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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
October 30, 2020
Atlanta, Georgia

Final - October 27, 2020

Friday, October 30, 2020

10:00	**Coronavirus Disease 2019 (COVID-19) Vaccines**	
	Introduction	Dr. Beth Bell (ACIP, WG Chair)
	Update from Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting	Dr. Doran Fink (FDA)
	NVX-CoV2373 Vaccine Candidate	Dr. Filip Dubovsky (Novavax)
	Janssen's SARS-CoV-2 Vaccine Program	Dr. Jerry Sadoff (Janssen)
11:45	***Break***	
12:00	Update on vaccine implementation planning	Dr. Janell Routh (CDC/NCIRD)
	Vaccinate with Confidence	Dr. Amanda Cohn (CDC/NCIRD)
12:30	***Lunch***	
1:15	FDA safety surveillance systems	Dr. Steven Anderson (FDA)
	Post-authorization safety monitoring plans	Dr. Tom Shimabukuro (CDC/NCEZID)
	Modeling strategies for the initial allocation of COVID-19 vaccines	Dr. Matthew Biggerstaff (CDC/NCIRD)
	Discussion	
2:30	***Break***	
2:45	Updates to immunity and epidemiology to inform COVID-19	Dr. Megan Wallace (CDC/NCIRD)
	Ethical principles for early vaccine allocation	Dr. Mary Chamberland (CDC/NCIRD)
	Work Group interpretation of data	Dr. Sara Oliver (CDC/NCIRD)
	Policy questions, Evidence to Recommendation Framework, and Discussion	Dr. Kathleen Dooling (CDC/NCIRD)
4:45	**Adjourn**	

Acronyms

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

Acronyms

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
AE	Adverse Event
AECI	Adverse Events of Clinical Interest
AESI	Adverse Events of Special Interest
BARDA	Biomedical Advanced Research and Development Authority
BEST	Biologics Effectiveness and Safety
BOP	Bureau of Prisons
CARES Act	Coronavirus Aid, Relief, and Economic Security Act
CBER	Center for Biologics Evaluation and Research
CBO	Community-Based Organization
CDC	Centers for Disease Control and Prevention
CMS	Center for Medicare and Medicaid Services
COI	Conflict of Interest
COU	Clinical Operations Unit
COVID-19	Coronavirus Disease 2019
CoVPN	COVID-19 Prevention Network
CRO	Contract Research Organization
DART	Development and Reproductive Toxicology
DE	Division of Epidemiology
DFO	Designated Federal Official
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DOS	Department of State
DUA	Data Use Agreement
DSMB	Data Safety Monitoring Board
ED	Emergency Department
EHR	Electronic Health Record
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EMR	Electronic Medical Record
ERD	Enhanced Respiratory Disease
ET	Eastern Time
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
FACA	Federal Advisory Committee Act
FDA	Food and Drug Administration
GBS	Guillain-Barre Syndrome
GMTs	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HCoVs	Human Coronaviruses
HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers
HHS	(Department of) Health and Human Services

HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IDCRP	Infectious Disease Clinical Research Program
IgG	Immunoglobulin G
IHS	Indian Health Service
IIS	Immunization Information Systems
IIV	Inactivate Influenza Vaccine
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
ISO	Immunization Safety Office
JHU	Johns Hopkins University
LTCF	Long-Term Care Facilities
MISC-A	Multisystem Inflammatory Syndrome in Children
mRNA	Messenger Ribonucleic Acid
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCIRD	National Center for Immunization and Respiratory Diseases
NEJM	*New England Journal of Medicine*
NHP	Non-Human Primate
NIH	National Institutes of Health
NVAC	National Vaccine Advisory Committee
OBE	Office of Biostatistics and Epidemiology
OWS	Operation Warp Speed
PCP	Primary Care Practitioner
PCR	Polymerase Chain Reaction
PICO	Population, Intervention, Comparison, Outcomes
PPE	Personal Protective Equipment
QI	Quality Improvement
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SLU	Saint Louis University
SMC	Safety Monitoring Committee
SME	Subject Matter Expert
STLT	State, Tribal, Local, and Territorial
UK	United Kingdom
US	United States
USG	US Government
VA	(US Department of) Veteran’s Affairs
VAERS	Vaccine Adverse Event Reporting System
VaST	ACIP COVID-19 Vaccine Safety Technical Sub-Group
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFC	Vaccines for Children
VMED	Vaccine-Mediated Enhanced Disease

VRBPAC	Vaccines and Related Biological Products Advisory Committee Meeting
VSD	Vaccine Safety Datalink
VTrckS	Vaccine Tracking System
VTU	Vaccine Treatment Evaluation Unit
wtVNA	Wild-Type Virus Neutralizing Antibodies
WG	Work Group
WHO	World Health Organization
YF	Yellow Fever

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

José Romero, MD, FAAP
ACIP Chair

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Romero called to order the October 30, 2020 emergency meeting of the Advisory Committee on Immunization Practices (ACIP) focused solely on the topic of coronavirus disease 2019 (COVID-19) vaccines. He emphasized that faced with a crisis of historic proportion, basic scientists, clinical scientists, clinical investigators, and volunteers have worked with unprecedented speed to develop, test, evaluate, and manufacture a plethora of potential vaccines against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The mandate given to the ACIP has been to develop equitable, just, and fair policy guidelines for the use of those vaccines that are proven to be safe and effective in preventing and mitigating SARS-CoV-2 disease. The volume of data that have been compiled, analyzed, synthesized, and presented to the ACIP voting members, liaisons, *ex officio* representatives and the public has possibly been more than ever presented for any other vaccine that has come before the ACIP. It can be said without hyperbole or exaggeration that no other national COVID-19 vaccine advisory group has dedicated as much time to addressing questions posed to the ACIP regarding the use of those COVID-19 vaccines.

Over the 7 months since its creation, the ACIP's COVID-19 Vaccine Work Group (WG) has met more times than any other non-standing ACIP WG. Dr. Romero publicly acknowledged the extraordinary work in terms of time, effort, and quality that the members of the COVID-19 Vaccine WG have dedicated to this effort. In addition to the official WG members, all ACIP members have given of their time to prepare for, attend, and meaningfully participate in the equivalent of 2 years' worth of open public meetings in a 10-month timeframe. Dr. Romeo also acknowledged the extraordinary leadership of Dr. Nancy Messonnier, Director of the National Center for Immunization and Respiratory Diseases (NCIRD); Dr. Amanda Cohn, ACIP Executive Secretary; and Jessica McNeil, Assistant Executive Secretary for ACIP. In addition, he acknowledged the important support work provided by Ms. Stephanie Thomas and Ms. Natalie Greene who have provided much of the materials to be reviewed prior to the meetings. In closing, he thanked all who have dedicated, are dedicating, and will continue to dedicate their time to ACIP's efforts to provide guidance for the use of safe and effective COVID-19 vaccines, emphasizing that he believed history would not forget their dedication to this task.

During the first day of the regular ACIP meeting on October 28, 2020, Dr. Cohn welcomed everyone and indicated that copies of the slides being presented during this meeting were available on the ACIP website and had been made available through a ShareFile link for ACIP Voting, Liaison, and *Ex-Officio* members; videos of the live webcast would be posted on the ACIP website approximately 1 week after the meeting; and that meeting minutes also would be posted on the ACIP website, generally within 90-120 days of the meeting. She reviewed meeting logistics and reminded everyone that 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 while serving on the committee, CDC

has issued limited conflict of interest (COI) waivers. Members who conduct vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those vaccines, but are prohibited from participating in committee votes on issues related to those vaccines. 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.

Dr. Romero conducted a roll call of ACIP members. During the roll call of the regular ACIP meeting on October 28, 2020, ACIP members stated any COIs. These remained unchanged during the October 30, 2020 emergency ACIP meeting:

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

- Dr. Sharon Frey is employed by Saint Louis University (SLU), which has a Vaccine Treatment Evaluation Unit (VTU) that is part of the IDCRC. She is currently serving as the Site PI for the Moderna and Janssen Phase 3 COVID-19 vaccine clinical trials.

- Dr. Paul Hunter owns a small amount of stock in Pfizer and has received a small grant from Pfizer to conduct a quality improvement (QI) project on pneumococcal vaccines.

Given that no specific vaccine products were being recommended during this meeting, all voting ACIP members were permitted to participate in the discussion.

A list of Members, *Ex Officio* Members, and Liaison Representatives is included in the appendixes at the end of the full minutes for the October 30, 2020 ACIP emergency meeting.

Coronavirus Disease 2019 (COVID-19) Vaccines

Introduction

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

Dr. Bell thanked Dr. Romero for his leadership, incredible assistance and support, and vision in the context of the ACIP's work in addressing the COVID-19 pandemic and working on COVID-19 vaccine policy. She then introduced the session for the October 30, 2020 emergency ACIP meeting, which focused on ACIP's continued response to the ongoing pandemic and accelerated vaccine development. She reminded everyone that during the September 22, 2020 meeting, ACIP reviewed the following topics:

- ❑ Overview of COVID-19 Vaccine Safety
- ❑ Enhanced Vaccine Safety Surveillance
- ❑ Vaccine Implementation
- ❑ Disparities Among COVID-19 Epidemiology
- ❑ Overview of Vaccine Equity and Prioritization Frameworks
- ❑ Phase 1 Allocation for COVID-19 Vaccine: WG Considerations

The COVID-19 Vaccine WG continues to meet on a weekly business. The topics this group has covered during October include the following:

- ❑ Review of Available Information on Reinfection of COVID-19
- ❑ Post-Infection Immunity
- ❑ Discussions to Finalize the Outcomes for GRADE (Grading of Recommendation Assessment, Development and Evaluation)
- ❑ Modeling Data for Initial Allocation of Vaccine
- ❑ Current Epidemiology of COVID-19 in Pregnant Women
- ❑ Review of Ethical Principles to Inform Initial Allocation of Vaccine
- ❑ Clinical Development Program for Two COVID-19 Vaccines, Including Data From Phase I/II Clinical Trials and Plans for Phase III Clinical Trials
- ❑ Further Discussions Regarding COVID-19 Vaccine Allocation

Dr. Bell indicated that during this session, presentations would be provided in the following topic areas:

Vaccine Development & Regulatory
- ❑ Update from VRBPAC meeting
- ❑ NVX-CoV2373 Vaccine Candidate
- ❑ Janssen's SARS-CoV-2 Vaccine Program

Implementation
- ❑ Update on Vaccine Implementation Planning
- ❑ Vaccinate with Confidence

Safety
- ❑ FDA Safety Surveillance Systems
- ❑ Post-Authorization Safety Monitoring Plans

Allocation and Epidemiology
- ❑ Modeling Strategies for the Initial Allocation of COVID-19 Vaccines
- ❑ Updates to Immunity and Epidemiology to Inform COVID-19 Vaccine Policy
- ❑ Ethical Principles for Early Vaccine Allocation

WG Interpretation
- ❑ WG Interpretation of Data
- ❑ Policy Questions, Evidence to Recommendation (EtR) Framework, and Outcomes

Dr. Bell reported that over 200 COVID-19 vaccines are currently under development. Within the US, 4 vaccines are in active Phase III clinical trials and 5 are in active Phase I/II clinical trials. In terms of the Phase III clinical trials in the US, AstraZeneca announced the removal of an FDA hold on its AZD1222 vaccine on 10/23/2020 and are resuming Phase III trials. Janssen announced the lifting of its safety pause for its Ad26.COV2.S vaccine on 10/23/2020 and is resuming Phase III trials. The Pfizer/BioNTech BNT162b2 vaccine trial reported having enrolled 42,133 participants as of 10/26/2020. Of these, 35,771 participants have received their second vaccination. In addition, Pfizer/BioNTech reported that approximately 30% of US participants enrolled have "diverse backgrounds." Enrollment is complete for Moderna's messenger ribonucleic acid (mRNA)-1273 vaccine. As of 10/22/2020, approximately 30,000 participants have been enrolled and 25,654 of those participants have received their second vaccination.

In terms of the distribution of demographic characteristics of the participants in Moderna's Phase III clinical trials in the US taken from their website, 63% of participants are White, 20% are Hispanic/Latinx, 10% are Black/African American, 4% are Asian, and 3% are Other Racial/Ethnic Groups. Approximately 8000 participants are ≥65 years of age. Of the participants, 22% are healthcare personnel (HCP) and 27% report living with comorbidities (e.g., diabetes, cardiac disease, lung disease, and obesity). Dr. Bell shared a table of the COVID-19 vaccines in human clinical trials in and outside of the US, pointing out that there are additional inactivated vaccines in Phase I/II/III, 10 protein subunit vaccines candidates in Phase I/II, 7 non-replicating viral vector vaccine candidates in Phase I/II, and 7 RNA vaccine candidates in Phase I/II.

Food and Drug Administration (FDA) Update

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

Dr. Fink provided an overview of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting on October 22, 2020 during this session. He first reminded everyone that the VRBPAC reviews and evaluates data concerning the safety, effectiveness, and appropriate use of vaccines and related biological products. VRBPAC is a committee of experts external to FDA that provides input upon request by FDA on certain regulatory actions (e.g., licensure of new vaccines) and on more general topics critical to advancing regulatory science. VRBPAC recommendations are non-binding, but are usually followed by FDA.
The VRBPAC met on October 22, 2020 for a general discussion of the development, authorization, and/or licensure of vaccines to prevent COVID-19. This was an open meeting with a live webcast that was accessible to the public. There was no discussion of specific COVID-19 vaccine candidates or any votes on recommendations. The agenda included the following topics:

- ❑ FDA Introduction and Presentation of Discussion Points
- ❑ Epidemiology, Virology, and Clinical Features of COVID-19 (CDC)
- ❑ NIH Activities in the Development of Vaccines Against COVID-19
- ❑ Biomedical Advanced Research and Development Authority (BARDA) Activities in the Development of Vaccines Against COVID-19

- ❑ CDC Plans for Safety/Effectiveness Monitoring & Evaluation During Emergency Use Authorization (EUA) Use and Post-Licensure FDA Surveillance Systems and Plans for Post-Marketing/Post-Authorization Evaluation
- ❑ Operational Aspects of COVID-19 Vaccine Distribution and Tracking (CDC)
- ❑ COVID-19 Vaccine Confidence (Reagan-Udall Foundation)
- ❑ Licensure and Emergency Use Authorization of Vaccines to Prevent COVID-19: Manufacturing and Clinical Considerations (FDA)
- ❑ Open Public Hearing
- ❑ Committee Discussion and Recommendations

During that VRBPAC meeting, the FDA explained the considerations for manufacturing and clinical information needed to support licensure for EUA of COVID-19 vaccines, as described in two recent FDA guidance documents. The purpose of the guidance documents is to provide reassurance that FDA will rely on sound science, established regulatory standards, and a transparent process for evaluating COVID-19 vaccine candidates.

Dr. Fink first explained the clinical considerations for an EUA in detail, which are summarized as follows:

- ❑ EUA for a COVID-19 vaccine may be requested to allow for the vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people, following a planned interim analysis in an ongoing Phase 3 trial

- ❑ A favorable benefit/risk determination to support issuance of an EUA in this scenario would require the following, in addition to adequate manufacturing information:

    - ➢ Efficacy data showing protection against SARS-CoV-2 infection or disease with a point estimate of least 50% versus a placebo comparator and an appropriately alpha-adjusted confidence interval lower bound >30%
    - ➢ At least half of Phase 3 study subjects followed for both safety and efficacy for at least 2 months following completion of the full vaccination regimen
    - ➢ Safety data from throughout clinical development (including well over 3,000 Phase 3 vaccine recipients) to evaluate reactogenicity, serious adverse events (SAEs), and AEs of special interest (AESI)
    - ➢ Sufficient cases of severe COVID-19 to assess for signals of enhanced disease

- ❑ Reasons for a median follow-up of at least 2 months after completion of the full vaccination regimen to support issuance of an EUA for a COVID-19 vaccine:

    - ➢ Allows time for potential immune-mediated adverse reactions to be evaluated (uncommon but clinically significant immune-mediated adverse reactions to preventive vaccines generally have onset within 6 weeks following vaccination)
    - ➢ Ensures that vaccine efficacy is assessed during the time period when adaptive/memory immune responses (rather than innate responses) are mediating protection
    - ➢ Allows for early assessment of waning protection and signals of enhanced disease

- Following a successful efficacy analysis that supports issuance of an EUA, further evaluation of a COVID-19 vaccine would be needed:
    - For ongoing benefit/risk assessments for continuation of the EUA
    - To accrue additional data to support licensure and/or to inform labeling
- Continued evaluation of a COVID-19 vaccine made available under EUA would include:
    - Longer-term follow-up for safety, including in larger numbers of vaccine recipients and in populations with lower representation in clinical trials
    - More precise estimation of vaccine effectiveness
    - More robust assessment of effectiveness against specific aspects of SARS-CoV-2 infection or disease
    - Characterization of duration of protection
    - Investigation of immune biomarkers that might predict protection
    - Ongoing monitoring for signals of enhanced disease
- Issuance of an EUA for a COVID-19 vaccine would be contingent upon the ability to conduct further vaccine evaluation through a combination of:
    - Active follow-up of vaccine recipients under the EUA
    - Passive monitoring for clinically significant adverse reactions using established reporting mechanisms (e.g., VAERS)
    - Observational studies, including those that leverage healthcare claims databases
    - Continuation of blinded, placebo-controlled follow-up in ongoing clinical trials for as long as is feasible and strategies to handle loss of follow-up
- FDA does not consider issuance of an EUA for a COVID-19 vaccine to necessitate immediate unblinding of ongoing clinical trials or offering vaccine to all placebo recipients
    - Trial participants may choose to withdraw from follow-up for any reason, including to receive vaccine made available under EUA

A number of specific topics were posed during the meeting for VRBPAC discussion, including the following:

- Please discuss FDA's approach to safety and effectiveness data as outlined in the respective guidance documents.
- Please discuss strategies for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine
- Please discuss studies following licensure and/or issuance of an EUA for COVID-19 vaccines to further evaluate safety, effectiveness, and immune markers of protection and evaluate the safety and effectiveness in specific populations.

To summarize the discussion from the meeting, VRBPAC expressed concerns about public vaccine confidence, consistent with those described in the Reagan-Udall Foundation presentation. Hesitancy around acceptance and use of COVID-19 vaccines will continue to be driven by speed of vaccine development and the perception of uncertainty and limitations of data. Issues with COVID-19 vaccine deployment could adversely impact public confidence in vaccines in general. Regulatory actions to make COVID-19 vaccines widely available therefore need to be transparent, effectively communicated, and above all supported by adequate data.

There was broad agreement that data to support issuance of an EUA for a COVID-19 vaccine should not be less than the standards outlined by the October 2020 FDA guidance. Some VRBPAC members expressed concerns that a median follow-up of 2 months after completion of the vaccination regimen would not be sufficient to support an EUA for rapid and widespread deployment, in particular for vaccines manufactured for novel platforms. A successful interim efficacy analysis, with more limited COVID-19 cases and wider confidence intervals compared to a final analysis, would not be sufficient to support an EUA for rapid and widespread deployment. Other VRBPAC members considered 2 months medium follow-up to be sufficient to support issuance of an EUA. They felt that rare AEs and waning immunity could be monitored by surveillance during vaccine use under an EUA.

Some VRBPAC members were concerned about COVID-19 of any severity as the primary efficacy endpoint in current Phase 3 trials, given that there may be limited information on severe disease. FDA and some VRBPAC members discussed that primary endpoints were selected based on feasibility and prior experience with preventive vaccines. Vaccines are typically approved based on data showing prevention of laboratory-confirmed disease, regardless of severity. Experience supports that vaccine effectiveness increases with more specific (e.g., more severe) case definitions. While analyses to support EUA will include some information on severe disease, insisting on an adequately powered analyses of severe disease (which has a lower incidence than less severe disease) could delay the availability of an impactful vaccine.

VRBPAC members expressed concern about clinical trial recruitment of, and accrual of data, in the populations most affected by COVID-19 (e.g., racial and ethnic minorities, elderly individuals, and individuals with medical comorbidities). FDA reported that published guidance and advice to COVID-19 vaccine manufacturers has advocated for inclusion of these populations in trials. While there is no regulatory mechanism for mandating trial recruitment, vaccine manufacturers have been publicizing enrollment demographics for their trials. This is important given that demographic and medical history data from trial participants will be considered in regulatory decisions and will be reflected in vaccine labeling to inform HCP and vaccine recipients. Vaccine manufacturers have been publicizing enrollment demographics for their trials.

There also was discussion regarding considerations for pediatric development and data to support use in pediatric populations, particularly with respect to careful evaluation of immune-mediated reactions or enhanced disease and immunobridging approaches. There is a need for safety assessments that include careful evaluation for immune-mediated reactions or enhanced disease (e.g., MIS-C/MIS-A) to support benefit/risk considerations for pediatric enrollment in clinical trials and for vaccine authorization or approval in pediatric age groups. Immunobridging approaches to infer vaccine effectiveness in pediatric populations will benefit from an evolving understanding of natural and vaccine-elicited immunity.

There was broad agreement among VRBPAC members that blinded, placebo-controlled follow-up in ongoing trials should continue for as long as is feasible, including after an EUA. Concern was expressed that if a COVID-19 vaccine were widely deployed under EUA based on limited data, it could harm further accrual of critical data from placebo-controlled follow-up. There was agreement with the need for robust strategies for vaccine evaluation following licensure or EUA to complement, and replace once it becomes infeasible, placebo-controlled follow-up.

VRBPAC raised questions about expanded access as an alternative to EUA. FDA explained that expanded access is another regulatory mechanism for making investigational products to address serious diseases available outside of clinical trials. An expanded access treatment protocol could be considered to allow for deployment of a COVID-19 vaccine. It is important to note that the benefit/risks considerations are similar to EUA, other considerations such as planning and implementation differ from EUA, and an expanded access treatment protocol would be conducted under Investigational New Drug (IND) regulations that require informed consent, Institutional Review Board (IRB) oversight, and investigator responsibilities for vaccine providers.

In terms of next steps, FDA will consider the October 22nd VRBPAC feedback provided in continuing to balance the public health goal of safe and effective vaccines to address the COVID-19 pandemic and the obligation to ensure that authorization or approval of any COVID-19 vaccine complies with regulatory requirements for sufficient safety, effectiveness, and manufacturing information to support favorable benefit/risk for vaccine recipients. The VRBPAC will be reconvened prior to any FDA action to approve or issue an EUA for a COVID-19 vaccine to evaluate and discuss data submitted in support of the licensure application/EUA request and vote on recommendations as to whether the data support vaccine licensure/proposed use of the vaccine under EUA.

Discussion Points

Dr. Romero asked what the considerations are for unblinding individuals who withdraw from a study with regard to whether they receive placebo or vaccine.

Dr. Fink indicated that FDA cannot mandate that any vaccine manufacturer conducting a clinical trial unblind or not unblind the trial, or that unblind or not unblind any individual participant. This is a matter of ethical and scientific consideration and FDA would like the vaccine manufacturers who are conducting a trials to think very carefully about balancing the ethical and scientific implications of their decision to unblind.

Dr. Ault asked whether there is a video archive of the VRBPAC meeting that is available to the public, and for the expanded access whether there ever has been one of this order of magnitude with millions of doses of vaccine.

Dr. Fink indicated that there is a YouTube video recording of the VRBPAC available at the following link: https://www.youtube.com/watch?v=1XTiL9rUpkg&feature=youtu.be. There are recent examples of expanded access treatment protocols that have been used to provide vaccine to thousands of individuals or tens of thousands of individuals. One example was to address the meningococcal B disease outbreak on several college campuses prior to FDA licensure of the meningococcal group B vaccines. More recently, there has been an expanded access protocol for the non-US licensed yellow fever (YF) vaccine Stamaril® due to a shortage

of the US-licensed YF vaccine YF-VAX® in travel clinics across the US. Having said that, these examples pertain to thousands and tens of thousands of vaccine recipients versus millions of vaccine recipients. The IND requirements for an expanded access treatment protocol certainly would add some complexities and feasibility concerns to using that regulatory mechanism.

Dr. Frey pointed out that safety may be a major driving factor for vaccine hesitancy. There have been two very nice examples of pause or halting rules to the studies that have occurred already. While this may be novel to the general community, it is actually a positive thing when people pause a study or hold a study from further enrollment until there are discussions and people are comfortable with the decision-making. She asked whether all of the studies being initiated are being scrutinized with the same rigorous standards of safety.

Dr. Fink responded that all of the Phase 3 studies underway have very close oversight from a DSMB that regularly reviews safety data and meets on an ad hoc basis to review, discuss, and consider whether any change in trial conduct is warranted following a safety signal, such as a SAE for which causal relationship to the study vaccine cannot be excluded. Furthermore, some studies in addition to the DSMB oversight have pre-specified study pausing rules that are triggered based on certain safety events.

Ms. McNally requested additional background on expanded access and how it differs from the traditional FDA approval process and the EUA, how a person who wanted to obtain a COVID-19 vaccine would go about receiving it under expanded access, and whether the Reagan-Udall Foundation had any discussions with consumers regarding expanded access during its listening session.

Dr. Fink clarified that expanded access is not an approval process. The only approval process is licensure. There are several regulatory mechanisms for making an investigational product, including investigational vaccines, outside of clinical trials. An EUA is one of those mechanisms and it is dependent upon declaration of a public health emergency, such as COVID-19. Expanded access does not require a declaration of a public health emergency, but it does have additional requirements for use of the investigational product as compared with an EUA. Expanded access is conducted under the IND regulations and can be of a range of sizes spanning from just 1 patient to hundreds or thousands of patients depending upon the need and data available to support its use. An idea was raised by the VRBPAC about use of COVID-19 vaccine under expanded access, and the FDA is in the process of considering whether this would be an appropriate mechanism for deployment of a COVID vaccine. If that is considered, the vaccine manufacturer that has an active IND on file with the FDA would submit a protocol for use of the vaccine under expanded access regulations and potentially would work with other governing agencies, as was the case with the YF vaccine expanded access experience, to organize and implement the expanded access protocol. In terms of the Reagan-Udall Foundation, this was a question that was raised during the end of a VRBPAC meeting and he did not think that expanded access was addressed by the foundation's efforts.

Dr. Lee expressed gratitude for all of the work FDA and VRBPAC have done to get them to this place. She asked how often FDA anticipates the continuing evaluations of COVID-19 vaccines data under an EUA to occur, and whether there have been discussions around potential thresholds that would change decisions as data continue to accumulate. In terms of Dr. Fink's mention that an EUA would be contingent on follow-up on safety and effectiveness and specifically observational studies that leverage healthcare claims databases, she wondered

whether there are plans to use Sentinal as one of the options for that versus manufacturer led studies.

Dr. Fink responded that continued evaluation of vaccine following deployment under either an EUA or licensure would include assessments that are made at scheduled intervals, as well as continuous assessments that would include passive reporting as well as mechanisms such as rapid-cycle analyses (RCA). He noted that further information would be provided about some of these systems later in the day in a presentation on FDA and CDC plans for post-licensure or post-authorization surveillance. He clarified that observational studies, including those that leverage healthcare claims data, would not necessarily in and of themselves be a requirement for an EUA, but the FDA does see these as a very important part of continued follow-up during deployment.

Dr. Bernstein expressed appreciation for Dr. Fink's concise and detailed summary of VRBPAC's ongoing extraordinary and challenging work. Regarding the clinical considerations for EUA and why 2 months was chosen, he recalled that Dr. Fink mentioned that the median time was 2 months. He requested clarity about whether it was the median or at least 2 months for all subjects.

Dr. Fink clarified that it is a median. At least half of the subjects will have at least 2 months of follow-up. It is expected that a high proportion of enrolled subjects will have at least 1 month of follow-up. They do recognize that the trials will continue to enroll, so it will not be feasible to demand that all subjects have a certain amount of follow-up to enable regulatory action and allow for deployment of the vaccine, especially in the face of very convincing efficacy data. The Phase 3 trials that are currently underway have enrolled very large numbers of subjects very rapidly, so they do not expect there to be any issues with the proportion of subjects who have safety follow-up.

Dr. Sanchez asked what the timeline for FDA approval is after VRBPAC makes a recommendation for a vaccine, and whether expanded access would pertain to a vaccine studied in persons 18 years of age being expanded to others like the pediatric population.

Dr. Fink replied that for a vaccine to be made available under expanded access to a large number of recipients, there needs to be sufficient data to support a favorable benefit-risk determination in a population. He would not envision a scenario in which a vaccine would be made available to pediatric populations outside of anything other than a clinical trial without data to support favorable benefit-risk in the pediatric population. That would include safety and immunogenicity data to at least support effectiveness specifically in pediatric populations of the age groups that would be under consideration. Expanded access would not be a mechanism for offering vaccine to pediatric populations outside of a clinical trial in the absence of data in pediatric populations. Regarding timing, FDA expects EUA reviews and reviews of licensure applications to be fairly expedited to address the needs of the ongoing pandemic. While he could not provide a definitive answer about how many days or weeks between a VRBPAC meeting and vote that includes recommendations to authorize or include the vaccine and when that vaccine is actually made available through FDA action, it will be as expediently and as quickly as possible.

NVX-CoV2373 Vaccine Candidate

Filip Dubovsky MD, MPH
Chief Medical Officer
Novavax

Dr. Dubovsky reported on the Novavax NVX-CoV2373 vaccine candidate in terms of vaccine design, the non-human primate (NHP) protection study, Phase 1 Day 35 safety and immunogenicity data, Phase 2 Dose 1 and Dose 2 reactogenicity data, and plans for Phase 3. In terms of the NVX-CoV2373 vaccine design, this is a baculovirus-expressed recombinant protein. This is a full-length spike, including transmembrane domain and the usual 2P mutations. It self-assembles into a native conformation trimer and is further processed into a stable nanoparticle. The adjuvant is saponin-based and is a natural product from the bark of a tree. It is processed into purified form into cage-like structures. The antigen and adjuvant are co-administered into a vial of ready-to-use liquid that is stable at 2^0-8^0 C.

In a protection study sponsored by Operation Warp Speed (OWS) that was conducted at Texas Biomedical Research Institute, rhesus macaques were vaccinated at Day 0 and Day 21 and were then challenged with 10^6 wild-type virus at Day 38. Subgenomic RNA was detected on Day 2 and Day 4 in the lower airway in the placebo group, which indicates that viral replication was ongoing. For both dose levels that were taken into clinical study, no RNA was detected indicating that no replication was detected. In the upper airway, replication was seen on days 2, 4, and 7 in the placebo group. No viral replication was detected in the vaccine groups. This is consistent with the other data collected from other NHP studies, as well as in small animals.

Regarding the clinical development plan, the first human Phase 1 study was conducted in Australia with 131 subjects 18 to 59 years of age. Based on the results from this study, Novavax launched 3 studies. One was a Phase 2 study in the US and Australia in 1288 subjects 18 to 84 years of age. At the same time, a Phase 2b study was launched in South Africa that was recently expanded to 4400 subjects and includes a small human immunodeficiency virus (HIV)-positive cohort. A 15,000 Phase 3 study was started in the United Kingdom (UK), which includes a small sub-study with inactivate influenza vaccine (IIV) co-administration to ensure that there are no safety or immunogenicity issues with that. Based on confirmation of the dose and safety from the Phase 2 study, Novavax is launching a large Phase 3 study in the US and Mexico with over 30,000 individuals.

The Phase 1 study, which was published in September 2020, is fully enrolled and safety and immunogenicity follow-up is ongoing. This is the study of the 131 subjects ages 18 to 59 years of age. There were 5 dose groups: placebo, 25 µg with no adjuvant given twice, 25 µg with adjuvant given twice, a high-dose adjuvant group, and a group that had 2 doses of 5 µg and 2 doses of 25 µg given twice. The study sites, investigators, contract research organization (CRO), and participants are blinded to individual vaccine/placebo allocation. Day 35 (14 days after Dose 2) safety and immunogenicity data, which is the basis of the publication, were reviewed by an independent Safety Monitoring Committee (SMC) and submitted to the FDA in advance of the Phase 2 study. The Day 35 safety summary for NVX-CoV2373 is consistent with previous nanoparticle vaccine with Matrix-M1. No SAEs were identified for NVX-CoV2373.There were no AESIs, including potentially immune-mediated medical condition AESIs, and no confirmed COVID-19 AESIs. All AEs were mild and moderate and were balanced in active arms.

In terms of the local reactogenicity symptoms collected 7 days after each dose, the majority of symptoms were none or mild. Pain and tenderness were the most commonly reported. The mean duration was less than 2 days for each of these events. Regarding reactogenicity symptoms, the majority of subjects reported none or mild and the mean duration was less than 2 days for both local and systemic reactogenicity symptoms. There were more systemic symptoms after Dose 2 versus Dose 1 in the placebo and active groups. The most common symptoms reported were headache, fatigue, and myalgia. Once again, the mean duration was less than 2 days.

Regarding the anti-spike immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA) kinetics, after 2 doses delivered on Day 0 and Day 21 there was pretty much no response. After the 2 doses with no adjuvant, there was a bump after Dose 2 that was stable throughout the observation period. The single dose of adjuvanted vaccine had a nice response after dose 1, which stabilized. There was a nice bump after Dose 2 that remained at high levels. From this data, Novavax concluded that adjuvanted vaccine is better than non-adjuvanted vaccine and furthermore, the 2 doses are superior to a single dose. There is a large dose-sparing effect with the adjuvant, because the 5 µg and 25 µg dose groups are comparable.

Regarding the peak immune responses on Day 35 anti-S IgG ELISA and 100% wild-type neutralization responses, the 2 dose groups with adjuvants performed quite well in terms of the IgG. Convalescent sera was donated by Dr. Pedro A. Piedra of Baylor College of Medicine. This is an un-curated panel serum that has the same samples on both the IgG and the neutralization responses. Seroconversion of 100% was achieved for IgG and neutralization. Furthermore, in a post-hoc analysis IgG was 5-fold to 7-fold higher than for convalescent sera and 3- to 4-fold for the neutralization. In addition, the confidence intervals do not overlap. To determine the quality of the immune response, a correlation between the neutralization response and the IgG response was assessed. For the Baylor convalescent serum, there is a nice correlation between IgG and neutralization. This indicates that when people get sick with wild-type infection, they generate antibodies and those antibodies neutralize the virus. For the 25 µg group with no adjuvant, the correlation breaks down. The adjuvanted dose groups recapitulated the pattern seen with wild-type seroconversion and the correlation is tight again. To Novavax, this indicated that the Matric-M1 adjuvant is important in generating desired immune responses, with a functional immune response against a broad range of antibody titer. This is thought to be important from a safety perspective because some people have postulated that antibody does not neutralize and may lead to enhanced illness in the future.

Turning to the intracellular immune response among the placebo, 2-dose 5 µg + Matrix-M, and 2-dose 25 µg + Matrix-M groups. In the placebo group, the Th1 immune response was flat. However, a signal was detected for IL2, IFNg, and TNFa in the other two groups. On the Th2 cytokines, they probed for IL5 and IL13 and found a small increase in those cytokines. This recapitulates what they have seen in small animal models, indicating that this adjuvanted platform is capable of generating a Th1-bias immune response. This is consistent with previous evaluation of this platform in humans. Looking at polyfunctional CD4 T-cells, there was a relatively large proportion of CD4 cells that generate double and triple cytokines for both dose groups, especially when compared to the double cytokines for the Th2 analysis. The beginning strategy was to look for CD45+ CCR7- CD4 cells. They postulated that this would help with the memory response going into the future.

Novavax Phase 1 study conclusions are that reactogenicity and safety profiles are reassuring for both the 5 µg and 25 µg dose groups when formulated with Matrix-M1 adjuvant. In terms of immunogenicity, the Matrix-M1 adjuvant is required to induce an optimal functional immune response, 2 doses of vaccine administered 21 days apart are superior to a single dose, 5 µg and 25 µg induce comparable immune responses when formulated with Matrix-M1, and Matrix-M1 induces a Th1 biased immune response with high levels of neutralizing antibody. The safety and immunogenicity profile of both 5 µg and 25 µg formulated with Matrix-M1 and administered on Day 0, 21 is acceptable for further clinical evaluation.

The Phase 2 study of 1288 adults ages 18 to 84 in the US and Australia is fully enrolled, Dose 2 has been administered, and safety and immunogenicity follow-up is ongoing. The study sites, investigators, CRO, and participants are blinded to individual vaccine/placebo allocation. Reactogenicity data were reviewed by the SMC and the FDA in advance of the Phase 3 study. Regarding local reactogenicity events in 2 Dose adjuvanted groups, pain and tenderness were reported most frequently. Increased rates were seen in the adjuvanted groups, especially after Dose 2, and reactogenicity was attenuated in adults ≥60 years of age. In terms of local reactogenicity events in the 2-dose adjuvanted groups compared to placebo, pain and tenderness were reported most frequently. Increased rates are seen in adjuvanted groups, especially after Dose 2. Reactogenicity events were attenuated in adults >60 years of age, which was exactly as expected based on previous experience. The aggregated terms were the same as previously (e.g., pain, tenderness, erythema, swelling). In terms of systemic reactogenicity events in the 2-dose adjuvanted groups, fatigue, headache, and myalgia were reported most frequently. Increased rates were seen in the adjuvanted groups, especially after Dose 2. Reactogenicity was attenuated in adults >60 years of age.

The Phase 3 pivotal safety and efficacy study will be conducted in the United States (US) and Mexico. This is a randomized, observer-blinded, placebo-controlled study in which participants are randomized 2:1 to receive 5 µg + Matrix-M1 vaccine or placebo with 2 doses 0.5ml administered on Day 0 and Day 21. The study will include up to 30,000 adults >18 years of age across the US and Mexico. The plan is to target at least 25% participants ≥ 65 years of age, at least 25% with high-risk co-morbidities, at least 15% black/African Americans, 10% to 20% LatinX, and 1% to 2% Native Americans. This is an endpoint-driven study with efficacy evaluations at 72, 108, and 144 cases. The primary endpoint is prevention of PCR-confirmed mild, moderate, or severe COVID-19 illness occurring 7 days after Dose 2 in baseline seronegative adults. Safety follow-up will be conducted through 2 years.

In summary, the NVX-CoV2373 vaccine candidate is based on the baculovirus/nanoparticle platform technology. The safety database includes over 12,100 nanoparticle vaccinees (RSV, influenza, Ebola) and over 2,500 nanoparticle vaccinees adjuvanted with Matrix-M1. Vaccine presentation will be in 10-dose vials with transportation and storage at 2^0-8^0 C. The vaccine is preservative-free and no admixing or reconstitution is required. A 0.5 ml dose is administered intramuscularly 21 days apart. The preliminary safety profile is reassuring with a favorable reactogenicity profile. A peak immune response is observed 14 days after Dose 2. There is a favorable immunologic phenotype, with a robust neutralizing antibody response and polyfunctional CD4+ Th1-biased cellular immune response. Efficacy evaluation is ongoing.

Discussion Points

Dr. Romero requested further information about when in the patients' illness the convalescent serum was obtained. In addition, he asked whether the protein is locked into the pre-binding or post-binding conformation in the vaccine.

Dr. Dubovsky indicated that the details of the convalescent serum are highlighted in the publication. In general, they were a median of 19 days after diagnosis. A small number were hospitalized, a small number were asymptomatic, and the vast majority were those who were considered to have moderate illness who presented to the emergency department (ED) for care, which is where they were recruited. The full-length protein has the stabilizing 2P mutations, which locks it into conformation.

Dr. Glenn added that it is in the pre-binding conformation and that the structure was published recently in *Science*.

Dr. Frey asked what the thinking was about the mechanism that would cause the AEs or local and systemic events post-vaccination to increase after the second dose, whether both vaccines are being given in the same arm, and whether that and/or the use of the adjuvant might play a role in this.

Dr. Dubovsky indicated that they recommend, but do not mandate, that the vaccine be given in alternate arms so that they can follow the local events. It is very typical for AEs to increase after Dose 2 because the immune response also bumps after Dose 2. These local reactogenicity events are thought to be related to the immune responses generated with vaccination, which is consistent with what has been seen previously and with what was seen in the Novavax Phase 3 influenza program. The unadjuvanted groups had a lower level of reactogenicity.

Regarding the Phase 3 planned trial, Dr. Szilagyi inquired as to what proportion of the 30,000 adults will be in the US.

Dr. Dunkle indicated that the estimate is that roughly 10% of the population will be in Mexico and 90% will be in the US.

Dr. Lee observed that with all of these vaccines, it seemed that local and systemic reactions were extremely common and should be anticipated regardless of COVID vaccine type. She recalled that one of Dr. Dubovsky's slides showed a Grade 4 reaction for which she requested further information.

Dr. Dubovsky said that they think the Grade 4 reaction was a fever of $>40^0$ that occurred in the placebo group. They are blinded to the individual, but that is what was indicated by the SMC. Given that saline is not believed to cause high fevers, the current opinion is that this is likely to be a data entry error. These are uncleaned live data, so this may be resolved as the cleaning progresses. Based on the reactogenicity profile. This is quite favorable as there was not a fever signal in the Phase 1 study at all. This is comparable to other licensed vaccines.

Dr. Fryhofer (AMA) observed that on Slides 18 and 19, reactogenicity is noted as being attenuated in adults 60 years of age and older and she wondered whether that was an indication that this vaccine may not work as well in older individuals.

Dr. Dubovsky indicated that this is a response that is seen with most vaccines. It is known that immune responses are attenuated in older adults, given that immunosenescence is part of what occurs in life and the impact on efficacy is unknown. The immunogenicity data are not yet available to them, but may help to understand what is going on.

Dr. Whitney-Williams (NMA) noticed in the Phase 2 trials that there were 240 HIV+ patients and wondered whether there are any plans to include that group in the Phase 3 trials.
Dr. Dubovsky indicated that the 240 HIV+ patients are in the South African study where HIV rates are extremely high, so part of the discussion with the regulators and the society groups there was the need to include those because that is the population that will be vaccinated in the future. Once safety and immunogenicity in that population are understood, they will be better positioned to make future plans. Those cohorts are being vaccinated currently, so there should be data soon.

Dr. Dunkle added that the Phase 3 trial does not exclude stable HIV-infected individuals.

Dr. Ault asked whether Novavax has any plans for Phase 2 or 3 trial in pregnancy. They recently published results in the *New England Journal of Medicine* (*NEJM*) for a respiratory syncytial virus (RSV) vaccine that uses the same platform in pregnant women.

Dr. Dubovsky indicated that they are in discussions with regulatory agencies about how to best go forward. The data that were published were not with the Matrix adjuvant, so there are other considerations that need to be assessed. They are concluding their development and reproductive toxicology (DART) study and will base decisions on that.

Janssen Investigational COVID-19 Vaccine Program

Jerald Sadoff, MD
Lead Clinical Investigator
Senior Advisor, Clinical Development
Janssen Infectious Diseases and Vaccines

Dr. Sadoff presented an update on Janssen's investigational COVID-19 vaccine program. The foundation of Janssen's investigational COVID-19 vaccine is its proprietary AdVac® Technology Platform. Janssen uses a replication incompetent human adenovirus 26 (Ad26), which expresses the target antigen. They have taken out a region of the virus so that it cannot replicate. It invades the cells and makes the transgene and its own antigens, but it cannot assemble them into a replicating virus. The antigen is not on the surface of the virus. It is only on the surface of the cells that the virus enters and is membrane bound. This vaccine has induced very good humoral and cellular antibody responses against structural proteins with neutralizing activity and/or other unique functionalities, as well as cellular CD4-T cell responses with a Th1 signature and CD8 T-cell responses. There has been no sign of vaccine-associated enhanced respiratory disease (ERD) in pre-clinical models after breakthrough infection. Janssen has extensive clinical experience with its Ad26-based vaccines, with over 110,000 participants vaccinated. These Ad26-based vaccines have shown to have a favorable safety and tolerability profile in the populations studied to date. On July 1, 2020, Johnson & Johnson received approval from the European Medicines Agency (EMA) for Janssen's Ad26-based preventive Ebola vaccine.

Janssen took the approach of looking at a number of vaccine constructs because of instability problems that were noted before, and of looking at theoretical considerations. Janssen has had a lot of experience with its RSV and HIV programs on how to construct stable expression vectors, so they assessed stabilization, signal peptide, expression of antigen, manufacturability of vaccine, and immunogenicity in pre-clinical animal models. Based on that, they were able to find a vaccine candidate that was clearly superior in terms of its immunogenicity and the other considerations, Ad26.COV2.S. It encodes a full length membrane-bound S-protein with stabilization mutations and a native initial signal sequence. After a single dose of Ad26.COV2.S, they were able to show protection in the lower and upper respiratory tract of SARS-CoV-2 challenged NHP. In other data, they have done down dosing studies and have shown that even when the vaccine is reduced, they have still been able to get substantial protection. This leads to the belief that the immunogenicity achieved will be protective.

Based on that, Janssen began a Phase 1/2a study, COV1001, to assess the safety, reactogenicity, and immunogenicity of this investigational vaccine in healthy adults 18 to 55 years of age (Cohort 1; N=400) and adults 65 years of age and older (Cohort 3; N=375) at 2 different dose levels ($5x10^{10}$ viral particles and $1x10^{11}$ viral particles) administered as a 1 dose or 2 dose regimen. They have the data on the 1 dose regimen and are currently accumulating the data on the 2 dose, so Dr. Sadoff focused mainly on the data after 1 dose. Cohort 2 is comprised of 270 participants 18 to 55 years of age in whom duration of the immune response, the ability to boost at various times if necessary, and anamnestic responses will be examined. There were very good seroconversion rates with the ELISA at 99% at a slightly lower dose and a similar 99% with very reasonable geometric mean titers (GMTs) for neutralizing antibody levels. There were very few differences between the elderly and younger adults in terms of immune response, and there was a rise between Day 15 and Day 29. The wild-type virus neutralizing antibodies (wtVNA) showed very good response rates as well of 92% at both doses, with a similar response in the elderly with comparable GMTs and overlaps. The GMTs rose quicker for the neutralizing antibodies, with a very good response at Day 14. Therefore, in the Phase 3 trial, they will start counting cases 2 weeks after single dose immunization. From this data, it is clear that there are no differences in immunogenicity between the younger and elderly groups in terms of ELISA or wtVNA, and they seem to be at the flat part of the dose response curve, which allows them to pick the lower dose as a single dose regimen going forward.

There was also a very good T-cell response in both groups of 76% and 83% for the 2 different doses in the younger age group and slightly lower in the older age group at 60% and 67%. These are Th1 responses measured by IFNg and/or IL-2. Only 2 individuals responded with Th2 and the rest were completely negative. The ratio in those 2 between the Th1 and Th2 was 28.9 and 20.2. Clearly, a Th1-type response dominated in both younger adults and the elderly with practically no Th2 response at all. With this vector, they also are able to induce fairly high percentages of CD8 T-cell functional responses that express gamma interferon and may play a role in protection as well, although they have yet to prove that. The CD8 responses are 51% and 65% in the younger age group and slightly lower at 36% and 24% in the older age group, which reflects a fairly high percentage of CD8 T-cell responses. They have a stringent test for discriminating between background and the higher responses compared to some other techniques that have been used, so these GMTs might be somewhat lower than normally seen.

This vaccine does cause some systemic AEs based on blinded data between the groups. Among the 402 subjects in Cohort 1, approximately 50% to 60% overall had systemic AEs. All were transient and lasted no more than 1 to 2 days before resolving completely. In terms of pyrexia, there was some fever in Cohort 1 that was considered Grade 3. These were very responsive to anti-pyrectics and they did not judge that any-pyrectics needed to be used prophylactically. In Cohort 3, there were far fewer systemic reactions and fever rates were very low with no Grade 3 fevers. Once again, reactogenicity was much lower in the older cohort than the younger cohort but the immunogenicity seemed comparable. Based on this, Janssen designed a Phase 3 efficacy trial, COV3001.

COV3001 is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study evaluating the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19. The primary endpoint is moderate to severe illness. The study is being conducted in Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the US with a target of about 50% of the subjects being in the US. From the beginning, there has been a plan to enroll a diverse population. This study does not have a fixed stop interim analysis. A continuous, sequential monitoring technique is used for safety and efficacy instead. This study is being conducted in healthy adults 18 years of age and above. The estimated enrollment is 60,000 and participants will receive a single dose of $5x10^{10}$ of Ad26.COV2.S or placebo. The endpoints are the number of participants with first occurrence of molecularly confirmed moderate to severe COVID-19 with seronegative status. The hope is to have a planned follow-up of up to 2 years. Janssen will attempt to follow participants as long as possible regardless of what happens, but there are plans for how analytically to deal with dropouts and people who want to receive the vaccine or knowing whether they received vaccine or placebo.

In terms of the Phase 3 pause, pauses are not uncommon in these types of studies. Janssen is dedicated to the safety of its participants. This particular pause was in an individual who had a safety event and was subject to automatic stopping or pausing rules. This was judged by the DSMB to be appropriate. Janssen evaluated this case extensively with the DSMB and outside experts. It is a complicated case that had multiple potential causes, which have not completely been determined. However, it is believed that there is no relationship between vaccination and the event. In consultation with the FDA, the DSMB agreed to restart the trials. The trial has restarted in the US and enrollment is continuing. Janssen plans to disclose the clinical data for its COVID-19 trials once those data are presented or published at prespecified milestones, and will proactively disclose the regulated trial holds as requested by health authorities. Janssen is planning to deploy this vaccine widely once a signal is reached and there is approval from the FDA and other regulatory agencies. The plan is to put it in a 2R glass vial that has 5 doses per vial, 10 doses per carton, and 8 cartons per shipper. The anticipated storage conditions under an EUA would be storage by Janssen at -20^0 C for up to 2 years, in end-user storage at 2^0 to 8^0 C for up to 3 months, and after first use at 2^0 to 8^0 C for up to 6 hours. More data are evolving with the hope that there will be much longer stability of up to 9 months or longer like Janssen's other vaccines in this platform.

Discussion Points

To respond to Dr. Ault's question regarding pregnancy trials, Dr. Sadoff reported that Janssen is currently conducting studies in its Ebola program in pregnant women. As soon as the toxicology data are available within the next month, they will be planning to start studies in pregnant women because they understand how important it is in this age group to be able to vaccinate.

Dr. Poehling recalled that the data on the AE profile had both doses combined, but she wondered whether there was a plan to assess those data by the dose. She also requested that Dr. Sadoff expand on the discussion that the vast majority of the CD4 T-cells were in the Th1 biased response with the exception of the 1 subject in each age group who had a ratio of Th1/Th2.

Dr. Sadoff said that on the Th1/Th2, they feel that the Th1 bias in the animals models may be strongly indicative of not being the type of pattern seen with ERD based on vaccine. That in combination with antibody is a telling signal of this. If there is a Th2 response with a predominantly Th1-type response in that individual in combination with neutralizing antibody, seems to be the type of immune response that is not associated enhanced disease. In terms of the AE profile, the FDA and other regulatory agencies have seen unblinded data on the limited number of individuals and there is a trend for less reactogenicity in the lower dose group. The plan is to publish these data after they have the second dose safety data from the 2-dose regimen of the ongoing study. They would then publish the safety data in the two groups in terms of the lower and higher dose, which should be available fairly soon. They want to maintain blinding in the Phase 1 study until they have looked at the safety data in the elderly age group at the second dose.

Dr. Szilagyi was interested that the primary outcome in the Phase 3 study is moderate to severe disease in healthy adults and wondered whether that meant that adults with diabetes, cardiac disease, lung disease, obesity, et cetera are excluded. In addition, he asked what percentage of enrollees would be in the US.

Dr. Sadoff indicated that the primary endpoint of the trial is moderate to severe disease. In the safety run in, comorbidities associated with accelerated disease are excluded. That will include the first 2000 participants in the younger age group and the first 2000 in the older age group. They can have other comorbidities. After those first 4000 are enrolled, in each age group separately, the plan is to enroll individuals with all of the comorbidities associated with accelerated disease. Diabetes, hypertension, et cetera will be a major part of the trial. The moderate definition was picked primarily based on their experience with vaccines against respiratory diseases, with vaccines having a better chance of working with more severe disease and a lower level of protection against mild upper respiratory disease. This provides two reasons to go from a moderate to severe endpoint, including a better chance for the vaccine to show its true effectiveness and a more clinically relevant endpoint to some extent. They are looking very carefully at mild disease. They have built 3, 6, and 12 month blood draws into the trial to look for seroconversion against the virus. This is an assay that does not include the S protein so that it is not interfered with by the vaccine to look for asymptomatic disease, so they should have a very good understanding of the vaccine's effectiveness against asymptomatic and all other forms of the disease. Furthermore, they are monitoring every case that they find by collecting nasal swabs and saliva samples every other day until two consecutive samples are negative. Then, they will compare the control to the vaccine group to determine whether the vaccine has an effect on the viral load even in the breakthrough cases. They are doing this because in a recent RSV challenge study conducted, they showed very good effectiveness of the vaccine in the upper respiratory tract to prevent infections. In the breakthrough cases, the number of viral particles and live virus in the recipients of the vaccine were dramatically lower than in the non-vaccine group. So, there may be an effect on transmission even if there is not

complete protection in the upper respiratory tract. Therefore, they are measuring that as well. At least 50% of participants are intended to be from the US.

Dr. Kimberlin (AAP Red Book) commended the manufacturers on their rapid yet deliberative approaches to this unprecedented situation and the need for a safe and effective vaccine. Toward that end, transparency as they all have done with their Phase 3 protocols is critically important. He expressed interest in knowing more about the subject halt for the Phase 3 study that was discussed in very broad terms. He thought everyone would benefit more by knowing what system that was related to.

Dr. Sadoff indicated that they have been very transparent about the case with the regulatory agencies, IRBs, and investigators. They have been reluctant to discuss the case in public because the study is still blinded and there is a matter of patient confidentiality that they are very concerned about. At this point, they have not felt it appropriate to disclose the nature of the AE other than to mention that it has been fully discussed with independent consultants, the IRBs, the IBMC, and the regulatory agencies, including the FDA, and that have all agreed that the study should go forward. They will be disclosing as much information as they can in a timely manner when it is appropriate, but fully respecting the patient's confidentiality. That is basically why they have not given information that might lead to speculation, which is not warranted based on the data they have.

Dr. Fryhofer (AMA) asked whether the diversity data of the trial participants will be posted on the website. She expressed the hope that Janssen understands how important transparency is in terms of developing vaccine confidence and asked if they could share the age of the person who had the safety event. In terms of the Th1 T-cell response and vaccine enhanced respiratory problems, she asked whether they are looking at thrombotic or inflammatory responses in the study.

Dr. Sadoff indicated that they will be posting the diversity figures just like the other companies and will be very transparent about that. They agree that transparency is very important for many reasons, so they will disclose as much information as possible that does not in any way violate patient confidentiality. This was a young individual in the younger age group. Thrombotic events are not AESI, but they are assessing this very closely. Every individual in the trial receives an electronic device, pulse oximeter, and thermometer. There is a broad trigger for symptoms that may be anything related to COVID. Patients can immediately begin taking their temperature and oxygenation levels, even for the mildest cases. Any thrombotic event is considered a trigger to immediately call the site or their own doctor. That is electronically triggered automatically when something similar to a thrombotic event occurs.

Dr. Lee noted that in comparison to the convalescent sera, the slide showing the ELISA and the neutralizing antibody assays looked somewhat lower and she wondered whether that was thought to be meaningful in any way. Secondly, she asked how convalescent sera could be standardized and if this is comparable across trials since assumably these all come from different lots and locations.

Dr. Sadoff said that while he did not go into the technical details, on that slide there was a dotted line across the top for the neutralizing antibody. That line represents the upper level quantitation. That means that there were quite a few sera in both the younger and elderly group that could have higher dilutions that had not been measured yet. The GMTs will go up

somewhat, but he would say that they were slightly lower than the convalescent sera. He strongly agreed with the need standardization of these sera so that they can directly look from a comparison point of view to learn how relevant it is. They have looked at several panels and have different results from different panels. One was higher and another was lower, so they think that standardization would be useful for the field and would encourage that to occur. As far as implications, they think that the convalescent sera is probably adequate. It is not yet known how difficult this virus is to neutralize and whether extremely high titers or low titers are needed.

Given the abbreviated timeline, Ms. McNally asked whether Dr. Sadoff could be more specific about the timely manner for disclosing more information about the unexplained illness in the study pause.

Dr. Sadoff indicated that they will be disclosing the database on the dose ranging. The blinded data on doses versus safety and immunogenicity would be done fairly shortly when the second dose evaluations are completed. In terms of evaluating more information about the pause and the case, that will be determined based on confidentiality and unblinding considerations. It may turn out that they will be able to disclose more information in a short period of time, depending on how the case evolves and also whether confidentiality issues may not be an issue at some point.

Dr. O'Leary (PIDS) echoed the sentiments that confidence in these vaccines is so crucially important, transparency takes on extra weight in the current environment. While the confidentiality concerns may very well be justified, from the perspective of the public in a trial of thousands of people, that will be hard to accept. Therefore, he encouraged them to be as transparent as possible.

Dr. Sadoff said that they understand that the dynamic between the two is a very delicate balance that has to be judged and continuously judged. They will take the comments into consideration and appreciate them. There has been some discussion about pediatric trials. Their view is that they would like to start pediatric trials in at least 12 to 18 year olds as soon as possible. Based on the safety and immunogenicity seen in that age group, they will move into the younger age groups as well because they think the pediatric population is very important to consider for vaccination, with safety being a very important consideration.

Dr. Kimberlin (AAP Red Book) asked how many subjects were enrolled before the halting event occurred in one subject.

Dr. Sadoff said he would have to acquire that number and report back. The trial just began in September, so there are not yet many thousands of subjects.

Dr. Maldonado (AAP) voiced very strong support for transparency, especially with regard to pediatrics. While she recognized that children under 18 years of age are considered to be in tier 3, it is critical during this time given the sentiments around vaccines in general and the downstream impact of vaccine confidence in all immunizations that these particular trials will have on pediatric populations and the ability to control preventable infectious diseases. Families want to make sure that their healthy children are going to be protected not only from this devastating illness, but also from others. Every single family and pediatrician must be confident in this vaccine. While it is known that the populations with highest risk are not children, in order to reduce the ultimate goal of reducing transmission and achieving herd immunity, pediatric

populations must be engaged. This is a critical group. Pediatricians know how to vaccinate. They do this all of the time and they depend upon the AAP and CDC for their guidance and that guidance is always dependent upon transparency.

Dr. Sadoff stressed that Janssen plans studies in children as soon as possible and very carefully in terms of safety.

COVID-19 Vaccine Implementation Planning Update

Janell Routh, MD, MHS CAPT, USPHS
Deputy, Implementation Planning Unit Vaccine Task Force
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Routh provided an update on vaccine implementation planning. She reminded everyone that the overarching objectives for the COVID-19 vaccination program are to: 1) ensure the safety and effectiveness of COVID-19 vaccines in order to build and maintain confidence in this program; 2) reduce mortality, morbidity, and incidence 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 in a multisectoral fashion. These objectives help to frame the work in which CDC is engaging with its jurisdictional partners in order to confirm their readiness to receive and administer vaccine product. These principles guide the planning efforts and push everyone toward readiness for the implementation of this program.

She shared an illustrative scenario for planning purposes, explaining that it would be adapted based on clinical and manufacturing information and that distribution would adjust as the volume of vaccine doses increases. Final prioritization will be decided by ACIP. On September 16, 2020, CDC published the “COVID-19 Vaccination Program Interim Playbook for Jurisdiction Operations.” All 64 jurisdictions returned a COVID-19 vaccination plan and federal agency plans have been received from the Veteran’s Affairs (VA), Indian Health Services (IHS), Department of Defense (DoD), Department of State (DOS), and the Bureau of Prisons (BOP). The plans were reviewed by at least three CDC subject matter experts (SMEs) and feedback was returned. Information about plans will be updated on the CDC website.

Not surprisingly, jurisdictional plans showed strengths and challenges. In terms of strengths, jurisdictions have organized their planning around the allocation phasing assumptions, set out clear plans to train and equip providers on the Vaccine Adverse Event Reporting System (VAERS), laid out deep operational details for second dose reminders (e.g., text, email, automated call) some of which are already live. Challenges include ensuring that public health messaging plans and expedited procedures for emergency communications are in place, that all data systems to administer and track vaccine have been identified, and that additional planning is in place to ensure equitable access to vaccine distribution in later phases.

In terms of next steps for vaccine implementation now that the plans have been returned and feedback incorporated, the goal is for jurisdictions to be ready by November 15, 2020 based on projections of vaccine availability. This includes having signed Data Use Agreements (DUAs) to ensure tracking of uptake, identifying pockets of low vaccination, identifying and intervening in coverage disparities, and allocating vaccine product. By this time, vaccination provider sites

should be identified and enrolled, especially of those sites that can administer vaccine product to Phase 1 populations and that can position ultra-cold product after possible EUA. Jurisdictions are to confirm that the selected facilities are enrolled in the Vaccine Tracking System (VTrckS) to order and receive product. State capacity will be augmented through federal pharmacy partnerships to support vaccination in long-term care facilities (LTCFs). Microplanning will continue to ensure readiness across various scenarios. Pharmacies can help to increase access to vaccines. Almost 90% of Americans live within a 10-mile radius of a pharmacy.

For Phase 2, a general pharmacy partnership strategy has been developed for the COVID-19 Vaccine Program. Once there is an adequate supply of COVID-19 vaccine to support broader vaccination efforts, it will be important to help jurisdictions increase access to COVID-19 vaccine for the general population in Phase 2. The federal government is partnering with pharmacies nationwide to increase access to vaccine. Partners who enroll in this program will receive a direct allocation of COVID-19 vaccine when supply is sufficient and vaccine is recommended for use beyond the initial critical populations. Pharmacy partners under consideration include national chains, large regional chains, and networks of independent pharmacies and regional chains. Of the eligible US pharmacies, 55% have already enrolled. A list of partners will be shared with jurisdictions shortly. Leveraging all resources and public and private partners will allow for the successful administration of the COVID-19 vaccination program. The CDC vaccine website contains information and resources for the general public, providers, and jurisdictions.

Vaccinate with Confidence for COVID-19 Vaccines

CAPT Amanda Cohn, MD
Chief Medical Officer (Acting), Office of Vaccine Policy, Preparedness, and Global Health
Office of the Director, National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention
Executive Secretary, Advisory Committee on Immunization Practices

Dr. Cohn provided an update on CDC's *Vaccine with Confidence* strategy. There has been a considerable decline in COVID-19 vaccine acceptability in the past 4 months due to concerns about side effects, efficacy, risk perception/need for vaccine, and associated costs. Attributes that make COVID-19 vaccine more acceptable include HCP saying that the vaccine is safe, making the vaccine free of cost, having high potential for the vaccine to help get people back to work and school, and ensuring easy access to the vaccine. Individuals across the demand continuum will have concerns, which are understandable and must be addressed with empathy and transparency. Concerns among HCP is a risk for overall vaccine confidence, given that HCP are the most trusted source for health information. Various communities will have unique experiences informing COVID-19 vaccine perceptions, which can be addressed through engagement with community organizations and leaders to communicate clear and accurate information about COVID-19 vaccines.

Vaccinate with Confidence is a national strategy to reinforce confidence in COVID-19 vaccines with the key priorities to protect communities, empower families, and stop myths. The objectives are to: 1) regularly share clear and accurate COVID-19 vaccine information and take visible actions to build trust in the vaccine, the vaccinator, and the system; 2) promote confidence among HCP in their decision to get vaccinated and to recommend vaccination to their patients; and 3) engage communities in a sustainable, equitable and inclusive way—using

two-way communication to listen, increase collaboration, and build trust in COVID-19 vaccine. There are tactics, sample products, and tools for each objective.

Vaccinate with Confidence is not an advertising, marketing, or communications campaign. Instead, it is a cohesive framework to support health departments, healthcare providers, immunization partners, and community partners and leaders' promotion of COVID-19 vaccines. This national strategy includes evidence-based content to amplify messages that enable an individual to make the decision to vaccinate, which is critical to ensuring that safe and effective COVID-19 vaccines can help control and reduce the impact of this pandemic. CDC is seeking feedback from a wide range of partners on the *Vaccinate with Confidence for COVID-19 Vaccines Framework*, and will send a short email to share with colleagues to review and provide input in addition to the input collected during this meeting.

Discussion Points (Routh & Cohn)

- From the broader healthcare perspective, there has been under-investment in vaccine implementation planning:
  - → ACIP expressed hope that going forward, CDC and others would be fully supported in this endeavor versus adding one more task to the already complex delivery system. Funding investments in this type of work is critical.
  - → Assuming that COVID-19 vaccine implementation will ramp up from January through March with more to do in April, there is concern that the Coronavirus Aid, Relief, and Economic Security (CARES) Act Provider Relief Fund that has paid for increases in the workforce will run out on December 31, 2020. Consideration must be given to what can be done at the state and local health department levels in terms of implementing COVID-19 vaccine activities if additional funding is not forthcoming.
  - → State and local jurisdiction funds are likely to depend upon local legislatures.
  - → There are major deficits in the healthcare delivery system, especially in primary care. More targeted support is needed for private practice to continue to deliver all types of vaccines.
  - → Implementation is where actual impact will happen or not. The same level of investment that has been made in vaccine development must be made in implementation. There must be national investment. While state support is important, federal support is crucial. This cannot be done in everyone's "free time." In order for implementation to be successful, the federal government must make a significant investment.
  - → Typically, ACIP approves a vaccine and then leaves implementation up to the states. This situation offers a good opportunity for ACIP to permanently change the model by which it operates.

- The planning process for delivering vaccines to children will be very different from the process for adults, given that the majority of children's vaccines are given in pediatric offices and many providers do no participate in Vaccines for Children (VFC). Although children are likely to be the last in line and pediatric trials are just beginning, planning for delivery to children should be done now.

- Much can be learned from influenza vaccines (e.g., make vaccination simple and easy, use reminders, use already planned visits, fund and support these activities where possible).

- While each of the 64 jurisdictions presented creative and unique plans based on their own jurisdictional issues that should be beneficial, it is crucial to keep in mind that different communities have different issues regarding vaccine acceptance, such as communities of color and Tribes:

    - → Many communities of color experience issues due to ongoing systemic racism and disparities that lead them to have distrust. Therefore, it is critical to work with communities of color to engender and earn trust, while being completely up front. It is particularly important to engage with community-based organizations (CBOs) and doctors of color who practice in these communities.
    - → Concerns from Tribes focus on the very compressed timeline that does not allow for the IHS to engage in meaningful conversations. Tribes are being asked to make decisions about distribution, prioritization, et cetera without having all of the information they feel they need. Despite efforts to address these concerns, issues remain about how vaccine will be distributed, ordered, and reported on. Many Tribes want to be ready, but they are challenged by whether to choose distribution through states or through IHS. It is preferable to have both doors open.

- Confidence in receiving COVID-19 vaccine must be increased within the HCP workforce. If the group they trust the most will not take these vaccines, patients are not going to want to take them either:

    - → Lack of confidence among HCPs can be boosted by providing them with language that helps them answer questions about such topics as how vaccine was licensed so quickly when other vaccines take 15 years.
    - → HCPs are constantly being asked whether they trust COVID-19 vaccines, to which some respond that when CDC and FDA say they trust it, HCPs will recommend it.
    - → Given that HCPs are the most trusted vaccine administrators, perhaps language should be included that permits them to be vaccinated in the first phase. Many private practitioners do not have access to personal protective equipment (PPE), yet they are the ones on the frontline to whom patients turn.

- Workers Compensation must be addressed.

- CDC is producing content that will be shared with partners in the near future. It is imperative for partners, HCP organizations, and community partners to amplify these messages as this will be much more powerful than messages coming just from CDC or HHS.

- Private practitioners have expressed interest in being able to order and receive vaccines through VTrckS. CDC encouraged them to speak with their local jurisdictions to enroll as providers in VTrckS, through which they can also order/receive vaccine.

- The two components of DUAs, identified and de-identified data, need to be separated in order to move quickly as vaccines become available.

- Many COVID-19 vaccines will require 2 doses, making it critical to be able to ascertain what vaccine was given for Dose 1 and when Dose 2 is needed:

  → Efforts to determine this information with existing Immunization Information Systems (IIS) can be frustrating.
  → State IIS for adults have lagged behind.
  → Ensuring that people received both doses and the correct products is very important to CDC, so immunization cards will accompany ancillary kits in order to have both IIS records and paper and pen solutions.

CBER Plans for Monitoring COVID-19 Vaccine Safety and Effectiveness

Steve Anderson, PhD, MPP
Director, Office of Biostatistics & Epidemiology
Center for Biologics Evaluation and Research
Food and Drug Administration

Dr. Anderson reviewed FDA's active post-licensure safety surveillance systems and Center for Biologics Evaluation and Research (CBER) plans for monitoring COVID-19 vaccine safety and effectiveness. FDA and CDC have weekly and bi-weekly coordination meetings on VAERS and pharmacovigilance activities between the CBER Office of Biostatistics and Epidemiology (OBE) and the OBE Division of Epidemiology (DE) and the CDC Immunization Safety Office (ISO). CBER DE physicians will be reviewing the SAE reports from VAERS for COVID-19 vaccines. This will include review of individual reports, death reports, aggregate analyses, case-series, et cetera. FDA will utilize statistical data-mining methods to detect disproportional reporting of specific vaccine AE combinations to identify AEs that are more frequently reported.

COVID-19 vaccine monitoring data considerations include rapid data access for near real time surveillance, large databases comprised of tens of millions of patients for evaluating vaccine rare SAEs, data representing the integrated care spectrum (e.g., outpatient, physician, inpatient, et cetera), high quality data to assess and confirm potential AEs or safety concerns for COVID-19 vaccines, and data with significant clinical detail or medical chart access. The FDA Biologics Effectiveness and Safety (BEST) system includes several partners, represents a variety of healthcare settings, and has an emphasis on inclusion of electronic health records (EHR), some claims, and linked claims-EHR data. BEST is a modern surveillance system that is able to perform a diversity of queries and studies. There has been an ongoing FDA-CMS partnership on vaccine safety since 2002. CMS data cover a very large population of approximately 55 million elderly US beneficiaries ≥65 years of age. Given that over 92% of US elderly individuals use Medicare, this database represents the elderly population and not a sample. It represents a variety of healthcare settings and consists of claims data with access to medical charts. Not all claims and EHR data systems can be used to address a vaccine safety or effectiveness regulatory question, and each data system has its limitations in terms of the populations, healthcare settings, clinical detail, necessary parameters, data lag, exposures, and outcomes that are captured.

In terms of COVID-19 vaccine safety surveillance planning, the FDA will utilize RCA to monitor 10 to 20 safety outcomes of interest to be determined based on: 1) pre-market review of sponsor safety data submitted to the FDA; 2) coordination with federal partners, international regulatory partners and organizations, academic experts, and others; and 3) literature and regulatory experience with similar vaccines, novel vaccine platforms, and using other relevant data. Dr. Anderson shared the following draft working list of possible AE outcomes:

• Guillain-Barré syndrome • Acute disseminated encephalomyelitis • Transverse myelitis/encephalitis/ myelitis/ encephalomyelitis/meningoencephalitis/meningitis /encepholapathy • Convulsions/seizures • Stroke • Narcolepsy and cataplexy • Anaphylaxis • Acute myocardial infarction • Myocarditis/pericarditis • Autoimmune disease • Deaths	• Pregnancy and birth outcomes • Other acute demyelinating diseases • Non-anaphylactic allergic reactions • Thrombocytopenia • Disseminated intravascular coagulation • Venous thromboembolism • Arthritis and arthralgia/joint pain • Kawasaki disease • Multisystem Inflammatory Syndrome in Children • Vaccine enhanced disease

In terms of experience, the FDA has conducted near real-time surveillance for annual influenza vaccine and Guillain-Barre Syndrome (GBS) since 2007 and Sentinel rapid surveillance for the 2017-2018 seasonal influenza vaccine to evaluate 6 health outcomes of interest.

Epidemiological analyses will require the capability to resolve potential safety signals identified from near real-time surveillance, TreeScan® signal detection efforts, and other sources. This may involve rapid queries and small epidemiological studies and/or larger self-controlled, cohort, comprehensive protocol-based studies. There may be limited information available at the time of licensure on the level and duration of effectiveness. Manufacturers may conduct certain COVID-19 vaccine effectiveness (VE) post-licensure studies. FDA may conduct COVID-19 general effectiveness studies, including subpopulations of interest; duration of protection studies; or other types of studies. FDA is coordinating COVID-19 VE efforts with the CDC/NCIRD through monthly and bi-monthly meetings.

The FDA, CMS, and CDC have extensive experience with the data and methods needed to conduct VE studies having produced several VE and relative VE for influenza and zoster vaccines and duration of effectiveness analysis of Zostavax® vaccine. Dr. Anderson emphasized that COVID-19 vaccine monitoring is a large US government effort that involves regular meetings, planned sharing of protocols, discussion of safety and effectiveness outcomes of interest, and coordinated planning and conduct of surveillance activities between the FDA, CDC, CMS, VA, and DoD.

Post-Authorization Safety Monitoring Plans

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 overview and continued the discussion of post-authorization/post-licensure safety monitoring of COVID-19 vaccines. He reported that ACIP has established a COVID-19 Vaccine Safety Technical Sub-Group (VaST) to advise CDC and other federal partners on planning and preparation for post-authorization/post-licensure safety monitoring of COVID-19 vaccines and independently review and evaluate safety data. Post-authorization/post-licensure safety data on COVID-19 vaccines will be presented regularly during public ACIP meetings. During this meeting, he provided updates on Vaccine Safety Datalink (VSD) monitoring, the CISA Project clinical consult service, HCP's role in reporting AEs to VAERS, and HCP's role in facilitating patient enrollment into the V-SAFE smartphone-based active surveillance system. VSD planned monitoring and evaluation for COVID-19 vaccine safety includes: 1) near real-time sequential monitoring using RCA; 2) monitoring for vaccine-mediated enhanced disease (VMED); 3) studies to evaluate COVID-19 vaccine safety during pregnancy, including fetal death and infant outcomes; tree-temporal scan data mining; and 4) a variety of projects to assess changes in healthcare utilization during COVID-19 and impact on AE monitoring; utility of smartphone technology to enhance vaccine safety monitoring; multisystem inflammatory syndrome in children and adults (MIS-C and MIS-A) as vaccine AEs; safety in an expanded underserved VSD population; and knowledge, attitudes, and beliefs around acceptance/refusal of COVID-19 vaccination.

CISA Project clinical consult service supports US HCP and health departments on complex clinical vaccine safety questions and assists with evaluations of patients with AEs after receiving COVID-19 vaccine or in making clinical decisions about administering COVID-19 vaccine to a person who may be at increased risk for an AE. Advice from CDC and the CISA Project is meant to assist in decision-making versus providing direct patient management and is available to US healthcare providers and health departments by contacting CDC-INFO. HCPs have been CDC's longstanding partners for reporting vaccine AEs to VAERS. VAERS depends upon HCPs to identify and report suspected AEs, even if they are not sure if a vaccine caused an AE. The Health Insurance Portability and Accountability Act (HIPAA) permits reporting of vaccine AEs and medical documentation to VAERS for public health purposes. HCP participation in VAERS reporting will enable public health officials to have accurate and timely information on the safety of COVID-19 vaccines. Specific guidance on VAERS reporting for vaccines authorized for use under EUA will be forthcoming.

V-SAFE is a new smartphone-based active surveillance program for COVID-19 vaccine safety that uses text messaging to initiate web-based survey monitoring and conducts electronic health checks on vaccine recipients. Health checks are conducted daily for the first week post-vaccination and weekly thereafter until 6 weeks post-vaccination. There are additional health checks at 3, 6, and 12 months post-vaccination. V-SAFE includes active telephone follow-up through the VAERS program with vaccine recipients reporting a clinically important event during any V-SAFE health check. A VAERS report will be taken during telephone follow-up, if

appropriate. V-SAFE captures information on pregnancy status and enables follow-up on pregnant women as well. V-SAFE will allow for estimation of rates of local and systemic reactogenicity and rates of clinically important AE following COVID-19 vaccination and symptoms and conditions associated with these AEs. HCPs will play an important role in V-SAFE enrollment by providing a one-page information sheet to patients at the time of vaccination (to be created by CDC) and counseling patients on the importance of enrolling in V-SAFE. CDC will provide information on how to briefly counsel patients on V-SAFE. Of note, V-SAFE will be translated into at least 5 other languages.

ACIP COVID-19 Vaccine Safety Technical Sub-Group

Melinda Wharton, MD, MPH
Director, Immunization Services Division
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Wharton described the ACIP COVID-19 VaST in more detail. VaST was organized in June 2020 and is comprised of independent expert consultants, ACIP members, liaison representatives, and federal agency SMEs. The focus of VaST is to prioritize AESI, develop USG plans for safety monitoring, and create a communication framework. VaST was built off of lessons learned from H1N1 vaccine safety monitoring. There was consensus that a Federal Advisory Committee Act (FACA)-chartered subgroup would ensure transparency, independence, and public accountability. VaST is currently comprised of ACIP and National Vaccine Advisory Committee (NVAC) representation, 7 independent expert consultants, ACIP *ex officio* members (NIH, FDA, OIDP, CMS, HRSA, IHS), and a VA and DoD liaison. The VaST's post-implementation objectives are to: 1) review, evaluate, and interpret post-authorization/approval COVID-19 vaccine safety data; 2) serve as the central hub for technical SMEs from federal agencies conducting post-authorization/approval safety monitoring to share vaccine safety surveillance data; 3) advise on analyses, interpretation, and data presentation; and 4) liaise with the ACIP COVID-19 Vaccines WG on issues of safety data presentation to the ACIP and application of safety data to policy decisions. The VaST's deliverables include development of frequent COVID-19 vaccine safety technical reports for internal ACIP and CDC and federal partner use, and frequent COVID-19 vaccine safety data summaries for public release.

Discussion Points (Anderson, Shimabukuro, Wharton)

Given that safety surveillance is critical, this immense and collaborative effort is impressive.

While the EHR can be a useful tool for data mining, finding AEs, and ensuring vaccines are distributed, it also has pitfalls that need to be stressed. Confidentiality goes without saying, but the biggest concern is that the use of the EHR is burdensome in terms of implementation and use when data registration or data mining are involved. For private practice, this is burdensome and costly. If this is required and there is a cost to integrate it into the health record, it could fail in the community setting.

The emphasis on collaboration among government agencies and groups working on vaccine safety in terms of harmonizing outcomes of interest, regular communication, and sharing data is very important and is applauded. This type of collaboration and coordination should continue

through the entire process so that signals are investigated. This also should help to ensure that communicating to the public is well-coordinated, transparent, and consistent.

It was observed that safety monitoring may be difficult in settings outside of VAERS and registries, such as monitoring vaccines administered in workplaces where employers have their own health insurance plans. This is an area that FDA is exploring.

Concern was expressed about the ability of the systems described to monitor for MIS-C, wild-type or vaccine-induced, particularly with respect to the case definition requirement of a positive test or exposure to a suspected or confirmed case within 4 weeks prior to symptom onset.

Concern was expressed about access to V-SAFE in under-served areas. It is important to be mindful that while most people have access to some form of communication, indigent populations may not have ongoing access to care. In addition, V-SAFE communication must be culturally sensitive.

Lessons learned from children being at home and not in school is that there are many barriers. As hard as it may be to believe, not everybody has internet access and many people purchase phone minutes for phones that are not smartphones. It would be beneficial to track or record V-SAFE use, perhaps by Zip Code, to ensure that it is inclusive of all communities in terms of access and recording long-term effects from the vaccine.

Consideration should be given to modernizing VAERS to accept data from EHRs and/or registries.

Modeling Strategies for the Initial Allocation of SARS-CoV-2 Vaccines

Matthew Biggerstaff, ScD, MPH
Data, Analytics, and Modeling Task Force
Centers for Disease Control and Prevention

Dr. Biggerstaff presented modeling strategies for the initial allocation of SARS-CoV-2 vaccines. The question posed to the group to model was, “What is the potential impact, in terms of preventing COVID-19 infections and deaths, of initially allocating vaccine to one of the following groups after vaccinating HCP in Phase 1A: Adults aged 65+, adults with high-risk medical conditions, and essential workers?” He described in detail the population stratification, vaccine product assumptions, completeness of protection, vaccine allocation assumptions for Phase 1a and Phase 1b, epidemic dynamics, administration assumptions, and approximate timing of vaccine rollout (before incidence rises, as incidence rises, as incidence falls). In terms of findings, initially vaccinating high-risk adults or essential workers in Phase 1B averts approximately 1% to 5% more infections compared to targeting age 65+. This difference is greatest in the scenario in which the vaccine is introduced before incidence rises. The findings are robust to assumptions of reduced VE in older populations. Initially vaccinating age 65+ in Phase 1b averts approximately 1% to 4% more deaths compared to targeting high-risk adults or essential workers. As before, this difference is greatest in the scenario in which the vaccine is introduced before incidence rises. The percentage of deaths averted changes if VE is reduced in older populations. Initially vaccinating high-risk adults, age 65+, or essential workers in Phase 1b averts a similar percentage of deaths across the scenarios. Initially vaccinating age 65+ in Phase 1b averts approximately 2% to 11% more deaths compared to targeting high-risk adults

or essential workers. Again, this difference is greatest in the scenario where the vaccine is introduced before incidence rises. The findings are robust to assumptions of reduced VE in older populations, but the percentage averted drops.

There are limitations to the study. The efficacy and ability of the vaccine candidates to prevent transmission, as well as the time vaccine may become available, is currently unknown. Modeled epidemic trajectories are only for illustration and are not forecasts. Overall averted burden should be interpreted cautiously, given that it will be sensitive to the future trajectory of the epidemic; findings reflect an idealized rollout with minimal delays and 100% uptake; and the aim of this study was to demonstrate the relative impact of different initial vaccine allocation strategies. The following inputs were assumed and will require reassessment as more information becomes available: 1) all infections confer protective immunity; 2) immunity, either naturally- or vaccine-acquired, does not wane significantly within a year of infection or immunization; 3) given exposure, younger age groups are just as likely to become infected as older age groups (susceptibility independent of age); 4) individuals with comorbidities are just as likely as their peers to practice social distancing and other protective behaviors; and 5) there was no reduction in VE among those with high-risk medical conditions. The findings are consistent in sensitivity analyses where the percentage of the population infected prior to vaccine introduction was varied. In terms of consistency with external literature, a review of peer-reviewed and pre-publication studies that model the impact of vaccination under different initial allocation strategies shows general agreement with the results presented here.

Discussion Points

This is an incredible, elegant, and impressive analysis and enormous amount of work.

From a clinical and public health medical consultant point of view, the assumptions in the model make sense. VE may be somewhat high, but it is reasonable.

Consider modeling the impact of poor nutrition, falling behind in school, and possible abuse and neglect if older adults are vaccinated first and schools remain closed. The modeling team noted that this is possible but may require a more complex framework such as agent-based models that model people and societal parameters.

Consider modeling hospitalizations and not just deaths. The modeling team noted that they started with infections and deaths because those estimates are easier to obtain, but infections and hospitalizations can be incorporated in future versions.

Consider modeling congregate care settings. The modeling team indicated that this was already done and was presented by Dr. Slayton during the August 2020 ACIP meeting. The take-away from that study was that vaccinating staff in these settings may be more beneficial than just vaccinating residents, likely because of infection-blocking such that the infection is not introduced into the congregate setting.

It is critical for ACIP to address equity and disproportionate impact on disadvantaged populations. Approaching this from a race/ethnicity standpoint is probably not the best approach.

Updates to COVID-19 Immunity and Epidemiology to Inform Vaccine Policy

Megan Wallace, DrPH, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Wallace provided updates to COVID-19 immunity and epidemiology to inform vaccine policy, including an overview of US COVID-19 epidemiology, COVID-19 post-infection immunity, COVID-19 reinfection, and epidemiology of COVID-19 in pregnant women. As of October 29th, there were 8,834,393 cases of COVID-19 and 227,045 COVID-19 deaths. From March 1, 2020 through October 17, 2020, the number of specimens tested and percent positive for SARS-CoV-2 from combined laboratories reporting to CDC was 6.3% at Week 42. In terms of what happens to anti-SARS-CoV-2 antibodies after infection, Rhesus macaques challenged with SARS-CoV-2 developed binding and neutralizing antibody responses. Re-challenge of rhesus macaques boosted SARS-CoV-2 antibody responses. In humans with SARS-CoV-2 infection, serum antibodies decline between the acute phase and 2 months post-discharge. In HCP with a history of mild SARS-CoV-2 infection, serum antibodies waned 2 months post-infection. Among hospitalized persons with SARS-CoV-2, neutralizing antibody titers demonstrated little to no decrease over 75 days since symptom onset. Pertaining to whether persons infected with SARS-CoV-2 mount cellular immune responses, in symptomatic COVID-19 patients, SARS-CoV-2 memory B-cells did not wane at the same rate as serum antibodies. Recovered COVID-19 patients have SARS-CoV-2-specific CD4+ T-cells and CD8+ T-cells. In conclusion, repeat exposure to SARS-CoV-2 may cause boosting of immune response. Several studies have now observed waning of serum antibodies in COVID-19 patients after a few months. However, the implications for protection are unknown. Neutralizing antibody titers demonstrated little or no decrease at 75 days post-symptom onset. SARS-CoV-2 specific cellular B- and T-cell responses have been detected in COVID-19 patients. Memory B cells did not wane as fast as serum antibody titers.

Discussion Points

Pregnant and lactating women should not be excluded from high priority populations for COVID strategies and treated separately. More than 75% of the HCP workforce are females. For instance, pregnant HCP and first responders who are pregnant should be prioritized alongside their non-pregnant peers.

Though reinfection appears to be uncommon at this point, it will be beneficial to have further guidance on this as soon as possible.

The summary about what is known and unknown about reinfection was phenomenal. However, using language such as reinfection is “likely uncommon within 3 months” suggests more is known that actually is. Perhaps “may be uncommon within 3 months” would be less challenging for management.

It is imperative for messaging around vaccine to emphasizes that vaccines are not likely to be 100% effective and that other measures must be utilized in combination with vaccines. The vaccine is not a panacea and will not result in immediate full herd immunity.

Dr. James Lee invited health care institutions and local/state public health entities interesting in discussing more about reinfections to email eocevent461@cdc.gov.

Ethical Principles for Phased Allocation of COVID-19 Vaccines

Mary E. Chamberland, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Chamberland discussed ethical principles for phased allocation of COVID-19 vaccines, which the COVID-19 Vaccine WG developed to assist ACIP in the identification of groups for early allocation of COVID-19 vaccine in the setting of a constrained supply. During the September 2020 ACIP meeting, 5 interim ethical principles were endorsed: Maximizing Benefits and Minimizing Harms, Equity, Justice, Fairness, and Transparency. During the July through August ACIP meetings, possible groups for Phase 1 vaccination were explored, including HCP in Phase 1a and essential workers (non-HCP), persons with high-risk underlying medical conditions, and adults aged ≥65 years in Phase 1b. The WG reviewed COVID-19 vaccine allocation frameworks including those from Johns Hopkins University (JHU), National Academies, and the World Health Organization (WHO). In addition, they reviewed the ethical literature and consulted with experts in health equity, ethics, and Grading of Recommendation Assessment, Development and Evaluation (GRADE). The interim ethical principles were updated to guide phased allocation and a manuscript was drafted on ethical principles to address key questions to guide allocation planning, and a health equity domain was incorporated into the Evidence to Recommendations (EtR) Framework. There are now 4 ethical principles (Maximizing Benefits and Minimizing Harms, Promote Justice, Mitigate Health Inequities, and Promote Transparency), and updates to the interim version included folding fairness into justice and styling the principles as action phrases. A series of Key Questions was developed to: 1) facilitate “translation” of the ethical principles; 2) assist ACIP in developing its national recommendations for early phase COVID-19 vaccine allocation; and 3) serve as a tool for State, Tribal, Local, and Territorial (STLT) health authorities as they develop vaccination implementation plans. Although ethical principles are fundamental for stewardship of a limited supply of vaccine, they also will be applicable when COVID-19 vaccines are more widely available. Dr. Mary Chamberland described in detail each Key Question for COVID-19 vaccine allocation planning stratified by ethical principles.

Application of the principle of transparency across the entirety of the allocation decision-making process is essential for building public trust and confidence and being clear about the level of certainty in available evidence. Methods and data used for ACIP recommendations are publicly available and include public participation. ACIP meetings are open to the public and are available on-line. Comments can be made to the *Federal Register* and/or during ACIP meetings and when ACIP engages with stakeholders and partners. Allocation of a limited supply of vaccine is complicated by efforts to address multiple goals, most notably reducing morbidity and mortality and minimizing disruption to society, the economy, and healthcare capacity. If the goals of a vaccination program are not clearly prioritized, it will be difficult to draw distinctions between groups for early phase allocation. There is increasing consensus among allocation frameworks for early vaccination of HCP, suggesting that maintenance of healthcare capacity as the highest priority. If vaccine supply remains constrained, ethical principles can help to guide identification of subsets of other groups for subsequent early phase allocation. The next steps for the WG are to seek ACIP’s views on the updated ethical principles and key questions,

publish ACIP's ethical principles, and engage in further discussion about application of the ethical principles to help inform Phase 1 allocation recommendations. The WG requested feedback on how application of these principles and key questions could be made more useful to STLT health authorities for COVID-19 vaccine allocation planning.

Discussion Points

While there was agreement with and endorsement of the principles, some members were struggling with how they fit into the overall pandemic response—especially having seen projections earlier showing that it seems to matter less *who* gets the vaccine first as far as numbers of infections and deaths. That is, the principles seem less important than how soon the vaccine gets deployed.

The WG pointed out that the modeling work measured only one dimension of the impact, aversion of cases and deaths. The ethical principles takes a more holistic view of several dimensions in the context of limited vaccine supply being guided by ethnical, scientific, and implementation considerations.

The Key Questions to help guide and integrate the process seem beneficial and are greatly appreciated.

One thing that will go a long way with the general population, especially in terms of trust and disparities, is a mechanism for reporting how vaccine products are actually being allocated.

One decision with which ACIP will be faced will be assessing the data in terms of benefits and risks for various groups once a vaccine is available. If a vaccine becomes available in the next month or two, this will be a relatively short timeframe for efficacy and safety data. With no long-term safety data, it will be difficult to balance the benefits versus long-term issues that historically have arisen. Balancing the scientific and ethnical aspects is going to be difficult.

The slide on promoting transparency harkens back to the earlier comments about Tribes and the dynamic tension that a compressed timeline is going to create.

WG's Interpretation of the Data

Sara Oliver MD, MSPH
Co-Lead ACIP COVID-19 Vaccine WG
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Oliver presented the ACIP COVID-19 Vaccine WG's interpretation of the data. In terms of COVID-19 vaccine and prior infection, data from Phase 3 trials for any possible vaccine-associated enhanced disease or reactogenicity after prior infection are not yet available. In the absence of concerning data from Phase 3 trials, having positive PCR, antigen, or antibody results is not a contraindication to receive COVID-19 vaccine. Any vaccine recommendations that rely on knowledge of prior immunity/antibody testing would be difficult to implement. In terms of COVID-19 vaccine and breastfeeding women in Tier 1a, most WG members agreed that breastfeeding would not be a contraindication to receive a COVID-19 vaccine. However, this needs to be evaluated for each vaccine, especially if any live virus/vector vaccines are

authorized/licensed. Regarding pregnant women in Tier 1a, limited data on pregnancy are expected from Phase 3 trials. The WG did not reach a consensus. The majority felt that if a woman is recommended to receive the vaccine in an early allocation phase, pregnancy should be a precaution but not a contraindication to receive a COVID-19 vaccine. The WG emphasized the need to allow women to make an informed decision, providing all current knowledge of COVID-19 vaccines/platforms with pregnancy and risk of disease. Concerning pregnancy diagnosed after receipt of the first dose of COVID-19 vaccine, the majority of the WG felt that the second dose could be given at the recommended interval. A minority of the WG felt that the second dose should be postponed until the second trimester or until after pregnancy, emphasizing the need to allow women to make an informed decision.

Regarding the WG's interpretation of the modeling data, the differences among the 3 strategies are thought to be minimal. Ethical principles and implementation considerations may greatly contribute to selecting the optimal sequence in Phase Ib. The largest impact in averted deaths and infections is the timing of vaccine introduction in relation to increases in COVID-19 cases. It is important to emphasize the need to continue non-pharmaceutical interventions (e.g., wearing a mask, social distancing) while awaiting available vaccine. Many factors will inform interpretation of modeling data and allocation decisions, such as VE in older adults, a vaccine's ability to prevent severe disease or transmission, and whether the goal is to prevent the greatest number of infections or greatest number of deaths. For vaccine candidates, both Novavax and Janssen are planning and enrolling large Phase 3 efficacy trials of 30,000 to 60,000 people. The primary endpoints include symptomatic, virologically confirmed COVID-19 disease. Both companies are attempting to enroll diverse populations in terms of race and ethnicity, age (<65 years and ≥65 years of age), and underlying medical conditions.

Concerning implementation and distribution, the WG's interpretation is that Phase 2/3 data from the vaccines show induction of binding and neutralizing antibodies as well as T-cell responses, favorable safety/reactogenicity profiles, supporting advance to Phase 3 trials. Both platforms have prior experience from other vaccines. Safety pauses are expected with large clinical trials, indicating the process is working appropriately. For the current Phase 3 clinical trials, the WG stressed the importance of enrolling diverse study participants, the importance of harmonizing safety and efficacy endpoints across all Phase 3 trials to the extent possible, and the need to report maternal and fetal outcomes for women who become pregnant during the clinical trials. The WG supports FDA's guidance for ensuring that Phase 3 trials conduct ongoing assessment of long-term safety and efficacy, and that issuance of an EUA is not grounds to unblind follow-up in an ongoing clinical trial.

Discussion Points

The American College of Obstetricians and Gynecologists (ACOG) urged ACIP to incorporate pregnant and lactating women clearly and explicitly in the prioritization framework should an EUA be issued.

The American Academy of Pediatrics (AAP) agreed with the ACOG statement and defers to them on matters of pregnancy and pregnant women. AAP also emphasized the need to move to pediatric trials when the data suggest that it is safe to do so and should monitor fetal outcomes. It is important for pregnant and lactating women to make an informed decision. CDC is engaging ACOG and AAP and is working with colleagues with expertise in this area to develop materials that can be provided at the time of vaccination.

Related to the unblinding of clinical trials should an EUA become available, particularly for participants in vaccine trials in which efficacy and safety are demonstrated, it is troubling that participants potentially will not have the benefit of receiving vaccine once efficacy is demonstrated. These volunteers have assumed the risk of study participation and in most clinical trial circumstance would be among the first to potentially benefit once efficacy is demonstrated. It is recognized that this is an issue that must be dealt with by the FDA and VRBPAC.

Policy Questions, EtR Framework

Kathleen Dooling, MD MPH
Co-Lead ACIP COVID-19 Vaccine WG
Medical Officer, National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Dooling reviewed the COVID-19 vaccine policy questions for the EtR framework and critical and important outcomes. As a reminder, the goals of the COVID-19 vaccine program are 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 economy, including maintaining healthcare capacity; and 4) ensure equity in vaccine allocation and distribution. The two ACIP policy questions proposed by the WG are: 1) Should COVID-19 Vaccine "A" be recommended to adults in the US?; and 2) Who should be recommended to receive COVID-19 Vaccine "A" during Phase 1? The EtR framework assesses the domains of Public Health Problem, Benefits and Harms, Values, Acceptability, Feasibility, Resource Use, and Equity. Dr. Dooling reviewed the population, intervention, comparison, outcomes (PICO) for vaccine policy for Question #1, including the critical and important benefits and harms identified by the WG. The WG's next steps for Policy Question #1 (Vaccine Recommendations) are to populate the EtR framework, start GRADEing the vaccine evidence and incorporating Phase 3 data when available, and discuss clinical guidance for special populations, concomitant administration, and scheduling. For Policy Question #2 (Allocation Recommendations), the WG's next steps are to publish the ethical principles manuscript and incorporate the latest information regarding science, implementation, and ethics to further refine Phase 1 allocation. For the health equity domain criterion question, the following sub-questions were posed: 1) Are there any groups or settings that might be disadvantaged in relation to the problem or options that are considered?; 2) Are there plausible reasons for anticipating differences in the relative effectiveness of the option for disadvantaged groups or settings?; 3) Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the option or the importance of the problem for disadvantaged groups or settings? Are there important considerations that should be made when implementing the intervention (option) in order to ensure that inequities are reduced, if possible, and that they are not increased?

Discussion Points

There was support for the two policy questions being evaluated separately and the important and beneficial outcome of serial PCRs for asymptomatic infection.

This is an unprecedented situation in which consideration may need to be given to conditional recommendations, which should incorporate the principles of informed consent and some higher level of clinical decision-making.

Perhaps consideration should be given to getting the vaccine out as quickly as possible in response to the modeling data suggesting that the faster vaccines are administered, the more deaths that will be prevented.

This does not take into consideration any time-phased protection or safety other than the data that will be provided should an EUA come through in a relatively short period of time. This is a virus like nothing they have seen previously, so the unknown and negative possibilities are always a consideration. They can look at objective information and arrive at a conclusion to move forward with allocation, but that presumes that there is not going to be some later problem.

Following participants for a mean of 2 months after the second dose as a timepoint to start making final decisions about safety is troubling. Concerns prevailed on making quick decisions on safety. While it is true that most AEs of interest will be captured in the first 6 weeks, there will be a need for long-term studies, particularly due to the potential for vaccine-enhanced disease. This highlights the need for a dynamic decision-making process.

The WG has considered mortality, morbidity, and preventing spread in a lumped manner. In the context of unknowns, perhaps those should be disaggregated.

The questions fit the PICO perfectly, with the caveat that there may be changes. There must be flexibility over time and flexibility in implementation. Local areas will have to deal with the reality of whether to save doses for Dose 2.

Given the uncertainties, perhaps the WG should review the data on a monthly basis and update the recommendations to account for concerns in balance with benefits and harms.

While the focus on safety is very important, it is also crucial to understand durability of the immune response.

The ethical principles will be very important to local jurisdictions. Concrete guidance will be needed in terms of equity and a sense of fairness in terms of how allocations actually are implemented.

Frequent messaging of information about COVID-19 vaccines will be very important to public confidence.

Certification

Upon reviewing the foregoing version of the October 30, 2020 ACIP meeting minutes, Dr. Jose Romero, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

ACIP Membership Roster

Department of Health and Human Services
Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
July 1, 2019 – December 31, 2020

CHAIR
ROMERO, José R., MD, FAAP
Professor of Pediatrics
Horace C. Cabe Endowed Chair in Infectious Diseases Director,
Pediatric Infectious Diseases Section
University of Arkansas for Medical Sciences and Arkansas Children's Hospital
Director, Clinical Trials Research
Arkansas Children's Hospital Research Institute
Little Rock, AR
Term: 10/30/2018-06/30/2021

EXECUTIVE SECRETARY
COHN, Amanda, MD
Senior Advisor for Vaccines
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA

MEMBERS
ATMAR, Robert L., MD
John S. Dunn Clinical Research Professor in Infectious Diseases
Departments of Medicine and Molecular Virology & Microbiology
Baylor College of Medicine
Chief, Infectious Diseases Service
Ben Taub General Hospital, Harris Health System
Houston, TX
Term: 7/1/2016 – 6/30/2020

AULT, Kevin A., MD, FACOG, FIDSA
Professor and Division Director
Department of Obstetrics and Gynecology
University of Kansas Medical Center
Kansas City, KS
Term: 10/26/2018 – 6/30/2022

BAHTA, Lynn, RN, MPH, CPH
Immunization Program Clinical Consultant
Infectious Disease, Epidemiology, Prevention & Control Division
Minnesota Department of Health
Saint Paul, Minnesota
Term: 7/1/2019 – 6/30/2023

BELL, Beth P., MD, MPH
Clinical Professor
Department of Global Health, School of Public Health
University of Washington
Seattle, WA
Term: 7/1/2019 – 6/30/2023

BERNSTEIN, Henry, DO, MHCM, FAAP
Professor of Pediatrics
Zucker School of Medicine at Hofstra/Northwell
Cohen Children's Medical Center
New Hyde Park, NY
Term: 11/27/2017-06/30/2021

FREY, Sharon E., M.D.
Professor and Associate Director of Clinical Research
Clinical Director, Center for Vaccine Development
Division of Infectious Diseases, Allergy and Immunology
Saint Louis University Medical School
Saint Louis, MO
Term: 11/27/2017-06/30/2021

HUNTER, Paul, MD
Associate Professor of Family Medicine and Community Health
University of Wisconsin School of Medicine and Public Health
Associate Medical Director
City of Milwaukee Health Department
Milwaukee, WI
Term: 7/1/2016 – 6/30/2020

LEE, Grace M., MD, MPH
Associate Chief Medical Officer for Practice Innovation
Lucile Packard Children's Hospital
Professor of Pediatrics, Stanford University School of Medicine
Stanford, CA
Term: 7/1/2016 – 6/30/2020

MCNALLY, Veronica V., JD
President and CEO
Franny Strong Foundation
West Bloomfield, Michigan
Term: 10/31/2018 – 6/30/2022

POEHLING, Katherine A., MD, MPH
Professor of Pediatrics and Epidemiology and Prevention Director,
Pediatric Population Health
Department of Pediatrics
Wake Forest School of Medicine
Winston-Salem, NC
Term: 7/1/2019 – 6/30/2023

SÁNCHEZ, Pablo J., M.D.
Professor of Pediatrics
The Ohio State University – Nationwide Children's Hospital
Divisions of Neonatal-Perinatal Medicine and Pediatric Infectious Diseases
Director, Clinical & Translational Research (Neonatology)
Center for Perinatal Research
The Research Institute at Nationwide Children's Hospital
Columbus, Ohio
Term: 7/1/2019 – 6/30/2023

SZILAGYI, Peter, MD, MPH
Professor of Pediatrics
Executive Vice-Chair and Vice-Chair for Research
Department of Pediatrics
University of California, Los Angeles (UCLA)
Los Angeles, California
Term: 7/1/2016 – 6/30/2020

TALBOT, Helen Keipp, MD
Associate Professor of Medicine
Vanderbilt University
Nashville, TN
Term: 10/29/2018 – 6/30/2022

EX OFFICIO MEMBERS

Centers for Medicare and Medicaid Services (CMS)
HANCE, Mary Beth
Senior Policy Advisor
Division of Quality, Evaluations and Health Outcomes
Children and Adults Health Programs Group
Center for Medicaid, CHIP and Survey & Certification
Centers for Medicare and Medicaid Services
Baltimore, MD

Food and Drug Administration (FDA)
FINK, Doran, MD, PhD
Deputy Director, Clinical, Division of Vaccines and Related Products Applications Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration
Silver Spring, MD

Health Resources and Services Administration (HRSA)
RUBIN, Mary, MD
Chief Medical Officer
Division of Injury Compensation Programs
Rockville, MD

Indian Health Service (IHS)
WEISER, Thomas, MD, MPH
Medical Epidemiologist
Portland Area Indian Health Service
Portland, OR

Office of Infectious Disease and HIV/AIDS Policy (OIDP)
KIM, David, MD CAPT,
US Public Health Service Director Division of Vaccines
Washington, DC

National Institutes of Health (NIH)
BEIGEL, John, M.D.
Associate Director for Clinical Research
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases (NIAID) Bethesda, MD

LIAISON REPRESENTATIVES

American Academy of Family Physicians (AAFP)
ROCKWELL, Pamela G, DO
Associate Professor, Department of Family Medicine,
University of Michigan Medical School
Medical Director, Dominos Farms Family Medicine Ann
Arbor, MI

American Academy of Pediatrics (AAP)
MALDONADO, Yvonne, MD
Senior Associate Dean for Faculty Development and Diversity
Professor of Pediatrics and Health Research and Policy
Chief, Division of Pediatric Infectious Diseases
Stanford University School of Medicine
Stanford, CA

American Academy of Pediatrics (AAP)
Red Book Editor
KIMBERLIN, David, MD
Professor of Pediatrics
Division of Pediatric Infectious Diseases
The University of Alabama at Birmingham School of Medicine
Birmingham, AL

American Academy of Physician Assistants (AAPA)
LÉGER, Marie-Michèle, MPH, PA-C Senior
Director, Clinical and Health Affairs
American Academy of Physician Assistants
Alexandria, VA

American College Health Association (ACHA)
CHAI, Thevy S, MD
Director of Medical Services
Campus Health Services
University of North Carolina at Chapel Hill
Chapel Hill, NC

American College Health Association (ACHA) (alternate)
MCMULLEN, Sharon, RN, MPH, FACHA
Assistant Vice President of Student & Campus Life for Health and Wellbeing
Cornell Health
Ithaca, NY

American College of Nurse Midwives (ACNM)
HAYES, Carol E., CNM, MN, MPH Lead
Clinician
Clinical Quality Compliance and Management
Planned Parenthood Southeast
Atlanta, GA

American College of Nurse Midwives (ACNM) (alternate)
MEHARRY, Pamela M., PHD, CNM
Midwifery Educator, Human Resources for Health
In partnership with University of Rwanda and University of Illinois, Chicago

American College of Obstetricians and Gynecologists (ACOG)
ECKERT, Linda O., MD, FACOG
Professor, Department of Obstetrics & Gynecology
Adjunct Professor, Department of Global Health
University of Washington
Seattle, WA

American College of Physicians (ACP)
GOLDMAN, Jason M. MD, FACP
Affiliate Assistant Professor of Clinical Biomedical Science, Florida Atlantic University, Boca Raton, Florida
Private Practice
Coral Springs, FL

American Geriatrics Society (AGS)
SCHMADER, Kenneth, MD
Professor of Medicine-Geriatrics
Geriatrics Division Chief
Duke University and Durham VA Medical Centers
Durham, NC

America's Health Insurance Plans (AHIP)
GLUCKMAN, Robert A., MD, MACP
Chief Medical Officer, Providence Health Plans
Beaverton, OR

American Immunization Registry Association (AIRA)
COYLE, Rebecca, MSEd
Executive Director, AIRA
Washington, DC

American Medical Association (AMA)
FRYHOFER, Sandra Adamson, MD
Adjunct Associate Professor of Medicine
Emory University School of Medicine
Atlanta, GA

American Nurses Association (ANA)
RITTLE, Charles (Chad), DNP, MPH, RN
Assistant Professor, Nursing Faculty
Chatham University, School of Health Sciences
Pittsburgh, PA

American Osteopathic Association (AOA)
GROGG, Stanley E., DO
Associate Dean/Professor of Pediatrics
Oklahoma State University-Center for Health Sciences
Tulsa, OK

American Pharmacists Association (APhA)
FOSTER, Stephan L., PharmD CAPT (Ret)
U.S.P.H.S.
Professor, College of Pharmacy
University of Tennessee Health Sciences Center
Memphis, TN

Association of Immunization Managers (AIM)
HOWELL, Molly, MPH Immunization Program Manager
North Dakota Department of Health
Bismarck, ND

Association for Prevention Teaching and Research (APTR)
McKINNEY, W. Paul, MD
Professor and Associate Dean
University of Louisville School of Public Health and Information Sciences
Louisville, KY

Association of State and Territorial Health Officials (ASTHO)
SHAH, Nirav D, MD, JD
Director
Maine Center for Disease Control and Prevention
Augusta, ME

Biotechnology Industry Organization (BIO)
ARTHUR, Phyllis A., MBA
Senior Director, Vaccines, Immunotherapeutics and Diagnostics Policy
Washington, DC

Council of State and Territorial Epidemiologists (CSTE)
HAHN, Christine, MD State
Epidemiologist
Office of Epidemiology, Food Protection and Immunization Idaho
Department of Health and Welfare
Boise, ID

Council of State and Territorial Epidemiologists (CSTE) (alternate)
LETT, Susan, MD, MPH
Medical Director, Immunization Program
Division of Epidemiology and Immunization
Massachusetts Department of Public Health
Boston, MA

Canadian National Advisory Committee on Immunization (NACI)
QUACH, Caroline, MD, MSc
Pediatric Infectious Disease Specialist and Medical Microbiologist
Medical Lead, Infection Prevention and Control Unit
Medical Co-director – Laboratory Medicine, Optilab
Montreal-CHUM
Montreal, Québec, Canada

Infectious Diseases Society of America (IDSA)
BAKER, Carol J, MD
Professor of Pediatrics
Molecular Virology and Microbiology
Baylor College of Medicine
Houston, TX

International Society for Travel Medicine (ISTM)
BARNETT, Elizabeth D, MD
Professor of Pediatrics
Boston University School of Medicine
Boston, MA

National Association of County and City Health Officials (NACCHO)
ZAHN, Matthew, MD
Medical Director, Epidemiology
Orange County Health Care Agency
Santa Ana, CA

National Association of County and City Health Officials (NACCHO) (alternate)
DUCHIN, Jeffrey, MD
Health Officer and Chief, Communicable Disease Epidemiology and Immunization Section
Public Health - Seattle and King County
Professor in Medicine, Division of Allergy and Infectious Diseases
University of Washington School of Medicine and School of Public Health
Seattle, WA

National Association of Pediatric Nurse Practitioners (NAPNAP)
STINCHFIELD, Patricia A., RN, MS, CPNP
Director, Infectious Disease/Immunology/Infection Control
Children's Hospitals and Clinics of Minnesota
St. Paul, MN

National Foundation for Infectious Diseases (NFID)
SCHAFFNER, William, MD
Chairman, Department of Preventive Medicine
Vanderbilt University School of Medicine
Nashville, TN

National Foundation for Infectious Diseases (NFID) (alternate)
DALTON, Marla, PE, CAE
Executive Director & CEO
National Foundation for Infectious Diseases (NFID)
Bethesda, MD

National Medical Association (NMA)
WHITLEY-WILLIAMS, Patricia, MD
Professor and Chair
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
New Brunswick, NJ

Pediatric Infectious Diseases Society (PIDS)
O'LEARY, Sean, MD, MPH
Associate Professor of Pediatrics
Pediatric Infectious Diseases
General Academic Pediatrics
Children's Hospital Colorado
University of Colorado School of Medicine

Pediatric Infectious Diseases Society (PIDS) (alternate)
SAWYER, Mark H, MD
Professor of Clinical Pediatrics
University of California, San Diego School of Medicine
San Diego, CA

Pharmaceutical Research and Manufacturers of America (PhRMA)
ROBERTSON, Corey, MD, MPH
Senior Director, US Medical, Sanofi Pasteur
Swiftwater, PA

Society for Adolescent Health and Medicine (SAHM)
MIDDLEMAN, Amy B., MD, MSEd, MPH
Professor of Pediatrics
Chief, Section of Adolescent Medicine
University of Oklahoma Health Sciences Center
Oklahoma City, OK

Society for Healthcare Epidemiology of America (SHEA)
DREES, Marci, MD, MS
Chief Infection Prevention Officer & Hospital Epidemiologist
ChristianaCare
Wilmington, DE
Associate Professor of Medicine Sidney Kimmel Medical College at Thomas Jefferson University
Philadelphia, PA