pregnant women commonly report local and systemic reactogenicity (e.g. pain, fatigue, headache). Pregnancy and birth outcomes following COVID-19 vaccination appear to be similar to rates reported in the literature.

Since the last ACIP emergency meeting at the end of January 2021, colleagues have published two additional vaccine safety publications in the *MMWR* and *JAMA* as Dr. Shimabukuro presented. CDC⁵⁴ and FDA⁵⁵ have each posted additional information on their web pages, with the anticipation that these will continue to be updated in the future.

In terms of VaST plans for the future, statistical signals should be expected in a robust monitoring program. Timely investigations will be conducted once signals are identified. Only 1 in 10 statistical signals have been true associations. Maternal vaccine safety data from multiple sources will be regularly reviewed in collaboration with pregnancy experts. Future vaccine safety surveillance activities will include the newly approved Janssen COVID-19 vaccine. VaST will continue to update the ACIP COVID-19 Vaccines WG, the ACIP Secretariat, and the full ACIP on a regular basis.

Discussion Points (Lee & Shimabukuro)

Dr. Hahn (CSTE) recalled that v-safeSM also includes questions about whether any AEs have impacted activity in any way and wondered whether there are any data on this. Some people will not get a second dose if they have a severe allergic reaction to their first dose, but she wondered whether there have been any reports of severe allergic reaction among people with no reaction to the first dose who have an anaphylactic reaction to the second dose.

Dr. Shimabukuro indicated that part of the v-safeSM process is that if a person reports that they received medical care in any health check-in, there is an attempt to contact that person to take a VAERS report. CDC is in the process of collecting that information and analyzing those reports, and will report the findings of the v-safeSM-generated VAERS reports during a future ACIP meeting. There are some automated data in which people self-report that they have missed work or cannot engage in daily activities. He will take this back to the v-safeSM group to find out what type of analysis can be done with the data they have within v-safeSM in terms of using that as a proxy measure for severity. In terms of anaphylaxis with the second dose, most of the cases occur after the first dose based on the most recent published data and only a handful occur after the second dose. These data are from early in the vaccine rollout, so this may just represent the status of the rollout. Anaphylaxis continues to be monitored, but there still are not a lot of cases following the second dose. There could be a variety of reasons for that, which will require a deeper look. The pattern continues with most anaphylaxis reports occurring after the first dose and a relatively small number following the second dose.

⁵⁴ <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety.html>

⁵⁵ <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance>

Dr. Bernstein emphasized what an amazing job CDC is doing in monitoring the safety of the COVID-19 vaccines. Referring to slide 11 from Dr. Shimabukuro's presentation, he observed that about 6% SAEs occurred, but it appeared that there was a lower number of doses in Pfizer than Moderna and more than twice as many SAEs after the Pfizer vaccine. He wondered whether that was because the data include more second doses. In addition, he asked whether Dr. Shimabukuro could comment on lymphadenopathy.

Dr. Shimabukuro stressed that these are spontaneous reports. The difference between 97% and 3% and 91% and 9% when dealing with spontaneous reports is difficult to determine. The two vaccines look fairly comparable in terms of the most common AEs. It is not clear whether in VAERS it will be possible to ascertain the true or meaningful difference, if any. Looking at the general pattern, about 90% non-serious and 10% serious is fairly standard depending upon the vaccine and the age of the individual being vaccinated. That is pretty standard for a lot of vaccines given for adults. Lymphadenopathy is not included as a pre-specified AE in the VSD RCA. There may be a variety of reasons for that, one of which regards whether it is medically attended. Typically for the VSD RCA, medically attended events are more conducive to monitoring. Lymphadenopathy and lymphadenitis reports have been received in VAERS and this was observed in the prelicensure clinical trials. These tend to be mild, non-serious, self-limited, and resolve pretty quickly on their own. No disproportional reporting has been observed for lymphadenopathy, nor has there been a safety signal for it. Lymphadenopathy occurs with other vaccines as well.

Dr. Lee reiterated that because VAERS is numerator only, VaST felt that it was hard to interpret the data due to the greater number of Pfizer doses given overall in the US at that time. There are differences in reporting behaviors. These reports are from people who actually report in. There was a lot of reporting in early on, which is terrific and encouraged, but there are changes over time and there could be changes in the numbers that do not actually translate into differences in AEs.

Dr. Bernstein said he was thinking that the 3-week interval for Pfizer products might be why there may be more second doses included, which tends to be more reactogenic.

Dr. Ault expressed gratitude for collection of all of the pregnancy data. He recalled that it was not that long ago that they were talking about the 300,000 HCP among the 20 million HCP and how that demographic skewed younger and female. These data should be very reassuring to the people who already have been vaccinated.

Dr. Poehling thanked Dr. Shimabukuro and his team for following the safety of these vaccines in real-time, which is incredibly important and demonstrates great confidence in this enormous effort. Referring to slide 21, she observed that the data on thromboembolism and pulmonary embolism appeared to be higher than the expected rates and requested additional information on this.

Dr. Shimabukuro indicated that it is still early and that follow-up time can impact the expected events. Their statisticians have indicated that the reason a small number like zero is expected sometimes is because some of the rare events have not accumulated follow-up time. In the unvaccinated concurrent comparator analysis does not rely on unvaccinated individuals moving through their follow-up time so certain vaccinated individuals can be compared with other vaccinated individuals. In this case, there are vaccinated versus unvaccinated so time can be accumulated right away. While there are limitations to this unvaccinated concurrent comparator analysis, in the early stages this was a way to obtain data as quickly as possible to get an idea

of what was occurring with associations and determine whether there was any statistically significant increased risks. They are in the process of transitioning into the VSD sequential vaccinated concurrent comparator, but need to accumulate more data and let more vaccinated individuals accumulate follow-up time. That will impact some of these numbers within expected events. Sequential statistical analyses are being performed on these. According to the thresholds, no statistical signals have been observed for any of these outcomes.

Ms. Bahta asked whether anything further could be said about nervous system disorders.

Dr. Shimabukuro indicated that these are primarily serious neurologic AEs such as GBS and other acute demyelinating disorders. It is important to remember that just because there are temporally associated cases of serious neurologic events does not imply that there is causal association or a safety problem. These are cases in which there is a temporally associated event and an astute HCP or public health partner is requesting consultation, in which case CISA will do a deep review of these cases.

Ms. Stinchfield (NAPNAP) emphasized how useful these data are. She has 80% of Children's Hospital of Minnesota staff vaccinated, but 10% have neither opted in or opted out. They are the people who are waiting and watching. She thinks these data will be extremely helpful to them in terms of safety. Regarding an earlier conversation, she wondered if consideration had been given to adding a question to v-safeSM such as, "Have you had a laboratory-confirmed case of COVID?" This might be a good time to do it with the addition of a third product.

Dr. Shimabukuro indicated that they do ask about COVID disease after vaccination. In some cases, that may be breakthrough disease and in others it may not depending upon the timing of the vaccination. They have had some long discussions and he could not recall why they opted not to include this. To get at the issue of reactogenicity and people who have been previously infected with COVID, a nested case-control study in v-safeSM is in the planning stages in which reactogenicity will be assessed in recipients, cases and controls will be selected, and then contact will be made with these individuals to ask about prior infection. There is a lot of interest in the issue of reactogenicity and whether prior symptomatic infection may predispose an individual to having more reactogenicity. They thought this would be the best way to analyze these data in v-safeSM.

Dr. Arthur (BIO) thought inclusion of the background rates was beneficial in helping people understand these data and make sure that the explanation of these incidents within the vaccinated groups are explained well to the general public. Referring to slide 8, Dr. Arthur said she has been hearing anecdotally that there is much more reactogenicity in younger people. Perhaps it would be good to see how the Dose 2 data split out by age groups and to communicate to people what to expect.

Dr. Shimabukuro indicated that they have a study underway that is assessing reactogenicity, which is much more detailed than what is presented on the two tables on slides 7 and 8. The investigators may already be doing this, but he will present Dr. Arthur's suggestion to them in case they are not.

Dr. Hayes (ACNM) reiterated that the background rates are critical in terms of AEs and pregnancy. She reported that she volunteered at two clinics where most of the people did not know about v-safeSM, so she feels like the promotion of this is still missing on some level. She has 10 friends who were vaccinated, none of whom were told about v-safeSM. Noting that there has been some concern about women getting a mammogram immediately after being

vaccinated because of the lymphadenopathy and having a false positive mammogram, she asked what CDC has heard about this and if they are monitoring it. In addition, she inquired as to whether there has been a way to track whether reactogenicity is related to body mass index (BMI).

Dr. Shimabukuro acknowledged that the acceptability of v-safeSM has been somewhat inconsistent, so CDC certainly will speak to the communications team to maintain awareness of v-safeSM as vaccination rolls out more broadly. He is aware of the issue of lymphadenopathy and mammograms, which would lie more within the purview of the group that issues clinical recommendations. Lymphadenopathy and lymphadenitis has been observed in post-authorization safety monitoring. BMI is not one of the variables used in the surveillance, so he could not comment on that or whether it is biologically plausible.

Dr. Long emphasized how remarkable it is to have so much data already. Regarding the background occurrence rate specifically related to pregnancy outcomes, it is known that there is overrepresentation in AEs of pregnancy in very young pregnant women in racially differentiation as well as socioeconomic status. She assumed that background pregnancies from the medical literature outcomes includes everybody and that there was no attempt to try to match outcomes by age, race, socioeconomic status (SES), et cetera. She presumed that vaccinated pregnant women are more likely to be white, educated, and SES advantage. The stillbirth rate was 1% for vaccinees and 0.5% from the medical literature. She wondered whether there were any concerns about mismatching of the groups being assessed.

Dr. Shimabukuro said that part of enrolling women into the v-safeSM pregnancy registry is to conduct detailed intake interviews, so they are likely to obtain demographic information. When the v-safeSM pregnancy registry begins to form up and has larger numbers and more detailed information, it may be possible to perform some subgroup analyses. While the numbers are still fairly small and there are not sufficient data to allow for detailed sub-analyses at this point, that is a possibility as they continue to develop the v-safeSM pregnancy registry.

Dr. Sanchez thought it would be helpful with the nested case-control study to ask who had a SARS-CoV-2 infection before being vaccinated. In terms of pregnancy, it would be interesting as new platforms are developed to assess the safety and AEs including overall side effects by vaccine type.

Dr. Duchin (NACHO) asked for which systems race and ethnicity data are available, and if there are sufficient data to stratify analyses by race and ethnicity. In addition, he wondered about participation rates.

Dr. Shimabukuro indicated that race and ethnicity data are captured on the standard VAERS 2.0 reporting form. Race and ethnicity have been added to the v-safeSM system. It is asked at initial intake and again during check-ins. The VSD also has information on race and ethnicity. In terms of stratifying analyses by race and ethnicity, VAERS is spontaneous reporting subject to reporting biases, so it is not necessarily representative of the population. V-safeSM is a voluntary self-enrollment system that may not be generalizable. Information is collected on race and ethnicity and that is analyzed, but they have to be careful about drawing conclusions from race and ethnicity in those two systems due to the limitations of the systems. Race and ethnicity are captured for VSD, so there is potentially an option to perform some population-based analyses. One limitation is that when the data are sliced very finely by age, vaccine, dose of vaccine, race, et cetera, the smaller the numbers which can lead to small numbers problems. It will definitely be possible to get participation rates from the v-safeSM system. It may not be representative, but it will be possible to know who is enrolling by race and ethnicity.

Dr. Ault noted that being Black in America is a risk factor for pre-term births, but stillbirths and miscarriage have 15 to 20 recognized risk factors. One reason HCP were placed at the front of the line in the original recommendations was due to the concern for occupational exposure and because they are a very diverse and broad group, so this group is not skewed toward all upper SES statistics.

Ms. Léger (AAPA) noted that anecdotally, more women are reporting side effects after the second dose of mRNA vaccine.

Dr. Shimabukuro will take this information back to investigators performing the reactogenicity study in v-safeSM. This has been observed in the past, especially with VAERS reporting.

Dr. Daley asked whether the ability to monitor post-authorization safety of the Janssen vaccine might be more limited due to the fact that additional doses may not be quite as high as seen for Moderna and Pfizer in the first couple of weeks, and the visibility v-safeSM may be even lower if the Janssen vaccine is used in mass vaccination settings.

Dr. Shimabukuro said that while that may be possible, the intent is to conduct enhanced surveillance for the Janssen vaccine in VAERS. There are also some things that can be done in v-safeSM to get early quick visibility with the Janssen vaccine, such as overenrolling in the pregnancy registry to try to even out the numbers. For VAERS, the plan is to monitor the Janssen vaccine with the same intensity as the Pfizer and Moderna vaccines were monitored when those rolled out and in their initial weeks of vaccination.

Emerging SARS-CoV-2 Variants: Considerations for Vaccine

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Dr. Scobie reported that multiple SARS-CoV-2 variants are circulating globally. After emerging, some disappear and others persist. CDC and others are studying these variants to understand whether they spread more easily from person-to-person, cause milder or more severe disease in people, can be detected by available diagnostic tests, respond to therapeutics currently used to treat people for COVID-19, and/or change the effectiveness of COVID-19 vaccines. Based on the evidence, some variants are classified as “variants of concern” and appropriate public health actions are taken.⁵⁶

Viruses constantly change through mutation, so new variants are to be expected. SARS-CoV-2 has a low mutation rate compared with influenza and HIV. The drivers of evolutionary selection are still being characterized but may include chronic infection (e.g., immunocompromised), interspecies transmission (e.g., minks), therapeutic treatment (e.g., monoclonal antibodies, convalescent sera), prior immunity to strains with limited cross-reactivity, increased transmissibility, and founder effect in which a small number of genotypes seed a new population by chance.

⁵⁶ <https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant.html>;
<https://www.who.int/publications/m/item/covid-19-weekly-epidemiological-update>

The D614G is an example of SARS-CoV-2 strain replacement. This variant was discovered in January 2020 and increased to almost 100% prevalence worldwide by June 2020. Compared with the ancestral strain, this variant has increased infectivity that has attributed to a more open conformation of the viral spike protein that helps it bind to host cells. The D614G variant likely has increased transmissibility giving it selective advantage, but it is not more clinically severe and current vaccines are still highly effective. This variant is not of particular concern, but it highlights the potential for similar replacements to occur with variants that may be more problematic.⁵⁷

There are general concerns with 3 SARS-CoV-2 variants of concern as shown in the following table:

Name (Pangolin)	Name (Nextstrain)	First Detected	Cases in the US	Countries Reporting Cases	Key Amino Acid Mutations	Transmissibility Rate
B.1.1.7	20I/501Y.V1	United Kingdom	Y	101	Δ69/70 Δ144Y N501Y A570D D614G P681H	~50% increase
B.1.351	20H/501Y.V2	South Africa	Y	51	K417N E484K N501Y D614G	~50% increase
P.1	20J/501Y.V3	Brazil/ Japan	Y	29	E484K K417N/T N501Y D614G	Not determined

<https://www.cdc.gov/coronavirus/2019-ncov/case-reports/variant-surveillance/variant-info.html>
Davies et al. Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England. medrxiv.org/content/10.1101/2020.12.24.20248822v2
Pearson et al. Estimates of severity and transmissibility of novel SARS-CoV-2 variant 501Y.V2 in South Africa <https://medrxiv.org/content/10.1101/2021.01.11.21011111>
<https://medrxiv.org/content/10.1101/2021.01.11.21011111> Transmissibility and severity of 501Y.V2 in SA.pdf

B.1.1.7 was first detected in the UK, B.1.351 was first detected in South Africa, and P.1 was first detected in Brazil and Japan. By now, these variants are being detected in many countries. Both B.1.1.7 and B.1.351 are estimated to be 50% more transmissible and have become the dominant strains in some areas. Each variant has 2 names, which adds confusion. The names point to the ancestry of the viruses and are recognizable because they contain periods. Another source of confusion is the many mutations under discussion. For instance, the abbreviation E484K means that an amino acid called glutamic acid (E) was replaced with a lysine (K) at position 484 in the spike protein, which is a negative to positive change that can be problematic if occurring in a key binding site. This will be important later on.

In terms of the US COVID-19 cases caused by variants of concern, 2400 cases have been detected of B.1.1.7 in 46 states, 53 cases of B.1.351 have been detected in 16 states, and 10 cases of P.1 have been detected in 5 states.⁵⁸ B.1.1.7 was first detected in the US in December 2020, but a study has shown that it likely arrived in November 2020 through multiple introductions. The current prevalence is estimated at 1% to 2%.⁵⁹ Commercial diagnostic data suggest that the US is in an early phase logistic expansion.⁶⁰ Two modeling studies suggest that

⁵⁷ Callaway E. Nature (2020). <https://www.nature.com/articles/d41586-020-02544-6>

Volz et al. Cell (2021). <https://www.sciencedirect.com/science/article/pii/S0092867420315373>

<https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html#ref2>

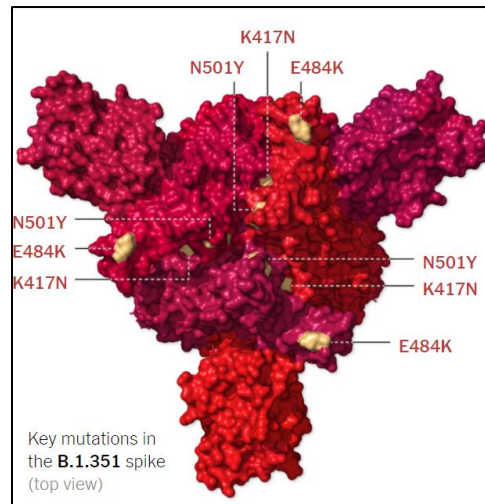
⁵⁸ <https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant-cases.html> (data as of 02/28/2021)

⁵⁹ <https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html>

⁶⁰ Washington et al. medRxiv preprint (Feb 7 2021): <https://www.medrxiv.org/content/10.1101/2021.02.06.21251159v1>

B.1.1.7 may predominate by late March 2021. One of the studies suggests that high vaccine coverage will blunt the public health impact of the variant's higher transmissibility.⁶¹

The receptor-binding domain (RBD) of spike protein binds the host ACE2 receptor, and interaction that is necessary for infection. For SARS-CoV-2, the majority of neutralizing antibodies bind the RBD, blocking this interaction and neutralizing the effect of the virus. Convergent evolution of different variants has revealed a cluster of several mutations in the RBD that increase the binding and infectivity and reduce the efficacy of antibody therapies. The mutations are N501Y, which occurs in all three variants, and E484K and K417N that occur in the South Africa and Brazil variants. This is illustrated in the following photograph:⁶²



All of the variants of concern are distinguished by the large number of mutations that they have in their spike proteins. There is also another variant called P.2 that is the dominant strain in Brazil that has an E484K mutation, with fewer spike mutations overall.

In terms of the impact of these variants on vaccine effectiveness, 26 available studies were reviewed of vaccines authorized or intended to be authorized in the US containing data on the ability of post-vaccination sera to neutralize SARS-CoV-2 variants. There were 8 published studies and 18 pre-print studies, all of which had small sample sizes of less than 50 sera. Among the studies, 13 assessed only Pfizer vaccine, 3 assessed only Moderna vaccine, 2 assessed studies on AstraZeneca vaccine, 7 studies assessed more than one vaccine study, and 8 studies evaluated the effect of single or limited sets of mutations found in the variants and generally found minimal impact. Exceptions were E484K and the triple mutation in the receptor binding domain, E484K-K417N-N501Y, which had relatively large effects. The largest impacts observed were for the B.1.351 (South Africa), followed by P.1, P.2 (Brazil), and then B.1.1.7 (UK). In most studies, B.1.351 had a 3- to 11-fold reduction in neutralization, but ranged up to 97-fold. Most B.1.1.7 studies generally had a less than 3-fold reduction, but ranged up to 9-fold. The threshold of concern for reduction in neutralization activity has not yet been established.

On average across the studies, B.1.351 had a larger reduction in neutralization than B.1.1.7. In the 2 variants from Brazil, P.1 and P.2 had an intermediate reduction within the few studies available. Several studies noted that a single E484K mutation could account for most of the

⁶¹ Galloway et al. *MMWR* 2021;70:95–99. https://www.cdc.gov/mmwr/volumes/70/wr/mm7003e2.htm?s_cid=mm7003e2_w

⁶² <https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html>

reduced neutralization of the South Africa and Brazil variants. One study assessed a B.1.1.7 variant with an E484K change that has been detected in the UK and other countries and found that neutralization was substantively reduced compared to B.1.1.7. Five studies have shown that postponing the second mRNA dose may leave some people less protected against the SARS-CoV-2 variants. Normally, minimal or no neutralization against B.1.351 was observed after one mRNA vaccine dose. In a few studies, people who had recovered from COVID-19 and received one vaccine dose had moderate protection against B.1.351. All of the studies noted improved neutralization of B.1.1.7 and B.1.351 after the second vaccine dose. One Pfizer vaccine study noted delayed kinetics of the antibody response against the variants. Antibody responses to B.1.1.7 and B.1.351 at Week 2 after the first dose were reduced relative to the dominant D614G strain, but improved slightly by Week 3, especially for B.1.1.7. Both B.1.1.7 and B.1.351 improved at Week 4 one week after the second dose. These results suggest that maturation of the immune response could be important in protecting against the variants.

It is difficult to estimate how laboratory results might translate to clinical protection, given that there is currently no immunological correlate of protection for SARS-CoV-2. In general, neutralization antibodies in sera from mRNA vaccine recipients have been shown to be higher than for COVID-19 convalescent sera. The variation in the results presented may be explained by differences in experimental conditions such as the type of neutralization assays used, differences in when and from whom the sera were collected, and whether recombinant viruses with limited or full sets of spike mutations were used versus viral clinical isolates. It is also important to note that the antigen used from the AstraZeneca vaccine is not the prefusion stabilized spike protein used in other authorized vaccines, so results with this vaccine may have limited generalizability to other vaccines. Limitation for all studies were small sample sizes and a lack generalizability. Many of the studies were pre-prints that had not yet been peer-reviewed.

Switching now to data from clinical studies of vaccine efficacy or effectiveness related to the variants, Dr. Scobie reviewed the point estimates in the following table with the caveats that this is a summary of the preliminary data available; most of it has not yet been peer-reviewed and it is not meant to compare across vaccines as the studies used different outcomes and occurred in different epidemiologic settings; and generating additional data on the relative vaccine effectiveness for each variant would be useful:

Vaccine Efficacy or Effectiveness (VE) Against Variants		
Vaccine	Study type	VE
Pfizer	Post-EUA	<ul style="list-style-type: none"> 86% in UK (predominate B.1.1.7 circulation)* 94% in Israel (up to 80% of cases from B.1.1.7)
Janssen	Pre-EUA	<ul style="list-style-type: none"> 74% in U.S. 66% in Brazil 52% in S. Africa
		73-82% for severe/critical disease in each country
Novavax	Pre-EUA	<ul style="list-style-type: none"> 96% against non-B.1.1.7 in UK 86% against B.1.1.7 in UK
	Pre-EUA	<ul style="list-style-type: none"> 60% in S. Africa (93% of cases from B.1.351)
AstraZeneca	Pre-EUA	<ul style="list-style-type: none"> 84% against non-B.1.1.7 in UK 75% against B.1.1.7 in UK
	Pre-EUA	<ul style="list-style-type: none"> 10% against B.1.351 in South Africa

Hall et al. Lancet preprint (Feb 22 2021): https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3790399; *VE for symptomatic & asymptomatic infection
Dagan et al. NEJM (2021) <https://www.nejm.org/doi/full/10.1056/NEJMoa2101765?query=TOC>
<https://www.fda.gov/media/146217/download>
Novavax: <https://ir.novavax.com/news-releases/news-releasedetail/novavax-covid-19-vaccine-demonstrates-89-3efficacy-uk-phase-3>
Madhi et al medRxiv preprint (Feb 12 2021) <https://doi.org/10.1101/2021.02.10.21251247>
Emery et al. Lancet preprint (Feb 09 2021): https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160

In summary of the preliminary data, the B.1.1.7 variant is exponentially increasing in prevalence in the US, but has minimal impact on vaccine effectiveness. However, variants with additional substitutions in RBD, such as E484K, deserve special attention. The B.1.351 variant is currently at low prevalence in the US. It has moderate impact on vaccine effectiveness, suggesting that it would be prudent to start evaluating variant vaccines in case prevalence begins to substantially increase. The P.1 variant has very low prevalence in the US, but has the same triple mediation in the RBD as B.1.351, which is worth watching closely. Additional data are still needed on the potential impact on vaccine effectiveness. It is important to emphasize that the current prevention measures and authorized vaccines offer good protection against SARS-CoV-2 variants. Efforts are needed to increase the speed and degree of uptake. Periodic updating of SARS-CoV-2 vaccines likely will be needed. One modeling study⁶³ has predicted that changing COVID-19 vaccines to target faster spreading viral variants will be more effective than targeting the slower dominant strain, despite initial prevalence.

Regarding the response to variants, the SARS-CoV-2 Interagency Group (SIG) was established by the HHS to improve coordination among several agencies, including: CDC, NIH, FDA, Biomedical Advanced Research and Development Authority (BARDA), US Department of Agriculture (USDA), and Department of Defense (DoD). The SIG focuses on rapid characterization of emerging variants and monitors the potential impact on SARS-CoV-2 diagnostics, therapeutics, and vaccines.⁶⁴

CDC is undertaking a number of efforts to improve genomic surveillance and epidemiology that are relevant for monitoring the variants⁶⁵. As part of the National SARS-CoV-2 Strain Surveillance (NS3), CDC process approximately 3,000 random specimens per month from public health laboratories across the US. CDC also has partnered with commercial diagnostic laboratories to sequence and addition 6,000 specimens per week. CDC also contracts and partnerships with state and local health departments and universities to conduct genomic surveillance.⁶⁶ In addition, CDC leads the SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance (SPHERES) Consortium⁶⁷ that includes approximately 170 domestic partners and facilitates the open sharing of SARS-CoV-2 sequencing data. CDC also conducts focused molecular epidemiologic studies that are relevant to characterizing the variants. This chart shows the cumulative number of published SARS-CoV-2 sequences by collection data from laboratories across the US beginning in January 2020 to the present:

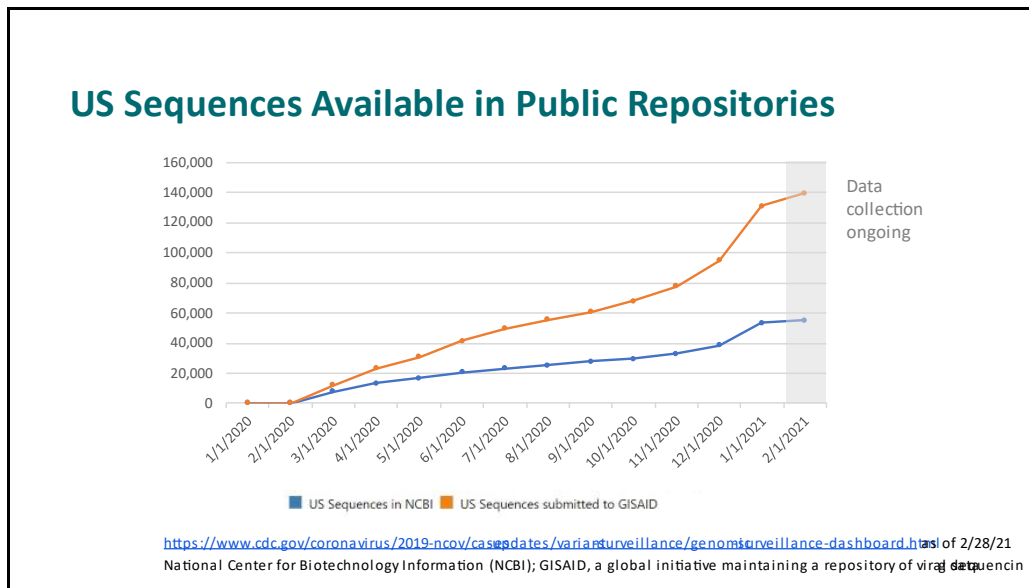
⁶³ Bedwick et al. medRxiv preprint (Feb 8 2021); doi: <https://doi.org/10.1101/2021.01.05.21249255>

⁶⁴ Walensky, Walke and Fauci. JAMA (2021): <https://jamanetwork.com/journals/jama/fullarticle/2776739>

⁶⁵ <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance.html>

⁶⁶ <https://www.aphl.org/programs/preparedness/Crisis-Management/COVID-19-Response/Pages/Sequence-Based-Surveillance-Submission.aspx>

⁶⁷ <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/spheres.html>



Despite high vaccine efficacy, vaccine breakthrough cases are still expected to occur. Some will be caused by the variants even if the vaccine has similar effectiveness against the variants. A vaccine breakthrough case is defined as “a person with SARS-CoV-2 RNA or antigen detected in a respiratory specimen collected at least 14 days after completing the primary series of an FDA-authorized COVID-19 vaccine. Cases are identified from the national case-based surveillance, VAERS, health departments, and healthcare providers. CDC works with state health departments on case investigations. Available respiratory specimens are used for whole genome sequencing (WGS) to identify variants. Data from investigations will be posted or published when available.

Moderna and Pfizer have announced that they are launching booster studies of current vaccines in the US⁶⁸ and are also developing second-generation vaccines against B.1.351. Moderna’s published strategy includes testing a vaccine specific to the South Africa variant and a multivalent vaccine that combines the previously authorized vaccine for the ancestral strain and the new vaccine for the variant. Still yet to be defined is the framework of evidence indicating the need for a modified vaccine and the process for evaluating, deciding, and recommending whether a modified vaccine is needed. The World Health Organization (WHO) likely will have a role in global coordination and is developing a risk assessment framework.

⁶⁸ <https://investors.modernatx.com/news-releases/news-release-details/moderna-covid-19-vaccine-retains-neutralizing-activity-against>;
<https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-it-has-shipped-variant-specific-vaccine>;
<https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biotech-initiate-study-part-broad-development>

The FDA recently published guidance on the evidence needed to support an EUA amendment for vaccines addressing the emerging SARS-CoV-2 variants.⁶⁹ The required evidence includes the following:

1. Good manufacturing practices and controls
2. Nonclinical data (e.g., laboratory studies, animal models)
3. Clinical data from immunogenicity studies — noninferiority with authorized vaccine
 - Primary series or booster dose
 - Could be single age group with extrapolation to other age groups
 - Safety data from during the immunogenicity evaluation period
4. Laboratory assays and immunogenicity endpoints
 - Correlates of protection not yet established

In closing, CDC will continue to monitor evidence on the emergence and spread of SARS-CoV-2 variants, vaccine effectiveness, breakthrough infections in vaccinated or previously infected persons, and the ability of post-vaccination serum to neutralize emerging variant viruses. The COVID-19 Vaccines WG and ACIP will review evidence submitted for any next generation vaccines if it becomes clear that they are needed to address variants.

Discussion Points

Dr. Romero asked what is known about recombination and whether it plays a role in the development and transmission of new mutations.

Dr. Scobie pointed out that SARS-CoV-2 does not have a segmented genome unlike influenza for which this is a major source of variant generation. It is possible for SARS-CoV-2, but it is not clear that this is a major source of evolutionary variation.

Dr. Romero noted that for poliovirus, the RNA will slip down, jump off, and move on to another virus.

Dr. Scobie replied that she has seen a few papers that mention that this may be the case, but it does not seem to be a major source of introduction of mutation. She called upon someone from the laboratory to comment further.

Dr. Wentworth added that it is a good question. RNA recombination is seen in coronaviruses, but it has not been observed to drive the evolution of the variants. These variants have evolved independently in a linear sense across the genome as point mutations that have occurred and then develop further point mutations. When so many mutations are occurring at the same time such as in the 351 variant, recombination cannot be ruled out. However, there is no evidence of that at this point. That would be intraspikes recombination events. Usually with coronaviruses, the recombination is everything 3 prime to some point downstream and it is easy to see.

Dr. Maldonado (AAP) pointed out that recombination events are quite frequent with RNA viruses. For example, they occur on a regular basis with polioviruses and are usually not canonical so they can happen at any point. There are some recent non-peer-reviewed papers suggesting that there are combinations that can occur. While these are different, it is not insignificant.

⁶⁹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19>

Dr. Zahn (NACCHO) commented that from a local public health level, it would be great to have a sense of a variant before it becomes a variant of concern. They have had the experience in California with researchers identifying new strains that may be reported in the local media and the literature and there may be speculation as to how important these news strains are, whether they are more infectious, whether they change the epidemiology, and so forth. When they are asked about this by local and state public health, it would be beneficial in terms of communication to have a roadmap to describe how these events are being assessed.

Dr. MacNeil indicated that this is a very active and ongoing discussion. From the USG standpoint, definitions are being developed that are in the interagency phase. CDC is also assessing this internally to make decisions about what constitutes a variant of concern. A clear definition is needed. Some of the key criteria that go into this include evidence of the virus having immune escape, evidence of convergent evolution, the potential impact of diagnostics or therapeutics, or evidence of increased transmissibility or disease severity.

Dr. Goldman (ACP) inquired as to whether the reason is known for Florida's seemingly disproportionate number of variants.

Dr. MacNeil replied that with regard to B.1.1.7, early on there were a number of different diagnostic PCR assays that were indicative of the deletion of amino acids 69 and 70. Early on using the S-Gene Target Failure (SGTF) screening assay, there were attempts to try to rapidly identify circulation of B.1.1.7, which somewhat depended on which diagnostic laboratory was involved. There was a natural concentration in terms of certain states and enrichment of B.1.1.7. That said, in addition to maybe some skewing of the data, there probably is increasing transmission in Florida. It may be partly artifactual, but there is evidence of the virus continuing to become more prevalent. Also related is that given the evidence that B.1.1.7 has a higher reproductive number, once a critical point of growth of that variant is reached, the variant's share is exponential. It may be partly a founder effect where a state like Florida had earlier introductions enough that it started the exponential growth phase.

Dr. Kimberlin (AAP Redbook) recalled that slide 20 mentioned that the AZ vaccine being studied in the time at South Africa was not a prefusion stabilized spike protein, which therefore limited generalizability to other vaccines. He inquired as to whether the mRNA vaccines and the Janssen vaccine are prefusion stabilized spike proteins and if the AZ vaccine was unique in not being a prefusion stabilized spike protein vaccine among the 3 currently authorized vaccines. Dr. Scobie confirmed that this was her understanding.

Dr. Kotton expressed gratitude for mention of immunocompromised hosts as an area of emerging interest. As someone who cares for many immunocompromised hosts, she is seeing an increased rate of refractory disease with months of infection and disease. She is very concerned that this may serve as an important reservoir for multiple mutations and potentially nosocomial transmissions, et cetera. She asked whether this would be an area of focus for vaccinations and/or research, given that this could be the most significant problem population.

Dr. Wentworth indicated that while there are not particular laboratory studies geared toward this at present, he agreed that this is an important population. There are specific cases periodically in which people refer to the CDC about a long-term shedder in whom infection cannot be resolved.

Dr. MacNeil added that he is not aware of any studies specifically focused on immunocompromised individuals. He agreed with the importance of this point and noted that this was one of the prevailing hypotheses behind the emergence of B.1.351 and the fact that quite a number of mutations emerged within a single variant. It is possible that immunocompromised individuals in essence shed for a long period of time, which will allow the virus to acquire quite a number of mutations. There may be an opportunity in locations where there is a high prevalence of HIV-positive individuals to conduct enhanced or further surveillance.

Dr. Kotton added for the record that she meant immunocompromised in general and not as much HIV as patients on rituximab and other potent immunosuppression. While they are not currently referring these cases to CDC, that could be done on a large scale. The immunocompromised host clinicians would need to be informed about that.

Regarding the emergence of the UK variant, Dr. Sanchez noted that a lot has been said about the UK delaying the second dose and he wondered whether any studies had examined the potential relationship between delay of the second dose and emergence of variants. He emphasized that Dr. Scobie's presentation seemed to clearly answer the question posed by the first presentation of the day about whether to continue with the 2-dose regimen without delay of the second dose.

Dr. Scobie clarified that sequentially, B.1.1.7 did arise and become prevalent before the delay in the second dose became a policy. She was not aware of any studies assessing the delay of the second dose, but quite a few studies are being published in the literature now on the real-world vaccine efficacy of 1 dose. She thought those were used as the rationale to support the policy in the UK. It is a good question and the more conservative approach is to follow the current recommendation in terms of the 2-dose series.

Dr. Long wondered whether there is any signal that children are affected differently with the mutant variants. She emphasized that pediatricians are concerned about the next respiratory season. It is not clear from whence comes the blessing that children seem to be less affected by SARS-CoV-2, but everyone is concerned that if part of the explanation is some cross-protection or being primed with other coronaviruses, it is going to be a very complicated next winter when there have not been any respiratory viruses such that there will be a double group experiencing their first influenza, respiratory syncytial virus (RSV), and potentially children who have not seen coronavirus. It will be important to understand the genetics of the organisms that have caused disease in children.

Dr. MacNeil indicated that the overall prevailing thought in general outside of B.1.1.7 is that these variants do not have differing impact on clinical outcomes. There are some data that have not yet been published from reports on a UK study that B.1.1.7 may be more associated with increased severity in terms of hospitalizations and deaths. However, he was not aware of any evidence as this point specific to children and differences in terms of outcomes.

Dr. Gluckman (AHIP) asked whether there is any idea about what the speed to market will be for the development of second generation Pfizer and Moderna vaccines, and whether it will be important to have consistency in the platform for whatever a patient received with first generation vaccines. That is, if their primary vaccine was with an mRNA vaccine any second generation vaccination also should be with an mRNA vaccine.

Dr. Oliver responded that they are going to have to wait to see what the development speed and recommendations will be. As mentioned before, FDA is laying the groundwork for how this would work. CDC would wait for data to be submitted to FDA and then bring those data to ACIP for future discussion and recommendations. As has been publicly stated, Moderna has indicated that they will be starting trials soon with the variant vaccines. CDC will keep ACIP updated on these vaccines moving forward.

Dr. Duchin (NACCHO) noted that it seems with the predicted prevalence of B.1.1.7 in the US and the increasing recognition of other variants, the US remains vulnerable to a potentially severe fourth wave of this COVID-19 pandemic. It is clear that vaccines ultimately will be the best weapon against COVID-19 and its variants, but it is important in this discussion to recognize that it cannot be the only strategy at this point. They must reinforce the importance of other COVID-19 prevention measures at this time, including limiting activities, well-fit and well-maintained face masks, good ventilation, avoiding crowded indoor spaces, et cetera. He noticed that one slide mentioned that high vaccine coverage will blunt the impact of higher transmissibility. Clearly, the more people who are vaccinated the more who are protected. He requested further comment on what “high vaccine coverage” meant in this context.

Dr. MacNeil indicated that the modeling team set up dynamic models for this, which he thought was based on vaccine coverage increasing over time. He did not immediately recall the assumptions, he noted that the study is published in the *MMWR*.

Dr. Weiser (IHS) asked about the completeness of the surveillance systems, particularly for rural areas. Related to that, he wondered who they should contact if interested in participating.

Dr. MacNeil acknowledged that representativeness is certainly a challenge, particularly for a large proportion of the pandemic during which there was reliance primarily on platforms that involved crowd sourcing of sequencing. As Dr. Scobie mentioned earlier, CDC has taken on a couple of initiatives to try to scale up the number of sequences and the representativeness of these. This includes the NS3 surveillance that functions through CDC’s state and jurisdictional public health laboratories as well as trying to generate sequences across the board from large number of specimens from commercial laboratories. He thinks they are getting much closer to being representative and in having a denominator in which they can be confident enough to begin generating representative prevalence estimates. That should be coming out soon. In terms of participating, NS3 is functioning through state and jurisdictional public health laboratories. Working with them would be the way to operate through NS3. There are a number of other sequencing efforts through state and local public health laboratories and academic partners. As much data as they can get in the public space is going to be helpful and will contribute to the overall understanding of the viruses that are circulating.

Dr. Arthur (BIO) suggested that it might also be beneficial for the ACIP to review the emerging data on the use of monoclonal antibodies in the preventive space, which could add some complexity to the discussion about prevention, particularly in the presence of variants. Some of the preliminary data are quite strong and might be worthwhile to provide an opportunity for the ACIP WG and members to review those data as they start to roll out.

Dr. Maldonado (AAP) suggested that it might be helpful for ACIP to hear a presentation on how the variants that recently have been circulating impact transmission and the concept of herd immunity based on current models.



Certification

Upon reviewing the foregoing version of the February 28-March 1, 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.

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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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