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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
August 26, 2020
Atlanta, Georgia

Agenda

Final - August 20, 2020

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention
Atlanta, Georgia 30329
August 26, 2020

	AGENDA ITEM	PRESIDER/PRESENTER(s)
Wednesday, August 26, 2020		
10:00	**Welcome & Introductions**	Dr. José Romero (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary, CDC)
10:30	**Coronavirus Disease 2019 (COVID-19) Vaccines**	
	Introduction	Dr. Beth Bell (ACIP, WG Chair)
	mRNA-1273 Clinical Development	Dr. Jacqueline M. Miller (Moderna)
	Pfizer/BioNTech COVID-19 mRNA vaccine Clinical Development	Dr. Nicholas Kitchin (Pfizer/BioNtech)
12:00	*Lunch*	
12:30	Overview of post-marketing safety surveillance	Dr. Tom Shimabukuro (CDC/NCEZID)
	Epidemiology of individuals at increased risk of COVID-19 disease	Dr. Nancy McClung (CDC/NCIRD)
1:40	*Break*	
1:50	Modeling allocation strategies for the initial COVID-19 vaccine supply	Dr. Rachel Slayton (CDC/NCEZID)
	Work Group interpretation	Dr. Sara Oliver (CDC/NCIRD)
	Prioritization and Work Group next steps	Dr. Kathleen Dooling (CDC/NCIRD)
3:00	*Break*	
3:15	**Public Comment**	
4:00	**Adjourn**	

Acronyms

CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease 2019
EtR	Evidence to Recommendations Framework
GRADE	Grading of Recommendations Assessment, Development and Evaluation
mRNA	Messenger ribonucleuc acid
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]
SAGE	Strategic Advisory Group of Experts
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WG	Work Group
WHO	World Health Organization
VE	Vaccine Effectiveness

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
AE	Adverse Event
AESI	Adverse Events of Special Interest
AFHSB	Armed Forces Health Surveillance Branch
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AOA	American Osteopathic Association
APC	Antigen-Presenting Cells
APhA	American Pharmacists Association
APHL	Association of Public Health Laboratories
BARDA	Biomedical Advanced Research and Development Authority
BEST System	Biologics Effectiveness and Safety System
BLA	Biologics License Application
BLS	Bureau of Labor Statistics
BMI	Body Mass Index
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CISA	Clinical Immunization Safety Assessment
CKD	Chronic Kidney Disease
CMS	Center for Medicare and Medicaid Services
COI	Conflict of Interest
CIOMS	Council for International Organizations of Medical Sciences
COPD	Chronic Obstructive Pulmonary Disease
COU	Clinical Operations Unit
COVID-19	Coronavirus Disease 2019
CoVPN	COVID-19 Prevention Network
CRP	C-Reactive Protein
CSTE	Council of State and Territorial Epidemiologists
CVD	Cardiovascular Disease
DEDP	IHS Division of Epidemiology and Disease Prevention
DFO	Designated Federal Official
DHA	Defense Health Agency
DHA-IHD	Defense Health Agency Immunization Healthcare Division
DMSS	Defense Medical Surveillance System
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DRC	Democratic Republic of Congo
DSMB	Data Safety Monitoring Board
ED	Emergency Department

EHR	Electronic Health Record
EIS	Epidemic Intelligence Service
ELISA	Enzyme-Linked Immunosorbent Assay
EMR	Electronic Medical Record
EMS	Emergency Medical Service
ERD	Enhanced Respiratory Disease
ESR	Erythrocyte Sedimentation Rate
ET	Eastern Time
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FFS	Fee-For-Service
GAVI	Global Alliance for Vaccines and Immunisation; The Vaccine Alliance
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HCoVs	Human Coronaviruses
HCP	Healthcare Personnel / Providers
HCS	Human Convalescent Sera
HCW	Healthcare Workers
HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus
ICS	Intracellular Cytokine Staining
IDCRP	Infectious Disease Clinical Research Program
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IIS	Immunization Information Systems
ISO	Immunization Safety Office
IT	Information Technology
LTCF	Long-Term Care Facility
MAAE	Medically-Attended Adverse Events
MDV	Multi-Dose Vial
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MMWR	*Morbidity and Mortality Weekly Report*
mRNA	Messenger Ribonucleic Acid
NAAT	Nucleic Acid Amplification Test
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAM	National Academy of Medicine
NAPNAP	National Association of Pediatric Nurse Practitioners
NAS	National Academy of Sciences
NASEM or the National Academies	National Academies of Sciences, Engineering, and Medicine
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
NFID	National Foundation for Infectious Diseases
NHP	Non-Human Primates
NHIS	National Health Interview Survey
NHSN	National Healthcare Safety Network

NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NMA	National Medical Association
NP	Nasopharyngeal
NPTC	IHS National Pharmacy and Therapeutics Committee
OWS	Operation Warp Speed
PCP	Primary Care Practitioner
PCR	Polymerase Chain Reaction
PFU	Plaque-Forming Units
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PII	Personally Identifiable Information
PPE	Personal Protective Equipment
PRISM Program	Post-Licensure Rapid Immunization Safety Monitoring Program
PRR	Proportional Reporting Ratio
PT	Preferred Terms (MedDRA)
QA	Quality Assurance
RBD	Receptor Binding Domain
RCA	Rapid Cycle Analysis
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RVSHs	Regional Vaccine Safety Hubs
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization
SAHM	Society for Adolescent Health and Medicine
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SES	Socioeconomic Status
SHEA	Society for Healthcare Epidemiology of America
SLU	Saint Louis University
SME	Subject Matter Expert
ULT	Ultra-Low Temperature
US	United States
USG	US Government
VA	(US Department of) Veteran's Affairs
VAECS	Vaccine Adverse Event Clinical System
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VPN	Virtual Private Network
VPU	Vaccine Planning Unit
VRBPAC	Vaccines and Related Biological Products Advisory Committee Meeting
VRC	Vaccine Research Center (NIAID/NIH)
VSD	Vaccine Safety Datalink
VTU	Vaccine Treatment Evaluation Unit
WG	Work Group

Call To Order, Welcome, & Introductions

José Romero, MD, FAAP
ACIP Chair

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Romero called to order the August 26, 2020 virtual Advisory Committee on Immunization Practices (ACIP) meeting. He thanked everyone for taking time out of their busy schedules to participate and for working with the Centers for Disease Control and Prevention (CDC) and ACIP on this virtual meeting.

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

https://www.cdc.gov/vaccines/acip/meetings/slides-2020-08.html

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

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

The next regularly scheduled ACIP meeting will be convened at CDC or virtually on October 28-29, 2020. Additionally, a virtual meeting has been added to the ACIP calendar that is tentatively scheduled for September 22, 2020. Registration for this meeting is not required as it is a virtual meeting. The link to the live virtual meeting can be found on the website the day of the meeting.

Dr. Cohn emphasized that ACIP is, at its heart, a public body. Engagement with the public and transparency in ACIP's processes is vital to the Committee's work. As part of ACIP's commitment to continuous improvement, ACIP has strengthened its oral and written public comment process to accommodate increased public interest in ACIP's work, maximize opportunities for comment, and make public comment more transparent and efficient. She announced that for this meeting, one oral public comment period would be held during the first afternoon at approximately 3:15 PM. Because there are typically more people wishing to make

public comments than there is time during meetings, people interested in making an oral comment were asked to submit a request online in advance of the meeting via the ACIP website. If more people request to speak than can be accommodated, a blind lottery is conducted to determine who will be the speakers. Speakers selected for this meeting were notified in advance of the meeting. Written public comments may be made via regulations.gov using the docket number ID CDC-2020-0083. Information on the written public comment process, including information about how to make a public comment, can be found on the ACIP website.

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

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

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

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

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

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

Dr. Romero requested that the Liaison and *Ex Officio* members introduce themselves. A list of Members, *Ex Officio* Members, and Liaison Representatives is included in the appendixes at the end of the full minutes for the August 2020 ACIP 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 reminded everyone that there are over 200 COVID-19 vaccines currently under development, including 4 in clinical trials in the US. The ACIP is responding to this ongoing pandemic and accelerated vaccine development through scheduling of monthly emergency ACIP meetings during which they have the opportunity to discuss evolving epidemiology and other relevant data and hear about the vaccines as they are being developed. As a reminder, during the July 29, 2020 meeting, ACIP heard presentations on the following topics:

- ❑ Overview of COVID-19 Vaccine Clinical Trials
- ❑ COVID-19 Vaccine Safety Considerations
- ❑ Considerations for FDA Licensure Versus Emergency Use Authorization (EUA) of COVID-19 Vaccines
- ❑ Considerations for Vaccine Implementation
- ❑ Epidemiology of COVID-19 in Essential Workers, Including Healthcare Personnel (HCP)
- ❑ COVID-19 Vaccine Prioritization: Work Group (WG) Considerations
- ❑ Evidence to Recommendations (EtR) Framework

The COVID-19 Vaccine WG has been meeting weekly since the last ACIP meeting. Topics covered during the August WG meetings included the following:

- ❑ Review of COVID-19 epidemiology among at-risk groups, including American Indian/Alaskan Native (AI/AN) populations and individuals with underlying medical conditions
- ❑ Manufacturer presentations on clinical development programs for 2 messenger ribonucleic acid (mRNA) vaccines, including data from Phase 1/2 clinical trials and plans for Phase 3 clinical trials
- ❑ Modeling allocation strategies to inform the initial COVID-19 vaccine supply
- ❑ Initial COVID-19 vaccine distribution scenarios
- ❑ COVID-19 vaccine prioritization considerations, especially for initial doses

The agenda for the August 26, 2020 ACIP meeting included presentations on the following presentations:

- ❑ Moderna mRNA-1273 Clinical Development
- ❑ Pfizer/BioNTech COVID-19 mRNA Vaccine Clinical Development
- ❑ Overview of Post-Marketing Safety Surveillance
- ❑ Epidemiology of Individuals at Increased Risk of COVID-19 Disease
- ❑ Modeling Allocation Strategies for the Initial COVID-19 Vaccine Supply
- ❑ WG Interpretation

In terms of considerations for prioritization of COVID-19 vaccines, as more information has become available, the WG has been able to advance its thinking on this topic with a view toward fulfilling the obligation to issue some guidance and recommendations. With that in mind, Dr. Bell indicated that this session would focus on individuals at increased risk of COVID-19 disease, including underlying medical conditions and age, and review the 4 priority groups for consideration of allocation of initial COVID-19 vaccine.

During the September 2020 ACIP meeting, the WG plans to focus on the epidemiology of risk of COVID-19 by race and ethnicity, review other published prioritization frameworks, and potentially vote on an interim prioritization schema for initial COVID-19 vaccine.

mRNA-1273 Clinical Development Program

Jacqueline M. Miller, MD, FAAP
Senior Vice President
Therapeutic Area Head
Infectious Diseases
Moderna

On behalf of Moderna, Dr. Miller expressed gratitude to the ACIP and the WG for the opportunity to provide an update on Moderna's mRNA-1273 clinical development program for its Phase 1 clinical data and Phase 2 and Phase 3 clinical trial findings. She explained that mRNA-1273 is a vaccine intended for protection against the severe acute respiratory syndrome (SARS)-CoV-2 virus. It comprises a messenger RNA sequence against the spike protein, which has 2 proline substitutions. Therefore, that protein is called S-2P. The 2 proline substitutions in the translated protein in the prefusion confirmation, which is the most immunogenic form. mRNA is delivered by a lipid nanoparticle targeting the antigen presenting cells, including dendritic cells and monocytes. Once the mRNA is delivered, the ribosome translates that mRNA into the SARS-CoV-2 protein. It then assembles into its wild-type trimeric confirmation and then is cell-surface expressed. The vaccine is a 100 µg dose. In addition, the vaccine has a 2-dose schedule given 28 days apart. The vaccine is shipped and stored at -20^0 and can be stored at the point-of-care at 2^0 to 8^0.

In terms of the pre-clinical data that enabled Moderna to progress forward in clinical development, in collaboration with the Vaccine Research Center (VRC) at the National Institutes of Health (NIH), a robust pre-clinical data package was compiled in mice and non-human primates (NHP). In both species, robust neutralizing antibodies have been observed to be induced. These neutralizing antibodies led to protection against lung challenge in mice[1] and pulmonary and nasal challenge in NHPs[2]. In addition, after challenge there was no indication of enhanced respiratory disease (ERD) after viral challenge even when lower and sub-protective doses of mRNA-1273 are used[2]. This offers reassurance going into clinical development regarding vaccine-enhanced respiratory disease. Finally, A Th1-dominant phenotype of CD4+ T-cells was induced in mice[1] and NHPs[2] [[1]Corbett KS, Edwards D, Leist SR, et al. SARS-CoV-2 mRNA vaccine development enabled by prototype pathogen preparedness. Nature 2020; Nature 2020; DOI: 10.1038/s41586-020-2622-0; [2]Corbett KS, Flynn B, Foulds KE, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primate. N Engl J Med. 28 July 2020; DOI: 10.1056/NEJMoa2024671].

With these data, Moderna discussed with the Food and Drug Administration (FDA) progressing into the clinical development program. This program has advanced relatively quickly over the last 7 months or so. It is really the mRNA platform technology that has enabled that, along with frequent reviews of data with the FDA. The first human study, which was sponsored by the NIH, was initiated in March and continues to be ongoing. The data reviewed by Dr. Miller during this session came from data published in July in adults 18 to 55 years of age, as well as from older adult cohorts 56 to 70 years of age and above 71 years of age. She also described the Phase 2 and Phase 3 study designs, both of which are funded by Moderna's partners at the Biomedical Advanced Research and Development Authority (BARDA). The Phase 2 study initiated in May and enrollment is complete. The Phase 3 study began on July 27th. Additional considerations for the clinical development program in the future will be in pediatric populations, pregnant women, and immunocompromised populations.

Regarding the study design for the NIH-sponsored Phase 1 clinical trial, this was a safety and dose-ranging study that was conducted in 3 age cohorts: 18 to 55 year of age, 56 to 70 years of age, and ≥ 71 years of age. The initial plan was to evaluate 3 dose levels (25, 100, 250 micrograms) in all 3 age strata in a sequential manner with stops for safety in between. A fever of 39^0 C was observed in a recipient 18 to 55 years of age with the 240 microgram dose. Therefore, the 25 and 100 microgram doses were the only ones continued into the two subsequent older age cohorts. Finally, 3 additional cohorts have been added to evaluate the vaccine at 50 micrograms. The study is currently fully enrolled and in its follow-up phase. The subjects were primarily healthy males and females at or above 18 years of age and "all-comers" were enrolled with respect to their baseline SARS-CoV-2 serostatus. Although, subjects who described a past medical history of COVID-19 disease were excluded. Safety endpoints include adverse reactions within 7 days after each injection, as well as unsolicited adverse events (AEs) within 28 days after each vaccination. Serious adverse events (SAEs) and medically-attended adverse events (MAAE) will be followed through the entire duration of the study. The immunogenicity assays being evaluated in this study include the enzyme-Linked Immunosorbent assay (ELISA), a pseudovirus neutralization assay that is the primary assessment for neutralizing antibodies moving forward in the development plan, live virus neutralization, and an Intracellular cytokine staining (ICS) assay for CD4 T-cells. Again, these subjects will be followed for approximately 1 year after their final vaccination.

As noted earlier, the 250 mcg dose was interrupted due to a single fever observed in a participant 18 to 55 years of age. The 100 mcg dose has now been selected for further clinical development. Based on the pseudovirus neutralization assay, and similarly with the other assays investigated, 41 subjects in the 18 to 55 year age cohort were tested after presenting with symptoms of COVID-19 disease. As of Day 14 post-dose 2, neutralizing antibodies were observed in all participants at all dose levels. However, the lowest responses were seen at the 25 mcg dose. The subjects in the 100 mcg and 250 mcg dose groups, the range of antibody titers was in the upper half of the range of convalescent sera. The higher antibody titers observed with the 100 mcg dose versus the 25 mcg dose was the reason for selection of the 100 mcg dose moving forward.

In terms of the safety data with the 100 mcg dose in all 3 of the age strata, mRNA-1273 was well-tolerated across age groups with injection site pain and solicited symptoms of fatigue, chills, headache, and myalgia being the most frequently reported symptoms. There were more reports observed after the second dose of vaccination, but there was no increase in

reactogenicity observed in the older age cohorts. The symptoms were primarily mild to moderate in severity, and the majority of the symptoms resolved within 2 days.

Moving to the immunogenicity data for the 3 age strata, binding antibodies were measured by an ELISA assay. With this 2-dose series, 100 mcg seroconverted all participants after the first dose of vaccine. The area under the curve also exceeded the median of convalescent sera. After the second dose, all age groups were equivalent to high-titer convalescent sera in the upper quartile of the dose. Importantly, these results are consistent regardless of age strata. With the pseudovirus neutralization assay, once again with the second dose pseudovirus neutralization responses were detected in all participants, including the upper age range. The titers were comparable across the 3 age strata and geometric mean titers (GMTs) remained above the median of the convalescent sera in all age groups Day 57 post-Dose 2.

Regarding the CD4+ T-cell data that were generated in the 3 age strata in the Phase 1 study, this study looked at the CD4+ T-cell response and the Th1 phenotype as measured by elaboration of interferon-γ, IL-2, and TNF-α. Similar to the humoral immunity assays, the CD4 Th1 T-cells were detected across the 3 age strata. The Th2 phenotype was rare, which can be seen in the Jackson publication for subjects 18 to 65 years of age [Jackson L, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2- preliminary report. N Engl J Med. 14 Jul 2020; DOI: 10.1056/NEJMoa2022483].

In terms of Moderna's ongoing clinical development program, there are two additional studies. The first is a Phase 2 study that is funded by BARDA and sponsored by Moderna. This study evaluates the safety and immunogenicity of 2 dose levels, 50mcg and 100mcg. Two cohorts have been enrolled in the study. Cohort 1 is comprised of participants 18 to <55 years of age and Cohort 2's participants are ≥55 years of age. Both cohorts include 300 subjects of whom 100 subjects each will receive 50mcg, 100mcg, or a placebo at Day 1 and Day 29. The participants are healthy males and females and "all-comers" have been enrolled with respect to baseline SARS-CoV-2 status. The safety endpoints are comparable to the ones described for the Phase 1 study. This study will be investigating the ELISA assay and the neutralization antibodies as generated by the pseudovirus neutralization assay. The follow-up will be approximately 1 year after the second dose for all subjects. This study is now fully enrolled, Dose 2 has been administered to the entire population, and the subjects are undergoing their active vaccination follow-up.

The COVID-19 Efficacy and Safety Study (COVE Study), Moderna's pivotal Phase 3 efficacy, safety, and immunogenicity study, ultimately will enroll 30,000 subjects. This study is conducted through multiple partnerships, including BARDA funding and the partnership of National Institute of Allergy and Infectious Diseases (NIAID) and the COVID-19 Prevention Network. This Phase 3 study will investigate the safety, efficacy, and immunogenicity in subjects who are either <65 years of age and not at risk (approximately 60% to 70% of the study population) those >65 years of age and combined with a cohort <65 who are at increased risk for complications of COVID-19 (approximately 25% to 40% of the study population). This was designed to generate results that are generalizable to the US population who are at risk for COVID-19 disease. The study started on July 27th and as of Friday of the previous week, there were over 13,000 subjects enrolled. Subjects will be randomized 1:1 to receive either 100mcg of vaccine or placebo. The subjects are "all-comers" with respect to the baseline SARS-CoV-2 serostatus. The study has 2 co-primary objectives, which are to: 1) demonstrate the efficacy of mRNA-1273 to prevent COVID- 19 disease; and 2) further evaluate the safety and reactogenicity profile of

the 2-dose regimen of mRNA-1273 given 28 days apart. This study will last for approximately 2 years after the second vaccination for each subject. The intent is for full safety and efficacy follow-up.

The case definition to define COVID-19 disease for the primary analysis in the COVE Study is that to be considered a case of COVID-19 for the evaluation of the primary efficacy endpoint, two criteria must be met:

1. The participant must have experienced:
   - At least **TWO** of the following systemic symptoms: fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s)

   OR

   - At least **ONE** of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia

   AND
2. The participant must have at least one nasopharyngeal (NP) swab, nasal swab or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR

The preference is for the NP swab taken in the clinic, but allowance has been made for subjects who may be too sick to travel to the clinic. The primary analysis will be conducted in those who are initially SARS-CoV-2 baseline serostatus negative. Cases begin to accrue at Day 14 after Dose 2 along with the immunogenicity data presented for the Phase 1 study.

Dr. Miller took a moment to talk about an initiative she is quite proud of at Moderna. They have established the COVE Diversity & Inclusion Advisory Committee. The purpose of this committee is to help Moderna achieve the goal to enroll a study population that is representative of the racial demography in the US. Moderna is committed to transparency in this initiative. Those interested in weekly updates for enrollment and current minority enrollment status can click on the COVE Study on the Moderna webpage. Currently, the study has enrolled 18% minority. With the help of the COVE Diversity & Inclusion Advisory Committee, Moderna hopes to improve upon those numbers. The role of this committee is to help Moderna: 1) review enrollment, race, and ethnicity demographics on a weekly basis; 2) review current outreach activities and outcomes; 3) review strategies to ensure participation of individuals from communities significantly impacted by COVID-19; and 4) support the development and implementation of retention strategies.

In terms of the limitations of the research, while the data shown are very encouraging in terms of the immunogenicity of the vaccine, they are at the moment limited and in a fairly homogeneous population. Further consideration is needed with regard to how the vaccine will be evaluated in pediatric subjects, pregnant women, and immunocompromised patients. The ongoing COVE Study will provide significantly more data in healthy adult subjects, older age cohorts, and subjects with pre-existing comorbidities.

In summary, mRNA-1273 vaccine encodes the pre-fusion-stabilized Spike protein (S-2P) with the 2 proline substitutions in a lipid nanoparticle dispersion, which is designed for delivery to the antigen-presenting cells (APCs) of the lymph node. The pre-clinical data package has demonstrated induction of neutralizing antibodies and protection against viral challenge in mice and NHPs. The interim data from Phase 1 study indicate that a 100 mcg dose of vaccine is generally well-tolerated across age strata, with solicited symptoms mostly mild-to-moderate in severity and self-limited duration. The vaccine has been observed to induce neutralizing antibody in the upper half of the range of convalescent serum across age strata, with the induction of Th-1 biased, CD4+ T-cells. The Phase 2 and the Phase 3 COVE studies are underway. Dr. Miller concluded that she looks forward to providing updates on Moderna's progress during future ACIP meetings.

Discussion Points

Dr. Hunter expressed concern that if convalescent titers were collected later than post-vaccination titers, they might be setting a lower target than is needed from a vaccine. He wondered on average how long after infection the convalescent titers were collected compared to the post-vaccination titers.

Dr. Miller indicated that the convalescent titers were collected between 23 and 60 days after the onset of symptoms, which represents the range of time points that she presented.

Dr. Poehling observed that there is a predominant Th1 response and rarely Th2 and requested elaboration on why that is so important.

Dr. Miller indicated that the Th1 responses are reassuring to Moderna in terms of the potential risk for vaccine-associated ERD. The reason is in the past with other respiratory viruses, such as respiratory syncytial virus (RSV) and measles virus, children have been observed to have enhanced disease after vaccination. When their T-cells were examined, they had a preponderance of the Th2 phenotype—so, elaborating cytokines such as IL4 and IL13. Th1, both in Moderna's animal models and the Phase 1 clinical trial, was reassuring to begin clinical development, especially because the clinical development is occurring with relatively rapid enrollment. They certainly are not relying on that information. They have a DSMB for the Phase 2 study that is supported by a Moderna Phase 3 study that is supported by NIAID. The DSMBs are reviewing the reported safety information throughout the trial and monitoring specifically for vaccine-associated ERD.

Dr. Kimberly (AAP Red Book) asked whether, in terms of the inflammation that goes along with natural disease, Moderna is measuring markers of inflammation in the studies.

Dr. Miller indicated that the markers of inflammation were measured in the Phase 1 study in order to expedite the enrollment and generation of data. The assays in the Phase 3 study have been limited to the ELISA and the pseudo neutralization assay. However, detailed information is collected on the patients who ultimately do test positive for COVID-19. While they are not specifically looking at cytokines they will be followed closely on a daily basis through telemedicine visits and hopefully they can then capture the symptomatic data and characterize what they see.

Dr. Talbot requested further information about how this vaccine will be stored and used and the requirements for refrigeration or room temperature.

Dr. Miller said that she was going to present the stability data that are available currently, but as much of the development program continues in parallel, they also continue to generate stability data. These conditions will be updated as the stability data allows them to be. At the time of launch, the vaccines will be shipped and stored up to 6 months at -20^0. Then the vaccine can be kept at 2^0 to 8^0 for 7 days in the refrigerator. That is really intended for sites that do not have the freezer capacity. The vaccine will be presented in a 10-dose vial without preservative. Once the vaccine is thawed and the rubber seal is initially punctured, there is a 6-hour window available to administer the remaining doses.

Regarding vaccine-enhanced disease, Dr. Fryhofer recalled that earlier in Dr. Miller's presentation, she showed a slide of preclinical data to support human clinical trials with mRNA-1273. There was a statement that there was no indication of ERD after viral challenge, even when the lowest doses of mRNA-1273 are used. She requested that Dr. Miller explain that more thoroughly.

Dr. Miller replied that in both the mice and the NHP, lung pathology was examined after viral challenge. The viral challenge in the mice was at a dose of 5×10^5 and in the NHP it was 7.6×10^5 plaque-forming units (PFUs). When the animals were sacrificed, no inflammation was seen in the lungs, even down to doses of .1 micrograms. While they used the 100 mcg, that statement was meant to reflect the fact that through all of the doses tested in the animal models, they did not see lung pathology.

Dr. Sánchez inquired about Moderna's plans for addressing the re-infections in the 3 individuals being monitored in the Phase 3 studies for 24 months in terms of beyond meeting or not meeting the primary endpoint, and if they would be doing sequencing of isolates.

Dr. Miller replied that Moderna will follow and capture every case of COVID-19, not just the first case of COVID-19. Depending on how many infections are observed, the intent is to look at cases that occur more than once at the request of the DSMB. They also will be looking at antibody persistence at various time points throughout the trial. They will be evaluating also by looking at the Phase 1 and Phase 2 data very carefully to see if there is a certain moment at which it would make sense to evaluate the booster dose. They do not plan to sequence the individual isolates now, but it is definitely an interesting idea that she is sure will generate some discussion with their partners. They will be testing the individuals for RT-PCR because that is how they will define all of the cases. They are investigating for viral shedding when individuals are actually positive by RT-PCR. Every 3 days or so for the first 14 days, subjects will either come into the clinic for an NP swab or they will submit a salivary sample.

In terms of the target population for the Phase 3 trial, Dr. Szilagyi emphasized that there has been a lot of national interest to ensure that the target population is reflective of the US population. While he appreciated the advisory committee and the regular reviews of race and ethnicity, he wondered whether there are targets or internal goals for race and ethnicity and age group above 65, for example, above 75. He also requested further information about the definition for race and ethnicity and whether there are any goals or targets beyond Black and Hispanic. He feels that confidence in any vaccine will be related to the representativeness of the population that has been enrolled in Phase 3 trials.

Dr. Miller indicated that how Moderna is monitoring race and ethnicity and is definitely an evolving picture and is the predominant topic of the weekly meetings they have with Operation Warp Speed (OWS). The goal always has been to enroll a study that is representative of the demography in the US. They know that in the past, it has been difficult to reach that goal and very few vaccine trials have been able to do it. Therefore, the outreach activities started early on. There are not specific targets at the moment, although targets are discussed on a regular basis. If there is an update to that information, she will be happy to provide it. African Americans and Hispanic Americans are certainly a focus of the trial, but they also are tracking the enrollment of Asian Americans and Native Americans because these are very important groups also at risk for COVID-19 disease. Recognizing that there is so much interest in how the diversity enrollment is progressing, they made a commitment to be transparent about the progress of enrollment. As mentioned, they will update this information on the Moderna website on a weekly basis, including the percentage of non-white enrollment in the trial. In terms of older age, there is not a specific stratification for older adults above 75 years of age. However, they have had patients in their 90s enroll in the study already. The hope is that at the end, there will be a reflective spread the demography there as well. So far, the older age cohort in itself has not been a challenge.

Dr. Hayes (ACNM) requested information about any adjuvants being used in the multi-dose vial of the current vaccine, and if mRNA-1273 is the vaccine that will be used in clinical trials for pregnant women.

Dr. Miller indicated that mRNA-1273 does not contain any adjuvants. It is purely the messenger RNA in the lipid nanoparticle dispersion and the excipient are limited to tris sucrose and acetate. It is the intent to use mRNA-1273 in vaccine trials for pregnant women. Recognizing the importance of COVID-19 disease in pregnant women, Moderna is considering the potential for further evaluation. What they would like to see is a larger safety database in non-pregnant adults before engaging in that work. For the Phase 3 clinical trial, there is an intent to report all pregnancies in the clinical study report. Because women are getting pregnancy tests before they are vaccinated, they anticipate that number to be small. However, they recognize the importance and will be further evaluating this as clinical development progresses.

Dr. Lee asked whether there is a possibility in terms of the outcomes to consider asymptomatic cases. It may be incredibly valuable throughout the trial to understand whether this vaccine candidate also could play a role in preventing asymptomatic transmission. In addition, she asked whether Dr. Miller could comment on the characteristics of the patients in whom a Th2-directed phenotype was observed, such as recent pregnancy status.

Dr. Miller indicated that she did not get into a lot of details about the COVE Study in the interest of time, but would be happy to present a deeper dive during a future ACIP meeting of all of the various secondary and exploratory objectives that Moderna will evaluate. While she reviewed the co-primary efficacy and safety objectives during this session, there are numerous evaluations of secondary and exploratory efficacy. In terms of the secondary efficacy, they will look at severe respiratory disease, COVID-19 symptoms according to the long list of potential symptoms that are available on the CDC website, so milder disease and asymptomatic disease. Patients will be monitored throughout the study at various time points looking at non-Spike protein antibody titers to look for elevations and seroconversion in those titers, representing the development of asymptomatic COVID infection. They will look at all COVID disease,

asymptomatic COVID disease, all-cause mortality, and so forth. With respect to the Th2, there was minimal Th2-directed phenotype. That was in the Phase 1 Study of healthy subjects. There is not a lot of clinical detail about them, but for Moderna it is extremely reassuring that the phenotype is heavily biased toward Th1.

In terms of enrolling all-comers, Dr. Bernstein inquired as to how baseline serology will be analyzed with the endpoints and what percentage of enrollees are seropositive at baseline.

Dr. Miller indicated that they will enroll all-comers and get their initial baseline serostatus. When it comes time to perform the efficacy analysis, the cases that accrue will be based on the first-time efficacy for the primary analysis. To be eligible for inclusion in the primary efficacy analysis, subjects should have been baseline serostatus negative. Nonetheless, by including some baseline serostatus positive subjects, they have the ability to conduct some of the sub-analyses and exploratory analysis. They have discussed looking at the history of the subjects who maybe were baseline serostatus positive to evaluate whether cases occur in those subjects. This is certainly among the questions that the DSMB has asked them to look into as they monitor the study. Regarding the percentage of enrollees who are seropositive at baseline, in the largest population, the Phase 3 COVE Study, the samples are being accrued and tested currently. In the Phase 1 and Phase 2 study, it has been relatively infrequent at about 1% or so of the study population.

Dr. Atmar observed that based on the Phase 1 data, at least by the pseudovirus neutralization assay, there were no seropositives. However, by the ELISAs, which may be cross-reactive with other human coronaviruses, some subjects had measurable antibody at baseline. He asked which assay would be used to determine baseline serostatus. In addition, he looked at the website and saw that the enrollment numbers were listed through the previous Friday, but the race and ethnicity data were not there. He wondered whether it was going to appear on the next update or if he missed something on the site.

Dr. Miller said that when she last went to the website, she saw the 18% race/ethnicity number and the breakdown, so she would need to investigate what happened and why Dr. Atmar was not able to see it. The intent is to provide/update race and ethnicity on a weekly basis given the amount of scrutiny that they are undergoing. Regarding baseline serostatus, only 1 or 2 subjects in the Phase 1 study were baseline seropositive out of 120 subjects in the trial overall. It is a relatively small sample size on which to make that assessment. There have been more baseline serostatus positive individuals in the Phase 2 study. At the pre-vaccination timepoint, both binding antibody titers and the neutralization antibody titers will be assessed. She did not know if they had progressed so much into the statistical development plan to define that, but positivity with either assay presumably would indicate previous exposure. In terms of whether the seroresponses differ among those who have baseline antibody, the data from Phase 1 are extremely limited. The Phase 2 data are actually currently in their stage of accrual, so subjects have been given the second dose and are in the process of waiting for 1-month post-vaccination to have their immunogenicity assessment. She should be able to give a better picture on that later in the fall.

Pfizer/BioNTech COVID-19 mRNA Vaccine

Nicholas Kitchin, MD
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Dr. Kitchin indicated that Pfizer has partnered with a German biotechnology company, BioNTech, on the development of a suite of COVID-19 mRNA vaccines. Pfizer has worked with BioNTech previously in other infectious disease areas, making the platform right to collaborate further on the SARS-CoV-2 pandemic. During this session, he presented an overview of the Pfizer/BioNTech clinical development program for the Phase 1 study that directed the decision of what to move forward with a larger scope development and the Phase 2/3 parts of the study. Development initially began in 2 clinical studies with 4 different types of mRNA vaccine for SARS-CoV2 virus. They were coding either just the receptor binding domain (RBD), part of the spike-antigen, or the whole spike and the P2-S prefusion stabilized form. The 4 candidates were based on either a modified RNA, unmodified RNA, or self-amplifying RNA. The majority of the large-scale development was of the 2 modified RNA candidates given as a 2-dose schedule separated by 3 weeks, the 162b1 candidate that encodes for the RBD only and 162b2 that encodes for the P2-mutated full spike protein. There are 2 ongoing clinical studies assessing the safety, tolerability, and immunogenicity of ascending dose levels of BNT162 modRNA vaccine candidates. The initial study in the US began as a Phase 1/2 study, but has now formally expanded into a Phase 3 efficacy evaluation. In Germany, a study is being conducted whereby all 4 types of vaccine are being evaluated in different doses. The importance of that study, particularly for this presentation and the decision to move forward, was that T-cells were collected and analyzed in that study as opposed to in the US study.

For the Phase 1 component of the US study, 15 healthy participants were enrolled per dose level, of whom 12 received the active vaccine and 3 received placebo. These participants were enrolled into 2 different age groups, either 18-55 or 65-85 years of age. These subjects were healthy and were pre-screened for absence of antibodies to SARS-CoV-2 or positive PCR on a nasal swab at the time of vaccination. The initial plan was to evaluate ascending dose levels of 10µg, 30µg, and 100µg. However, a tolerability profile was seen for the 100µg dose level for the 162b1 candidate that was not thought to be a good fit for a vaccine that was going to be implemented at the population level. Therefore, attention was turned to lower dose levels of 10µg, 20µg, and 30µg. Vaccine was administered as 2 doses on Day 1 and Day 21. The 100µg cohort did not receive a second dose because of the reactogenicity finding. Comparisons also have been made informally with a human COVID-19 convalescent sera (HCS) panel from 38 human SARS-CoV-2 infection/COVID-19 convalescent sera from subjects over a broad age range of 18-83 years of age broken down into two groups: N=29, 18-55 years of age and N=9, 56-83 years of age. These sera were collected at least 14 days after a PCR-confirmed diagnosis at a time when subjects were asymptomatic. The majority of serum donors predominantly had symptomatic infections (35/38) and one had been hospitalized [Mulligan, M.J. et al. Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults. Nature https://doi.org/10.1038/s41586-020-2639-4 (2020); and Walsh EW, Frenck R, Falsey AR, et al. medRxiv 2020.08.17.20176651; doi: https://doi.org/10.1101/2020.08.17.20176651 [preprint]].

In the Phase 1 part of the US study, 195 subjects total were enrolled as the various dose levels. The safety and tolerability profiles of the prophylactic BNT162 vaccines were reported out by participant-reported outcomes solicited via electronic diary (E-diary) for local reactions, systemic events including fever, and use of analgesics or antipyretics. AEs were collected for up to 1 month after last dose and SAEs are collected for up to 6 months after last dose. In the early part of the study, standard hematology and biochemistry were collected. To describe the immune responses elicited by prophylactic BNT162 vaccines, attention was focused on SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels. Dr. Kitchin presented just the neutralizing titers as they feel that those are likely to give the best representation of potential future performance of the vaccines.

In terms of 162b1 versus the 162b2, the vaccine encoding the RBD versus the vaccine encoding the full spike protein, the full length spike encoded vaccine was selected at the highest of the 3 refined dose levels for the focus of the late-stage Phase 2 and Phase 3 development. A number of criteria were used to determine how best to choose the candidate and the dose level based on acceptable safety and reactogenicity, SARS-CoV-2 neutralizing titers at or above the HCS panel as an informal reference, and strong Th1-type CD4+ and CD8+ T-cell responses. Both BNT162b1 and BNT162b2 looked potentially strong as vaccine candidates. The totality of data favored the selection of BNT162b2 based upon the findings that the reactogenicity profile was more favorable than BNT162b1 in both younger and older adults, there was a trend toward stronger CD8+ T-cell responses, and there was earlier clearance of SARS-CoV-2 RNA in the nose of BNT162b2-immunized and challenged Rhesus macaques. Based on the totality of data, the decision was made to advance BNT162b2 at the 30µg dose level.

In terms of the BNT162b2 reactogenicity data from Phase 1 in participants 18-55 years of age, participants reported outcomes in an E-diary on the evening of each of the 7 days after vaccination. The local reactions and systemic events were all graded by participants according to the standard FDA grading scale. Across all 3 dose levels at both doses and in both age groups, pain at the injection site was the most common local reaction, perhaps with an indication at least in the younger age group of mild to severe increasing with dose. This was less common in the older subjects than in the younger subjects. While pain was a common symptom, redness and swelling were relatively uncommon. Regarding systemic reactogenicity, just 2 subjects reported fever in the younger age group after Dose 1, one mild and one moderate, and 3 after Dose 2—one in the 20µg group and 2 in the 30µg group. Again, there appeared to be an increasing severity with increasing dose, but very tolerable. These reactions tend to occur on either Day 1 or Day 2 after vaccination and are short-lived, resolving within 1 to 2 days. BNT162b2 also showed a favorable systemic reactogenicity profile in Phase 1 participants 65-85 years of age, with a better tolerability profile amongst the older compared to the younger subjects. For example, there was only a single report of fever in all of the dose levels in 1 subject in the 30µg dose group, which was mild at 38.5^0 C after the second dose. In the Phase 1 part of the study, no SAEs were reported by any subjects.

Regarding immunogenicity data, robust SARS-CoV-2 50% neutralization titers after 2 doses of BNT162b2 in Phase 1 exceeded those in a HCS panels. Comparing the 10µg, 20 µg, and 30µg dose levels in the younger subjects, there was an increase in the GMTs after the second dose at Day 28. Biding antibody was seen at Day 21, but neutralizing antibody really picked up after the boost with the second dose. There was a subject who had their blood sample taken out of the protocol window at only 2 days after the second dose. When that subject was excluded, the

GMTs were at a similar level seen after the 20µg dose. Comparing the 30µg dose levels, b2 and b1 showed similar levels of neutralizing antibody titers. Therefore, the selection of the b2 candidate was driven by similar immunogenicity but better reactogenicity. Also noteworthy was that when the younger age group was compared to the older age group for the same dose level for b1 and b2, the GMTs were lower in the older subjects than in the younger subjects as might be expected. However, what is key is that comparing all of the groups after they received the second dose, the GMTs were significantly higher than that observed in the HCS panel. It is difficult to know at this point what the true meaning of HCS neutralizing titers are, Dr. Kitchin thinks they represent the best benchmark available at this time to help guide the selection of what to take into further development.

Finally, in terms of immunogenicity, T-cells were not collected in the US study but were collected in the German study. The data for the b2 candidate are still under preparation, but they look at least as good as the b1 candidate and show a similar pattern in terms of inducing strong CD4+ and CD8+ T-cell responses, with a Th1 dominance. A week after the second dose, there were nice rises in IFNγ IL-2 and very little response for IL-4.

Phase 1 demonstrated encouraging safety and immunogenicity for BNT162b2, which supported advancement to Phase 2/3 of BNT162b2 encoding the full length spike antigen. It looked like a good candidate from a reactogenicity perspective where the reactogenicity observed was lower after the first vaccination compared to the second, was lower in older than younger participants, and had a profile that appears to be at least as good as approved adult vaccines and therefore should be supportive of a widespread immunization program. In terms of immunogenicity, strong neutralizing antibody responses were seen 7 days after the second dose. These subjects will be included for 2 years after their second dose, and data are still being collected and analyzed at different time points beyond that. Strong CD4+ and CD8+ T-cell responses were seen with Th1 dominance.

Therefore, the decision was made to take the BNT162b2 candidate vaccine into Phase 2/3 development at the 30µg dose level. The Phase 2 component represents the first 360 subjects enrolled in the larger Phase 3 component, so 80 per age group and per vaccine randomized 1:1 unlike the first part of the study in which randomization was 4:1. The primary endpoint for the Phase 3 component is efficacy, randomization is 1:1 vaccine to placebo, with an aim to enroll an overall target of approximately 30,000 subjects, with approximately 60% of the subjects being 18-55 years of age and 40% being 56-85 years of age. The primary objectives in this part of the study are to: 1) further define the safety profile of and immune responses to BNT162b2 in the first 360 Phase 2 participants; 2) evaluate the efficacy of BNT162b2 against confirmed COVID-19 in Phase 2/3 participants without evidence of infection before vaccination and with and without evidence of infection before vaccination; and 3) define the safety profile of prophylactic BNT162b2 vaccine in Phase 2/3 participants via E-diary (local reactions, systemic events incl. fever, use of analgesics/antipyretics) in a subset of at least 6000 and identify all AEs up to 1 month after the last dose and SAEs up to 6 months after last dose. There are additional secondary and exploratory objectives to assess severe disease using the broader CDC case definition and looking at SARS-CoV-2 infection.

The Phase 2/3 study started on July 27, 2020 and enrollment is already more than 50% accrued. Subjects will receive 2 doses of vaccine in the same way as in the Phase 1 part separated by 3 weeks and capturing reactogenicity and AEs. There will be active surveillance for potential COVID-19 symptoms. A subject experiencing a symptom that potentially could

represent COVID-19 is to contact their investigational side, which will trigger either a telehealth or in-person visit and nasal swab. Cases will be defined based upon both the presence of one or more symptoms and a positive SARS-CoV-2 nucleic acid amplification test (NAAT). Efficacy analyses will be performed in participants without evidence of infection before vaccination and with and without evidence of infection before vaccination. Subjects will be followed for up to 2 years after the second dose with regular follow-up visits.

Pfizer/BioNTech are focused on enrolling a diverse population. This is an international study including the US, Latin America, Europe, and South Africa. The majority of subjects will come from the US. Current enrollment shows that approximately 19% of the subjects are either Black or Hispanic and 4% Asian. Work is also being done with sites to enroll Native Americans. In Latin America and the other regions, there will be increased diversity as well.

Mr. Gleeson described BNT162b2 storage, handling, and administration. He reported that the first primary packaging is going to be filled into 2 ml type 1 glass preservative free multi-dose vial (MDV). A MDV has 0.45 ml frozen liquid drug product, with 5 dose per vial. The secondary packaging is a single tray that holds 195 vials 2 ml vials for a total of 975 doses per tray. The tray is a white box that is approximately 229 X 229 x 40 mm square. The secondary packaging is then placed in a tertiary thermal shipping container in which a minimum of 1 tray (975 doses) or up to a maximum of 5 trays (4875 doses) can be placed. This is then placed in a payload carton. The payload carton is submerged in 23 Kg of dry ice pellets. Each thermal shipper will utilize real-time temperature monitoring devices and GPS tracking technology to allow for 24/7 in-transit control, security, and mitigating actions on temperature deviations. Each thermal shipper's internal dimension are 245mm X 245mm X 241mm and external dimensions are 400mm X 400mm X 560mm. The total weight of the thermal shipper is approximately 35 kg or 70 pounds.

When the thermal shipper arrives at the point of vaccination, there are a number of options. Various sizes of ultra-low temperature (ULT) freezers are available in the market in which the vaccine trays can be removed from the thermal shipper and stored as frozen liquid at -70° C ±10°C where it can be stored as a frozen liquid for long-term storage of up to 6 months. Small volume ULT freezers store up to about 30,000 doses and large store up to about 200,000 doses. Long-term stability studies will continue on the protocol to inform product shelf-life at -70° C. The second option is to use the thermal shipper for extended storage. Each thermal shipper is validated to keep the vaccine payload at ULT up to 10 days if stored at 15°C to 25°C temperatures without opening. Upon receipt of the vaccine and after opening, the box should be replenished with dry ice within 24 hours (23 Kg of dry ice pellets; 10 mm- 16 mm pellets). The thermal shipper should be re-iced every 5 days to extend the storage. If there are difficulties in sourcing dry ice, Pfizer has strategic dry ice suppliers that can be used and there is a reference website for suppliers that Pfizer will share in due course. The cost of this service must be incurred by the customer. The recommendations for the thermal shipper are not to open it more than twice per day and to close it within 1 minute (or less) after opening. The final option is to remove the vaccine from the thermal shipper and place it in a refrigerator at 2°C to 8°C where it can be stored for up to 24 hours or at room temperature for no more than 2 hours after thawing based on current stability data. Ongoing stability studies will continue to characterize storage stability. Over time, the expectation is that new data from these studies will help optimize or allow those storage temperatures if 2 days. Post-dilution in-use period is expected at 6 hours at 2°C to 30°C.

Discussion Points

Dr. Cohn expressed gratitude for all of the very important information just shared for both products on vaccine storage and handling. She requested that listeners not start going online right now to purchase freezers. CDC is working on solutions through its distribution and administration planning for these very complex storage and handling requirements at this time. As soon as possible, information will be shared about how CDC and HHS, through OWS, are going to be supporting programs at maintaining this vaccine at this temperature. Additionally, she expressed her hope that Pfizer could comment on the timeline for additional studies on stability that may shift these plans.

Dr. Romero asked what the window is for the timing of signs and symptoms for adverse reactions, which is going to cause some problems because they mimic the signs and symptoms of COVID-19 and may lead to excessive COVID testing in vaccinees. In addition, he asked what the plans are for measuring antibody persistence over time.

Dr. Kitchin indicated that they provide some guidance to their investigators about recording potential COVID symptoms in the first 7 days after vaccination. There is a potential overlap between some of the more common symptoms and the reactogenicity. They do not anticipate an over-testing for COVID during that period based upon that guidance. In terms of persistence of immunogenicity, the study is currently planned to follow subjects for up to 24 months after they have been vaccinated and there will be bleeds across that whole period. These are going to be the first subjects vaccinated in hopefully what will be an ongoing program.

Dr. Lee asked whether there are ways to capture the full benefits of vaccination, recognizing that respiratory disease or some of the systemic symptoms that are presented are classic COVID presentations. With regard to the potential to capture other disease manifestations secondary to COVID infection, particularly in the future in trials in children, it might be helpful to widen and capture that. Perhaps that is in the secondary outcomes. She emphasized that asymptomatic infection, and thinking more about the response earlier regarding PCR versus serology, she feels that with serology and asymptomatic infection, they are sometimes not seeing as strong a response as with symptomatic infection. In order to think about herd immunity in the way that they would like to, such as comparing polysaccharide vaccine to conjugate vaccine in children and the differential impact it has on the population, it would be extremely helpful to understand the potential for each of the vaccine candidates to have that impact.

Dr. Kitchin responded that a number of things Dr. Lee mentioned are probably going to have to be examined in further studies, perhaps even in implementation studies assuming efficacy and safety are demonstrated. Keeping in mind the number of subjects needed to be enrolled in the study and the urgency, Pfizer has tried to keep the study as pragmatic as possible in the first instance rather than overloading it with it with a lot of additional procedures that might make the implementation of the study difficult. Those are things that they can look at in future studies. Regarding pediatrics, they are in dialogue with regulators in the US and elsewhere about plans for studies in children, pregnant women, and other potential groups as early as possible.

Dr. Lee noted that follow-up for severe adverse events in the Phase 3 studies is up to 6 months. Given that follow-up is 2 years with regard to efficacy and post-vaccination infection, she wondered whether it would be possible to extend safety monitoring out to 2 years, at least for serious adverse events.

Dr. Kitchin confirmed that it is surveillance for “serious” rather than “severe” adverse events, which is an important distinction, up to 6 months after the second dose. The active surveillance does not preclude reporting of adverse events beyond that. They have some experience of long-term follow-up vaccine studies where investigators continue to report adverse events during that period. That is the current plan for reporting of all serious adverse events. Beyond that would depend upon whether any adverse events of interest or signals were observed that would make it necessary to focus on additional safety surveillance beyond that. The investigators are at liberty to report adverse events at any time during the trial.

Dr. Lee suggested that perhaps for all trials, safety monitoring should be standardizing post-vaccination in the Phase 3 study. Given that each of the vaccine candidates potentially has unique profiles, it would be helpful to ACIP in terms of assembling and reviewing the data for vaccine safety for there to be a standard approach.

Dr. Szilagyi asked whether the subjects 18 to 85 years of age are healthy individuals and what the representativeness is in terms of underlying high-risk conditions.

Dr. Kitchin said that in terms of underlying illness, they are including a healthy population currently between the ages of 18 and 85 and they are in dialogue to potentially extend that range. Saying “healthy” permits potential participants with chronic medical conditions provided they are considered stable, which is defined as meaning no changes in therapy or significant intervention within the past 6 weeks. That is the same across all sites. They already can see from the baseline medical history data that they have started to accrue significant numbers of people with underlying medical conditions. As they across more, they will be able to better represent what that population looks like. The intention, obviously within the constraints of a Phase 3 efficacy study, are to recruit a population that is as representative in all ways as possible. Hypertension, obesity, and diabetes are at the top of the list and a significant number of subjects with those conditions are already enrolled.

Dr. Poehling noted that under Phase 1 and 2, Dr. Kitchin said there was a predominance of Th1 response and he showed data for Th1. She asked whether he could share what they have seen with the Th2 response and if he could clarify whether the Th response would be included in the Phase 3 study.

Dr. Kitchin indicated that the operational complexity of collecting samples for T-cell analysis is quite substantial, so typically they will collect those only in relatively small and very controlled settings. In the large Phase 3 study that they are now conducting, they do not plan to collect T-cell samples. However, the nature of those analyses means that the analysis they were able to perform in the early Phase 1 studies give a good representation of what the T-cell responses would look like. He did present those data for the b1 candidate, but what he did not say in the presentation was that the subjects who received the b1 candidate were the first ones enrolled into the study. Therefore, the data for them becomes available sooner than for the B2 subjects who were recruited a few weeks later. For the b2 data, what he could say was that the

preliminary data look at least as good as for b1 and they hope to be publishing that in very short order—probably within the next week or so—at least on the pre-print server.

Ms. Bahta requested clarification with regard to the telehealth and in-person visits in terms of why nasal swabs are not being done for all subjects.

Dr. Kitchin replied that the way it works is that if someone experiences one of the trigger symptoms, which are the typically recognized symptoms for COVID-19, they are advised to contact their investigational site by telephone in the first instance. If it is confirmed that they do indeed have one of those symptoms, depending upon their circumstances, the country in which they are enrolled, and the site circumstances, they can perform a self-nasal swab with the swab kit they are given to take home upon enrollment and ship that directly to Pfizer, or they can go to a site to have an in-person swab performed there. Either way, those who have a confirmed symptom that could represent COVID-19 are all intended to have a swab performed.

Dr. Fryhofer (AMA) emphasized the importance of collecting diversity information, particularly given the number of vaccines that are under investigation with possibly different profiles. She asked whether there are any plans to include that information on the website.

Dr. Kitchin emphasized that they are very cognizant of the importance of diversity, particularly with the pattern of COVID and how it disproportionately affects minority groups. That is something they are actively working with their partner sites to put in place, with outreach to the population. As noted earlier, it is not straightforward to enroll minority groups in large numbers into clinical trials in general. He believes they have made good headway so far, but are always seeking to do better.

Dr. Kimberlin (AAP Red Book) asked whether Pfizer is measuring any markers of inflammation, given that another characteristics of this disease is inflammation throughout the body, even something as crude as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

Dr. Kimberlin indicated that they are not measuring those in their study. If these parameters are part of someone’s medical care, they will capture them. However, they are not performed under the study protocol.

Dr. Fryhofer (AMA) noted that Dr. Kitchin pointed out that there was actually less reactogenicity in older versus younger participants in the Phase 1 study. She asked whether it concerned him in any way that perhaps the vaccine may not work as well among older adults.

Dr. Kitchin confirmed that immunogenicity and neutralizing antibody titers were lower in the older subjects than in the younger, but were at least as high as the HCS. Ultimately, the efficacy within the study as a whole will be how they can assess the vaccine’s affect overall and in different parts of the population. Until they have those data, they cannot really speculate about that.

Dr. Cohn requested additional details about the breakdown of the age groups in terms of the younger population and the older population in the immunogenicity and safety data from the Phase 1 trial, and also specifically in the older group the proportion of patients over 70 versus between 65-85.

Dr. Kitchin indicated that in the Phase 1 study, Pfizer enrolled two age groups: 18-55 and 65-85. Each group who received the active vaccine comprised 12 subjects at each dose level, which is a relatively small number in terms of looking at the overall distribution. However, they did have representation across the whole age range from 65 through 85.

Dr. Madonado (AAP) said she understood from the previous speaker that they were not going to be collecting samples for genotyping. But it seemed to her that if there is a breakthrough infection or infection symptoms and they are collecting swabs, they would want to genotype those to see what the sequences look like compared to the circulating strains.

Dr. Kitchin responded that they do not currently plan to do that. The plan is to use those swabs to assess, by PCR, whether there is presence of SARS-CoV-2 genomes or not. However, genotyping is certainly something they could think about looking at in the future.

Dr. Poehling said that if she understood correctly, the b2 Th1 and Th2 data are being assembled for publication soon. She wondered whether there were any characteristic in those who developed a Th2 response.

Dr. Gruber, Senior Vice President of Pfizer Vaccine Clinical Research and Development, responded that the shift was so dramatic in terms of Tth1 that there actually was very little to discern where they got an IL-4 response. He would say there was nothing distinguishing in that group. They continue to look at those data and are preparing it for publication. They have commented in a press release that the very nature of the platform lends itself to a Th1 response, which is part of the reason that is was attractive to begin to begin with. The data are supporting that and, in fact, by virtue of having the larger set of antigens to be able to simulate immune response by using the full length spike protein, they have the potential that there is a greater repertoire of CD4 and CD8 response because there are more epitopes to respond to. It was not clear from the very start where most of the attention would be directed, which was part of the reason for looking at receptor-binding domain versus the full length construct. They are seeing responses against the full length of the peptide, N-terminally and hydroxy-terminally. He would say that the response is so robust, there does not seem to be anything to dissect out in terms of a Th2 response because there is so little there.

Dr. Quach (NACI) asked, given the decreased sensitivity of the nasal swab compared to the NP swab, how Pfizer is going to handle the differences between people presenting in-person to be swabbed at the vaccine center versus those who self-swab at home.

Dr. Kitchin clarified that the same swab is used for either procedure, which is a nasal swab as opposed to an NP swab.

Dr. Quach (NACI) asked whether they are worried about the decreased sensitivity of the nasal swab compared to the NP.

Dr. Kitchin said that having seen some of the data regarding the amount of virus that is present when people have true COVID symptoms, that is not something he is overly concerned about.

Dr. Messonnier thanked Pfizer, Moderna, and all of CDC’s pharmaceutical company partners for their work to try to rapidly develop these vaccines and fulfill a clear public health crisis need. She understands that the need to move quickly sometimes means that they have to deal with

the realities of imperfection. She emphasized that the complexities of Pfizer's plan for vaccine storage and handling will have major impact on the ability to efficiently deliver the vaccine. In that context, she asked whether Pfizer could provide any more details about when they would have more information regarding storage and handling conditions that are less stringent, and about the possibility of shipping it in boxes that have less quantity that would provide more flexibility in implementation.

Mr. Gleeson indicated that for the pandemic supply, the current minimum shipping quantity is the 195-vial pizza box. They are investigating the viability of a less than 195-vial smaller box, but are not yet able to confirm the feasibility of that. They can report back to ACIP on this at a later time.

COVID-19 Vaccine Safety Monitoring

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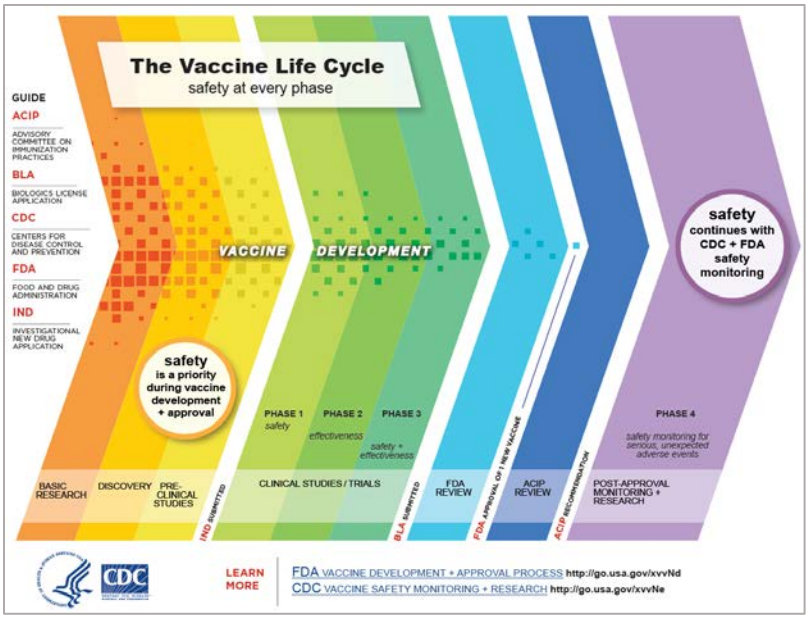
Dr. Shimabukuro provided an overview of vaccine safety monitoring in terms of some of the basic issues, plans, systems, and populations. He indicated that he was presenting on behalf of some of CDC's partners including the Food and Drug Administration (FDA), Department of Defense (DoD), Indian Health Services (IHS), and the US Department of Veterans Affairs (VA).

Safety is a priority during all phases of vaccine development, approval, and use. Post-licensure (post-authorization) safety monitoring is an established part of the vaccine life cycle. Monitoring COVID-19 vaccine safety will be a coordinated effort by multiple federal agencies. This schematic depicts the vaccine lifecycle and is posted on the CDC website:



While this graphic describes the traditional pathway, the concepts are also relevant. The vaccine life cycle begins with basic research, discovery, and pre-clinical studies and then moves on to the phased clinical trials. Once the Phase 3 trial is completed, the Biologics License Application (BLA) is submitted to the FDA for review and approval. Shortly thereafter, there is an ACIP review and recommendation. Then the process moves into Phase 4 during which there is post-approval safety monitoring for serious, unexpected adverse events. Traditionally, CDC and FDA perform most of the safety monitoring. Other federal partners participate in this monitoring as well. For COVID-19 vaccines, this will be a coordinated effort by multiple federal agencies.

In terms of the rationale for post-licensure/post-authorization vaccine safety monitoring, the safety standards for vaccines are high. Vaccines are for primary prevention and they are being given to many generally healthy people who do not have the disease, so it is not meant for treatment. Therefore, the tolerability for risk is lower than for drugs or other things that are used to treat illness. Furthermore, the pre-licensure trials are not optimal for detecting rare AEs. The numbers enrolled are too small, even with large clinical trials like the ones for COVID-19 with 30,000 individuals. Pre-licensure trials also are not optimal for monitoring vaccine safety in a real-world environment or for assessing safety in special populations. Groups like pregnant women or individuals with certain pre-existing medical conditions are often excluded, or at least excluded in the initial clinical trials. Finally, evaluating AEs with delayed onset such as vaccine-enhanced disease requires monitoring for months to possibly years.

Manufacturers and the US government (USG) both have roles and responsibilities in terms of vaccine safety monitoring. Vaccine safety monitoring as far as safety is a federal responsibility. Manufacturers have Phase 4 responsibilities for their individual products. These are based on standard regulatory obligations as specified by the FDA. They can be guided by results from the clinical trials. They are conducted or managed by manufacturers' pharmacovigilance programs with regulatory oversight by the FDA. These may include post-marketing commitments, post-marketing requirements, and pregnancy registries. Also included are vaccine AE monitoring and reporting of AEs to the Vaccine Adverse Event Reporting System (VAERS).

The USG has a responsibility for public safety. Many of these requirements are laid out in the 1986 National Childhood Vaccine Injury Act, which authorized the creation of VAERS. Monitoring is independent from manufacturers. There is no financial stake, there are less real and perceived conflict of interests (COIs). This type of monitoring is important for public confidence. Monitoring covers all vaccines from all manufacturers in a comprehensive and integrated fashion. The USG manages large data systems that are standing, long-term investments in public health surveillance like VAERS, the Vaccine Safety Datalink (VSD), and Center for Medicare and Medicaid Services (CMS). Surveillance data from VAERS are made publicly available online to anyone and surveillance findings from Phase 4 monitoring by the USG are presented at federal advisory committee meetings in a transparent manner.

Manufacturers play a critical role in post-authorization safety monitoring, however; it is not possible to get all of the answers from manufacturer monitoring. The USG maintains and has constant access to the largest, most robust, and most sophisticated electronic monitoring systems available. The systems and the methods used by USG agencies are complementary. USG agencies can freely cooperate, collaborate, share information, leverage expertise in other agencies, support each other's surveillance efforts, and act in a coordinated and integrated way.

To further describe vaccine safety monitoring systems and populations, VAERS is a national spontaneous reporting system that is co-managed by the CDC and FDA. VAERS includes all 320 million or so US residents as a covered population for safety monitoring. This includes individuals of all ages, races, states and territories, healthy people, those with co-morbidities, et cetera. In recent years, VAERS has received approximately 60,000 reports per year and a small number of foreign reports. That averages out to about 1000 reports per week.

Specifically focusing on older adults, Dr. Shimabukuro discussed some of the active surveillance systems in the USG's arsenal. The FDA's CMS data monitoring, Medicare fee-for-service (FFS) and Medicare Advantage, includes 55-60 million persons ≥65 years of age. This represents about 92% of the US older adults. CDC's VSD is a collaboration between 8 integrated healthcare systems that has data on about 1.8 million persons ≥65 years of age per year. The VA data warehouse and electronic health record (EHR) has about 1.56 million persons ≥65 years of age who are typically vaccinated annually for influenza and who are anticipated to be a priority group for the VA. These are EHR, claims, or encounter-based systems through which active surveillance is conducted. Therefore, there is complete or near complete information depending upon the system on a population. Therefore, it is possible to calculate rates and assess risk.

CDC's VSD active surveillance in the age range of 19-64 years and 2.3 million persons <18 years of age. Routine active surveillance is conducting through the VSD each season for influenza and when new vaccines are licensed and recommended for use. FDA's Biologics Effectiveness and Safety (BEST) System has data from claims, EHRs, and the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Program that is part of the FDA's sentinel program that has EHR data from large health insurers with claims data and access to medical charts on about 100 million persons. DoD conducts VAERS monitoring in collaboration with CDC through a VAERS data sharing agreement. There are roughly 1.4 million Active Duty and 860,000 Reserves, the majority of whom are <30 years old. This also includes their dependents and beneficiaries if seen in DoD healthcare facilities. DoD also has the capacity to conduct active surveillance. For COVID-19, the DoD Defense Health Agency Immunization Healthcare Division (DHA-IHD) plans to collaborate with the Armed Forces Health Surveillance Branch (AFHSB) to monitor vaccine safety in the DoD EHR systems, primarily using the Defense Medical Surveillance System (DMSS) and the DoD Personnel and Readiness COVID-19 Registry. There is a new VAERS data monitoring collaboration between CDC and the IHS through a VAERS data sharing agreement. The IHS is comprised mainly of American Indian and Alaska Native (AI/AN) patients seen in IHS and Tribal healthcare facilities. CDC is working with IHS to identify reports in their patient population for individuals vaccinated in their facilities. The analyses for the IHS data will be conducted by the National Pharmacy and Therapeutics Committee (NPTC) and the IHS Division of Epidemiology and Disease Prevention (DEDP).

Case reviews and inquiry response is also a component of monitoring and surveillance and provides a service to providers and individuals who have questions or concerns about vaccine safety. CDC's Clinical Immunization Safety Assessment (CISA) Project assists US healthcare providers with complex vaccine safety questions about their patients by conducting in-depth clinical case reviews. CISA also plans to establish a call service for clinician assistance during the COVID-19 response. CDC's Immunization Safety Office (ISO) manages an inquiry response program and responds to vaccine safety inquiries and questions from the public, including patients, parents, healthcare providers, public health partners, and others. DoD's Regional Vaccine Safety Hubs (RVSHs) for case evaluation and Vaccine Adverse Event Clinical System

(VAECS) evaluate and track cases of AEs following immunization in DoD and DoD-affiliated populations.

There are some new initiatives for enhanced monitoring programs to meet the challenge of COVID-19. One of the challenges identified is that during the early phase of a national COVID-19 vaccination program, initial doses may be distributed to specific groups such as healthcare personnel and other essential workers. In this scenario, activities to enhance normal public health monitoring systems will be necessary. One potential solution to address this challenge is to include active surveillance in early recipients through smartphone- and email-based web surveys, with directed reporting to VAERS for clinically important or clinically significant AEs. This is a combination of active surveillance for reactogenicity and enhanced passive surveillance as well. Another potential solution is vaccination capture and enhanced passive surveillance through other data sources from healthcare facilities, partners within CDC, and other government agencies.

The current plan to conduct smartphone-based monitoring in early recipients of COVID-19 vaccine in a scenario in which limited vaccine doses are available, CDC is in the process of establishing a program to identify these potential early recipients and register them in anticipation of scheduling vaccination, administering vaccination, and communicating with them during vaccination through reminder recalls. The plan is to piggy-back on this process to send text messages beginning as soon as someone receives vaccination, frequently early on to assess reactogenicity, and to ask some specific questions in the first week or so and out to 6 weeks about any clinically important adverse health events the individual feels may be related to vaccination. Depending upon the answers to these text messages, which can be either through a text or web-based or email survey, these individuals would be directed to report medically important AEs to VAERS that ultimately would be sent to CDC and FDA through the normal VAERS process. Through this process, there would be both numerator and denominator data on these early recipients. CDC thinks this will be a good way to characterize the basic safety profile early on of COVID vaccines in a real-world environment.

Other potential data sources to assist with vaccine safety monitoring include state Immunization Information Systems (IIS) capture denominator data for AE rates. Information can be captured through telehealth encounters in CDC's VSD. With COVID 19, CDC understands that there has been a fundamental change in the way healthcare encounters occur, so they want to be able to assure that they can capture data to the extent possible from these telehealth encounters in the surveillance systems. It is also possible to gauge healthcare provider and general public concerns through CISA inquiries and the Vaccine Safety Inquiry Response Program. CDC conducts thematic analyses on what types of concerns providers and the general public have. It is a pulse check on what the public thinks about vaccine safety and what concerns are rising to the top. CDC's partners at FDA plan to develop new electronic data sources through EHR partners they are working with.

Regarding signal detection and signal assessment, the Council for International Organizations of Medical Sciences (CIOMS) proposed a signal as:

> "Information…from one or multiple sources…, which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action."

In practice, efforts focus on detecting signals for “adverse” events rather than beneficial events [Practical Aspects of Signal Detection in Pharmacovigilance: Report of CIOMS Working Group VIII. Geneva 2010].

Focusing on spontaneous reporting and VAERS data, there are traditional methods used for signal detection and signal assessment. In VAERS, clinical review of individual reports is an important component of what CDC does. They plan to identify a select group of adverse events of special interest (AESIs) up front, but also review any report with any outcome and monitors all reports in VAERS. The clinical reviews are to verify the diagnosis and onset interval, characterize clinical and laboratory features, and identify other potential risk factors. They also do aggregate report reviews in VAERS, which is looking at automated data to get case counts, frequencies of AE coding terms, reporting trends over time, and reporting rates. Statistical data mining methods are utilized in VAERS to detect disproportional reporting of specific vaccine-AE combinations in the VAERS database. The two methods used are empirical Bayesian data mining, which is conducted by the FDA, and proportional reporting ratio (PRR) analyses. These generate statistical signals when pre-specified thresholds are reached. One of the first thing that is done when a signal is detected is to perform a clinical review of individual reports to verify the diagnosis, check the onset interval, and look for biological plausibility to characterize the reports.

VAERS timeliness for signal detection and assessment is important. CDC and FDA receive updated VAERS datasets daily. On a daily basis, both the CDC and the FDA receive what is essentially an updated version of the entire database from the VAERS contractor because it is dynamic and updated. This is from the beginning until the current day, so 1990 to the present. The processing actions for VAERS reports as they come in include Medical Dictionary for Regulatory Activities (MedDRA) coding of symptoms by certified MedDRA coders, redaction of personally identifiable information (PII), quality assurance (QA), and preparation for posting individual reports on the secure virtual private network (VPN) for investigator access. The processing times for COVID-19 vaccines for death reports will be 1 day, for reports classified as serious will be 3 days, and reports classified as non-serious will be 5 days.

One approach to monitoring in EHR, administrative, and claims data is near real-time sequential monitoring through Rapid Cycle Analysis (RCA) in the VSD. Data are refreshed weekly in high volume situations. A familiar high volume situation would be influenza vaccination when 100 or so million doses area administered in a span of a couple of months in the fall. In this case, the data are refreshed every week. Pre-specified outcomes are identified in advance and are monitored. RCA is a surveillance activity. It is not the same as an epidemiologic study. It is designed to detect statistical signals, which are values above pre-specified statistical thresholds. When a statistical signal occurs, assessment requires a series of evaluations using traditional epidemiologic methods. Not all statistical signals are indicative of an increased risk or a vaccine safety problem. They need to be assessed. Chart-confirmation of diagnoses to confirm or exclude cases as true incident cases is a key part of statistical signal assessment. In VSD, the ability to pull the charts and review them is rapid. Typically, a rapid review can be done of a chart within 1 to 3 days. A more detailed chart analysis sometimes requires seeking additional information. Applying case definitions can generally be conducted within a week.

In summary, real-time or near real-time safety monitoring will be critical during the early stages of the COVID-19 vaccination program in order to characterize the safety profile of COVID-19 vaccines in a real-world environment, and rapidly assess COVID-19 vaccine safety in risk-based priority groups, such as older adults and individuals with certain pre-existing health conditions. During a broad-based vaccination program, large amounts of COVID-19 vaccine are anticipated to be administered during a short period of time. It is important to have established, high-functioning systems and validated methods in place to rapidly detect and assess potential safety signals so public health action can be taken if necessary.

In terms of process, there is an ACIP COVID-19 Vaccine WG that is Chaired by Dr. Beth Bell. The mission of this group is to advise on planning for the use of COVID-19 vaccines, advise on all components of program implementation during a large-scale COVID-19 immunization program, and review post-authorization or post-approval vaccine safety surveillance data. There also is an ACIP COVID-19 Vaccine Technical Subgroup, which is a subgroup of the ACIP COVID-19 Vaccine WG that is chaired by Dr. Grace Lee. The purpose of this subgroup is to advise on the safety of COVID-19 vaccine candidates in development and safety monitoring of vaccines authorized/approved for use, and review post-authorization or post-approval vaccine safety surveillance data.

In closing, multiple USG agencies will use complementary systems and methods to monitor COVID-19 vaccines. Current monitoring systems have the capacity to effectively monitor COVID-19 vaccine safety both under EUA and post-licensure. Analytic methods have been validated through years of development and refinement. Data refresh and updates are timely, and analyses occur in near real-time. New data sources will contribute to COVID-19 vaccine safety monitoring, especially early in the vaccination program. Topics for future presentations to ACIP include COVID-19 vaccine safety monitoring plans and methods, vaccine safety outcomes and AESI from COVID-19 monitoring, and the process for reviewing and presenting safety data as it becomes available during the implementation of a program.

Open Discussion

Dr. Hunter asked whether Dr. Shimabukuro could comment during this or in future presentations about how often potential signals turn out to not be concerning or to not have a biologically plausible cause-and-effect relationship.

Dr. Shimabukuro reminded everyone that he has said in the past that about 90% of statistical signals that are detected in the monitoring systems do not turn out to be true signals after assessment, though that is somewhat arbitrary. The assessment includes a quality check on the actual data and biological plausibility. Most of the signals detected turn out to be not true signals.

Dr. Poehling observed that the active surveillance in early recipients is really exciting. As people are thinking about launching their influenza vaccines campaigns, including in healthcare workers, she wondered whether any work was underway to test the system to determine how it works before COVID-19 vaccination begins.

Dr. Shimabukuro deferred to the immunization program on the text monitoring part of that. The safety component is piggybacking on the actual text monitoring. For the other systems, he does think there is an opportunity with some of their other data sources working with other partners

within CDC. The National Healthcare Safety Network (NHSN) is one of the systems they are working with. There is an opportunity to evaluate how well they are collecting vaccine exposure and to work on education and outreach on directing individuals who have AEs or healthcare providers who evaluate them to report to VAERS.

Regarding active surveillance and early COVID-19 recipients, Dr. Frye was curious to know how many individuals they anticipate following and why they would choose a certain group of individuals so she could better understand whether they would be capturing any SAEs. It is known that typically, thousands if not more people must be followed to find some of the rarer complications.

Dr. Shimabukuro said he believed the answer to that question is that they would follow as many people as they are able to capture in the initial registration process for vaccination. There is not a limit. They are not saying they need a certain number. The system is capable of sending text messages and implementing the online survey in as many people as they can send the messages out to. He did not believe there is a hard limit. Certainly, for safety they are not saying they need to meet a certain number and that would be good enough work. They are interested in getting as much data on the early recipients as possible.

Regarding the case reviews and inquiry responses, Dr. Bernstein asked whether the call service to be established for clinician assistance was intended to be retrospective or prospective, what kinds of calls they are expecting, and if availability will be 24/7 or otherwise. Given the number of vaccines that are planned to be administered in such a short period of time, this will be a great service to clinicians at point-of-care.

Dr. Shimabukuro replied that it is intended to be prospective if clinicians have general, specific, or topical vaccine safety question. It is intended to be available as a service for clinicians as they need it and have a vaccine safety question about which they want to speak to a CDC subject matter expert (SME).

Dr. Arthur (BIO) asked whether they will be planning as part of the communication strategy for the rollout leading up to the vaccine to do educational activities for clinicians on the various safety monitoring systems. They have found that many doctors do not necessarily understand how to use VAERS and it probably would be good to have some general education before launch on the various systems to which they will be reporting given how many immunizers there will be for the vaccine.

Dr. Shimabukuro said the short answer is that they plan to do outreach and education. The active role providers could take would be largely around VAERS, but certainly will pertain to educating healthcare providers on vaccine safety monitoring and how thorough the USG is, how seriously they take it, and how transparent they want to be.

Ms. McNally asked for an explanation about how CDC receives post-licensure safety monitoring information from the manufacturers and the timing of that.

Dr. Shimabukuro indicated that most of the post-licensure safety monitoring data CDC receives from the manufacturers come through VAERS. The manufacturers are required by FDA to submit a VAERS report for any AE that comes to their attention. That reporting process goes through FDA and then funnels into VAERS. He deferred to the FDA as far as other Phase 4

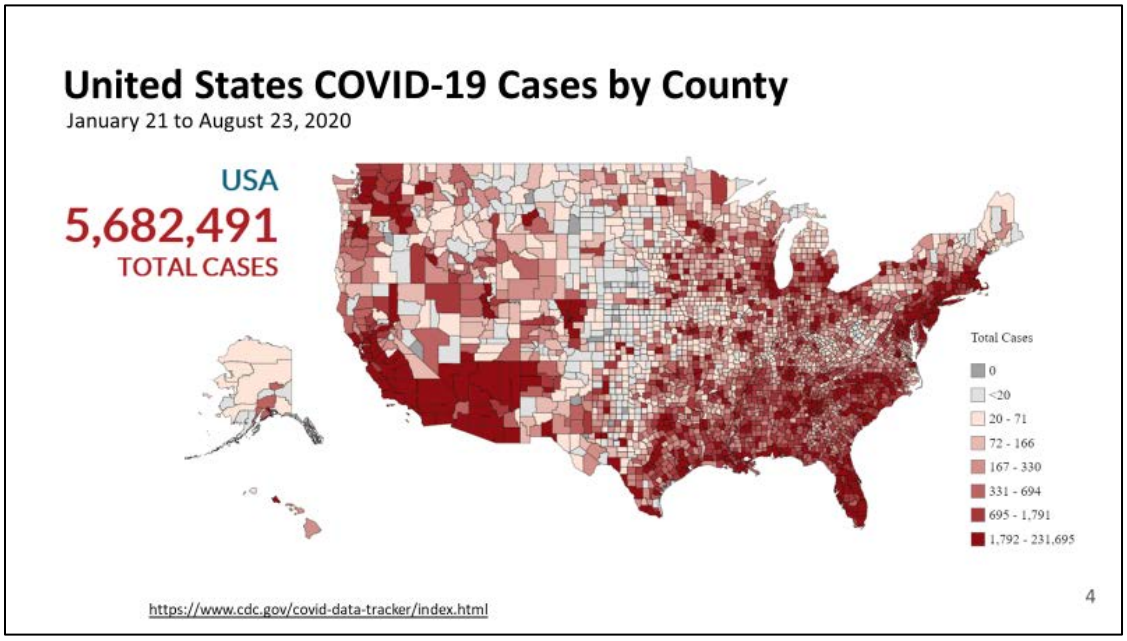
safety information that the manufacturers communicate to FDA. There is a reporting requirement that any AE be reported to VAERS so that both CDC and FDA have access to those manufacturer reports.

Dr. Fink (FDA) added that manufacturers are required to submit yearly safety reports to the FDA that include safety data from spontaneous reports that they may receive from patients or healthcare providers, as well as results of post-marketing studies that they conduct in the US and worldwide. FDA reviews those reports and examines the data to inform any regulatory actions that they might take.

Epidemiology of Individuals at Increased Risk of COVID-19 Disease

Nancy McClung, PhD, RN
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

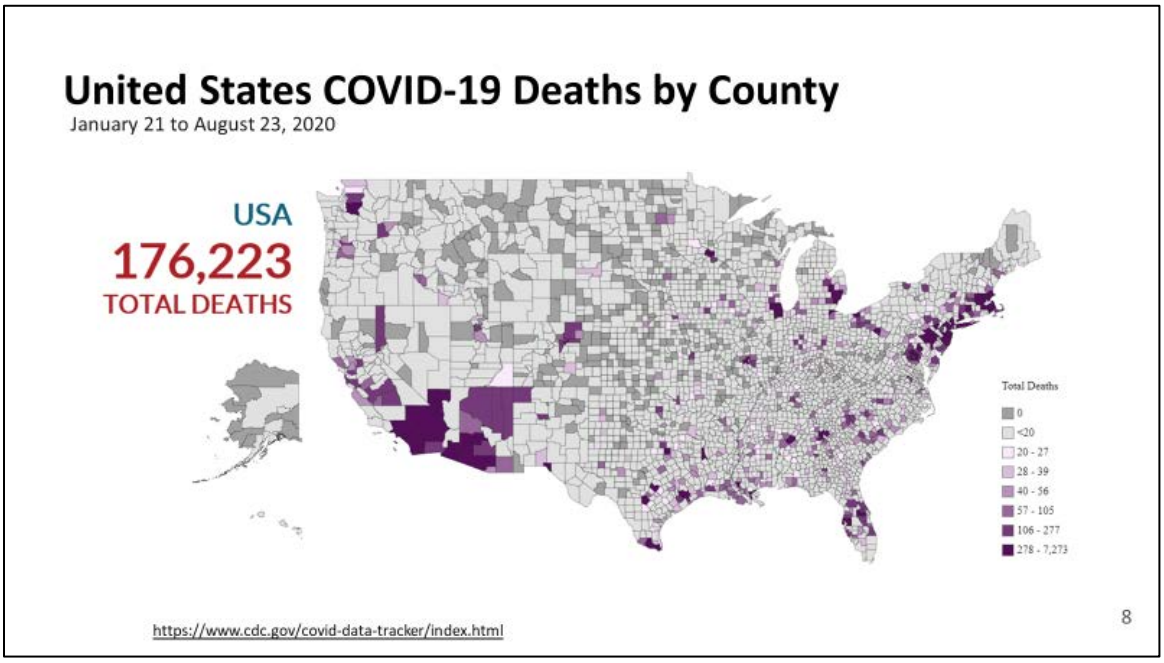
Dr. McClung presented a brief update to the overall US COVID-19 epidemiology and epidemiology among individuals at increased risk of severe COVID-19 disease, including older adults aged 65 years or older and adults with underlying medical conditions. As of August 23, 2020 a total of 5.6 million cases had been reported to CDC. This map shows the cumulative case counts by county, with the darker red representing larger numbers of cases:



Regarding the trends in the number of COVID cases reported per day in the US through August 23rd, cases peaked nationally in mid-July and have been decreasing over the past month. However, daily cases reported remain higher than was seen before increases in June [https://www.cdc.gov/covid-data-tracker/index.html#trends].

In terms of the number of specimens tested for SARS-CoV-2 using a molecular assay and reported to CDC by public health laboratories, the percentage of specimens nationally testing positive for SARS-CoV-2 have continued to decrease since mid-July. The past week (Week 33), the overall percent positive at public health laboratories was 6.6%. The percentage of specimens testing positive in commercial laboratories reporting to CDC also has been decreasing since mid-July. The past week, the percent positive was 6.3% [https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html].

As of August 23rd, a total of 176,223 deaths due to COVID-19 have been reported to CDC. This map shows the cumulative number of deaths by county, with the darker purple representing larger numbers of deaths:



Regarding trends in the number of COVID deaths reported per day in the US nationally, the number of deaths peaked at the end of April, then declined through the end of June, and began to increase again in July. For the past month, the number of deaths has remained relatively stable at approximately 1000 COVID-19 deaths per day [https://www.cdc.gov/covid-data-tracker/index.html#trends].

Older adults and people of any age with certain underlying medical conditions are at increased risk for severe illness from COVID-19. Severe illness from COVID-19 is defined as hospitalization, need for intensive care unit (ICU) care, need for intubation or mechanical ventilation, or death. In the US, older adults aged 65 years or older represent 16% of COVID-19 cases but nearly 80% of COVID-19 deaths. Case-level data reported by health departments to CDC for approximately 4.2 million cases and 131,000 deaths demonstrate that the percentage of deaths increases with age.

Dr. McClung noted that much of the data she would be presenting came from COVID-NET. COVID-NET conducts hospitalization surveillance with 14 states, representing about 10% of the US population. Patients must be a resident of the surveillance area and have a positive SARS-

CoV-2 test within 14 days prior to or during hospitalization. Chart reviews are conducted and data include underlying medical conditions. Older adults aged 65 years or older have the highest cumulative rate of COVID-19 associated hospitalizations. As of Week 33, August 15th, hospitalization rates among older adults was almost 4 times the rate of adults aged 18-49 years [https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html].

In terms of the percent of severe outcomes by age group in adults reported to COVID-NET surveillance through August 15th, adults aged 50 years and older were more likely to have severe outcomes during COVID-19 associated hospitalizations compared to adults age 18-49 years. Of note, 25% of adults 65 years or older died during hospitalization compared to 2% to 10% of younger age groups [https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html].

Among 2491 adults with COVID-19 associated hospitalizations reported to COVID-NET between March 1 and May 2, 2020, older age was the strongest, independent risk factor for in-hospital death. With regard to the adjusted rate ratios and 95% CI from a multivariable model of risk of in-hospital death, not only was age the strongest risk factor, the risk increases with increasing age. Hospitalized adults aged 85 years or older had 11 times the risk of in-hospital death compared to hospitalized 18-39 year-olds [Kim et al, 2020, https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1012/5872581].

Based on data from a recently published multi-center US cohort study including 65 hospitals across the US, among 2215 adults with COVID-19 associated ICU-admission between March 4 and April 4, older age was the strongest, independent risk factor for in-hospital death within 28 days of admission, after adjusting for patient and hospital level characteristics. Similar to COVID-NET findings, with increasing age, the odds of in-hospital death increased. Adults 80 years or older admitted to the ICU had 11 times the odds of death compared to 18-39 year-olds admitted to the ICU [Gupta et al, July 2020; https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2768602].

COVID-NET data available through August 15th for selected underlying medical conditions among adults aged 18 years or older with COVID-19 associated hospitalizations showed that the most common underlying conditions were hypertension, obesity, diabetes, and cardiovascular disease (CVD). Some of the conditions include multiple conditions. For instance, CVD includes coronary artery disease, congestive heart failure, and other conditions. The most common underlying medical conditions among hospitalized adults varied by age group. Obesity was in the top 1-2 conditions reported for younger and middle aged-adults, but was only reported in 34% of the adults 65 years and older. Hypertension was the most common among adults 50-64 and 65 and older. Diabetes was in the top 5 most common conditions in all age groups. Over 60% of hospitalized adults aged 18 years or older had 3 or more of the selected underlying medical conditions. Only 12% of hospitalized adults had no underlying medical condition. Regarding the number of conditions by outcome (e.g., death, need for mechanical vent/intubation, or ICU admission), nearly 80% of deaths occurred in hospitalized adults with 3 or more underlying medical conditions. Approximately 70% of adults requiring intubation or ICU admission also had 3 or more conditions. Based on the same data by age group, of hospitalized adults 65 years or older, 80% had 3 or more underlying medical conditions versus 60% of 50-64 year-olds and less than 40% of 18-49 year-olds [https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html].

Although it is known that nearly all adults with COVID-19 associated hospitalizations have at least one underlying medical condition, it is not known whether underlying medical conditions are independently associated with COVID 19-associated hospitalizations among adults aged 18 years or older at the population level. A recent analysis by the COVID-NET Investigation Group combined population-based data from COVID-NET and the Behavioral Risk Factor Surveillance System (BRFSS) to answer this question. COVID-NET includes community-dwelling adults ≥18 years of age who are residents of the catchment area prior to hospitalization, with chart-abstracted data on underlying medical condition. The analysis included about 5000 individuals hospitalized from March 1 to June 23. BFRSS is an annual, cross-sectional survey on health behaviors and self-reported underlying medical conditions among community-dwelling adults or residents of the surveillance area ≥18 years of age in all 50 statues, DC, and 3 US territories. The data were weighted to be representative of population residing in the COVID-NET catchment area. For the statistical analysis, prevalence of underlying medical conditions was calculated among hospitalized adults, COVID-NET catchment area, and nationwide. Unadjusted and adjusted rate ratios and 95% confidence intervals (CIs) for hospitalization were calculated for each medical condition and the models were adjusted for age, sex, and race/ethnicity.

The overall prevalence of underlying medical conditions was greater among COVID-19 hospitalized cases compared to COVID-NET catchment areas and the US. COVID-NET catchment area estimates were similar or slightly lower than nationwide estimates. The magnitude of risk for COVID-19 associated hospitalization was greatest for adults with severe obesity, chronic kidney disease (CKD), and diabetes. Adults with these conditions had 3 to 4 times the risk for hospitalization compared to hospitalized adults without these conditions. Adults with hypertension, obesity, and diabetes had approximately 3 times the risk for hospitalization compared to adults without these conditions. The magnitude of risk for COVID-19 associated hospitalization was greatest for adults aged 65 years or older for all underlying medical conditions. Compared to adults aged 18-44 years, adults 65 and older had 2-4 times the risk of hospitalization. Although of smaller magnitude, adults aged 45-64 years also had an increased risk for hospitalization compared to the younger group. The magnitude of risk for hospitalization increased with the number of underlying medical conditions, with the greatest risk among adults with 3 or more conditions. In the adjusted model, any number of conditions increased risk for hospitalization, but adults with 3 or more conditions had 5 times the risk of hospitalization compared to adults with no conditions.

To summarize this analysis from COVID-NET/BRFSS, accounting for age, race/ethnicity, and sex, higher hospitalization rates were observed for adults with underlying medical conditions in the general population in the COVID-NET catchment area. Adults with 3 or more medical conditions had the highest hospitalization risk. Certain underlying medical conditions were associated with higher risk, including severe obesity and CKD, with almost 4 times the risk compared to adults without these conditions. Diabetes, obesity, and hypertension were associated with approximately 3 times the risk for hospitalization compared to adults without these conditions. Accounting for the presence of an individual underlying medical condition, higher hospitalization rates were observed in adults 65 years or older compared to younger age groups [https://medrxiv.org/cgi/content/short/ 2020.07.27.20161810v1].

Returning to the previously shown COVID-NET multi-variate model for risk of in-hospital death, in addition to age, certain underlying medical conditions were independent risk factors for in-hospital death with each having 1.2 to 1.4 times the risk of death compared to hospitalized adults without these conditions[1]. Now coming back to the large, multi-center US cohort study of adults with COVID-19 associated ICU admission previously showing older age as an independent risk factor, in the same model, certain underlying medical conditions also were independent risk factors for death within 28 days of admission. Even after adjusting for patient- and hospital-level characteristics, the odds of death after ICU admission increased 1.5 to 2.2 times for individuals with severe obesity (BMI >40), coronary artery disease (a cardiovascular condition), and active cancer[2]. Regarding data on the number of underlying medical conditions among COVID-19 deaths reported by supplementary US case-based surveillance data reported to CDC, among a convenience sample of 10,647 COVID-19 deaths that occurred during February 12–April 24 by 16 health jurisdictions, 76% of decedents had at least one underlying medical condition and the majority of decedents of any age had multiple conditions. Overall, the most common underlying medical conditions in all ages were cardiovascular disease (60.9%), diabetes mellitus (39.5%), chronic kidney disease (20.8%), and chronic lung disease (19.2%) [[1]Kim et al, 2020 https://academic.oup.com/cid/advancearticle/doi/10.1093/cid/ciaa1012/5872581; [2]Gupta et al, July 2020 https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2768602]; [3]Wortham et al, 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6928e1.htm].

In addition to COVID-19 surveillance of severe COVID-19 disease, CDC has an ongoing, evidence-informed process to assess the risk for severe COVID-19 disease for individuals with underlying medical conditions. This includes a comprehensive ongoing literature review on underlying conditions, with an internal database to track both published peer-reviewed and pre-print articles and the key findings, collaboration with SMEs across the agency, and monthly updates to the CDC website. The list of underlying conditions is organized in two tiers based on the level of evidence. The conditions that are associated with increased risk are informed by strong evidence defined as “consistent evidence coming from multiple smaller studies or a strong association from a larger study.” Conditions listed in the second tier that might be associated with increased risk are informed by mixed or limited evidence. Mixed evidence is defined as “multiple studies that reached different conclusions,” and limited evidence is considered “that which is from a small number of small reports.” Specific evidence for each condition is on the CDC website.

This is CDC’s list of conditions that are associated with increased risk for severe illness, listed alphabetically:

- ❑ Cancer
- ❑ Chronic kidney disease
- ❑ Chronic obstructive pulmonary disease
- ❑ Immunocompromised state from solid organ transplant
- ❑ Obesity (Body Mass Index of 30 or greater)
- ❑ Serious heart conditions (heart failure, coronary artery disease or cardiomyopathies)
- ❑ Sickle cell disease
- ❑ Type 2 diabetes mellitus

This is a list of conditions that might be associated with increased risk for severe disease. These conditions are also listed alphabetically and include:

- ❑ Asthma (moderate-to-severe)
- ❑ Cerebrovascular disease
- ❑ Hypertension
- ❑ Immunocompromised state from blood or BMT, immune deficiencies, HIV, steroid use, or other immunomodulators
- ❑ Neurologic conditions
- ❑ Liver disease
- ❑ Pregnancy
- ❑ Pulmonary fibrosis
- ❑ Smoking
- ❑ Thalassemia
- ❑ Type 1 diabetes mellitus

Of note, nationally, 41% of adults in the US have at least one underlying medical condition that puts them at higher risk for severe COVID-19 illness. By county, the prevalence varies from almost 1 in 4 to as many as two-thirds of adults having at least one underlying medical condition. In half of US counties, almost 50% of adults are estimated to have an underlying medical condition [Razzaghi et al, 2020].

In summary, as of August 23rd, over 5.6 million cases of COVID-19 were diagnosed and over 176,000 COVID-19-associated deaths reported in the US. Older adults ≥65 have the highest risk of severe COVID-19 disease. Within this age group, risk increases with increased age. Adults with underlying medical conditions also are at increased risk for severe COVID-19 disease. Obesity, diabetes, and CVD are common conditions observed across data sources. Importantly, multi-morbidity increases risk of severe COVID-19 disease. Surveillance and projects are ongoing to continue to monitor COVID-19-associated hospitalizations and deaths and identify persons at higher risk for severe COVID-19 disease.

Discussion Points

Dr. Gluckman asked whether they were noticing a shift in the frequency of use of mechanical ventilation, given that it appears that it may actually increase the risk of mortality. The presentation demonstrated that there is a correlation between the presence of chronic conditions and severe COVID, with a significant increase in older patients. However, it seemed like many of the younger patients had 1 or 2 chronic conditions or none. He asked whether there are any hypotheses as to why some young people may develop serious COVID without co-existing chronic conditions.

Dr. McClung indicated that COVID-NET does not specifically look at an association with ventilation and death, so she did not think those data could be used to comment on that. Regarding the younger patients, it probably has more to do with the fact that the younger population is generally healthier and are less likely to have multi-morbidity as opposed to the older population. It is likely an interplay with a younger, healthier population as a whole.

Dr. Lee asked whether the 41% estimate of the ≥ 1 medical condition included the lists that showed the risk factors that “are” associated versus “might be” associated.

Dr. McClung said she thought those included on the ones that are associated with COVID-19 disease, but they will check on that.

Dr. Messonnier asked whether COVID-NET has data on treatment and whether it is possible to correct for treatment that might also be having an impact on outcome, and whether there are data from other countries that are finding the same things that could corroborate the findings in terms of the trends that were found in the US.

Dr. McClung indicated that a global meta-analysis was recently published on co-morbidities and mortality, and the findings are similar to what is being observed in the US. They can make that paper available.

Dr. Shikha Garg indicated that they do collect data on treatments in COVID-NET for remdesivir, convalescent plasma, and other medications. They have been adapting that as the pandemic has been evolving. They have an “other” field in which they continue to collect new and emerging treatments. They have not yet thought through methods specifically looking at the impact of treatments on outcomes, but that is something they are interested in looking at in the future. They are still collecting data, so they do not have complete treatment data on all cases. They need to think through the biases about who is receiving treatment versus who is not before they perform that analysis.

Dr. Bell asked the extent to which data in COVID-NET can be disaggregated to evaluate regional differences in the outcomes of interest.
Dr. McClung indicated that it is 10 study sites that are geographically spread across the US, representing about 10% of the US population. The BRFSS data were matched to the same communities as the COVID-NET catchment areas.

Dr. Shikha Garg added that there are 4 additional sites, so there are about 99 counties across the 14 states. They have not done specific state-by-state analyses, but potentially could try to group some regions together to perform those types of analyses.

Dr. Bernstein asked what the COVID-NET Hospitalization Surveillance Team’s plans are for pediatric populations under 18 years of age.

Dr. McClung indicated that COVID-NET surveillance does capture all COVID-19 associated hospitalizations and all ages, so those data are publicly available thought she did not present data on children during this session.

Modeling Allocation Strategies for the Initial SARS-CoV-2 Vaccine Supply

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Dr. Slayton presented on a two models that the Data, Analytics, and Modeling Task Force developed, a US Population Stratification Model and a Nursing Home Model that focuses specifically on nursing home-related issues. She first outlined some considerations for mathematical modeling. Mathematical modeling is an iterative process based upon the best available data at the time the models are developed. Models should be updated as new data become available, and sensitivity analyses enable systematic exploration of uncertainties. She described some initial sensitivity analyses in this presentation, and invited ACIP's ideas about additional sensitivity analyses that may be beneficial.

Beginning with the US population stratification model, this model is a stratification model based upon data from the National Health Interview Survey (NHIS) from 2016-2018. Self-reported data are used on age, race/ethnicity, occupation, and medical conditions. The age groups employed in this model were children 0-17, adults 18-64, and adults ≥65 years of age. Race and ethnicity groups included Non-Hispanic White, Non-Hispanic Black, Hispanic, and Other. The sample size included 85,187 adults and 28,221 children 0-17 years of age. A risk status was included within each age group that was a dichotomous variable which represented individuals having no high-risk medical conditions or ≥ 1 high-risk medical conditions. The conditions came from NHIS self-reported data and included obesity, chronic obstructive pulmonary disease (COPD), chronic cancer, weak/failing kidney, chronic heart problem, and chronic diabetes. Additionally, the model looked at occupational groups, with 2 priority groups assessed. The first was healthcare personnel defined as "any individual working in a healthcare setting, whether paid or unpaid." The second priority occupational group included essential workers comprised of food supply, emergency services, utilities, critical financial services, government, and education.

A scenario was modeled that included partial reopening and social distancing measures. This included school contacts being reduced by 70% from baseline and workplace contacts being reduced by 50% from baseline for all individuals except healthcare and essential workers. In this initial analysis, there were 2 sets of vaccine efficacy (VE) assumptions by age group per 2-dose course. These are broad assumptions and are not meant to represent any specific product. The first analysis evaluated a 70% VE for persons 18-64 years of age and a 50% VE for persons ≥65 years of age. The second analysis evaluated an assumption of 70% VE for all adults. The model assumed a prior immunity as stratified by age group (0-17 years 2.8%, 18-64 7.9%, ≥65 years 4.4%) that was derived from seroprevalence surveys in Louisiana from CDC's prior work. Mortality included unadjusted risk ratios by age, race/ethnicity, and risk factors and were adjusted to model strata using raking methods.

The model considered the incremental and relative impact of vaccination courses and looked at contact rates among the 72 strata of the model based on age and location-specific contact rates in homes, schools, workplaces, and other. A deterministic compartmental model framework was employed and assessed the estimated incremental impact, which included both direct and indirect benefits. The model assessed the impact on population-wide incidence and derived the estimates from the rates of most probable transmission among groups before and after vaccination.

For the first analysis in which VE was assumed to be 70% among adults 18 to 64 years of age and 50% among adults ≥65 years of age, the population-wide decrease in rate of COVID-19 infections and COVID-19 deaths per 10 million vaccine courses are shown in this table:

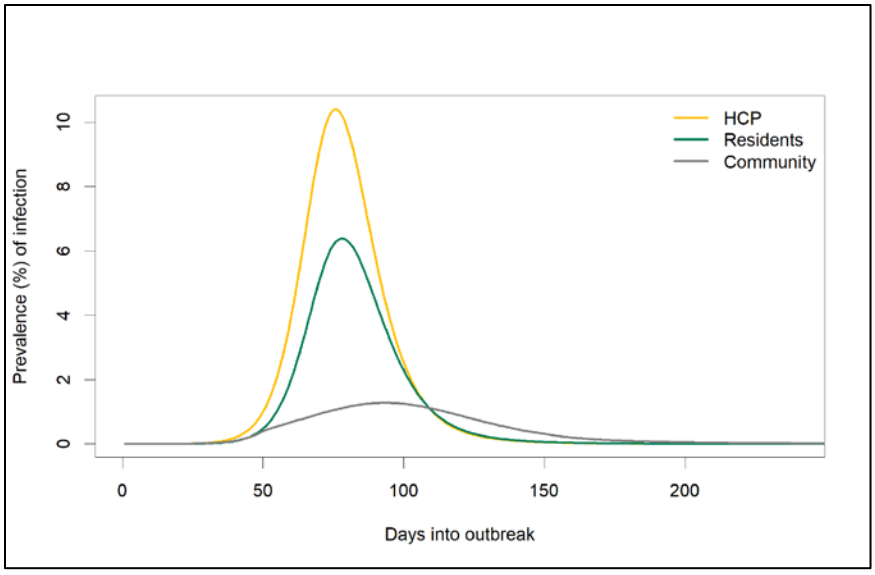
Population-Wide Decrease in Rate Per 10 Million Courses

Group Vaccinated	COVID-19 Infections	COVID-19 Deaths
Healthcare Personnel	3.5%	3.3%
Essential Workers	3.1%	3.1%
With Underlying Conditions	3.8%	4.3%
Persons ≥65 Years Old	0.7%	6.1%

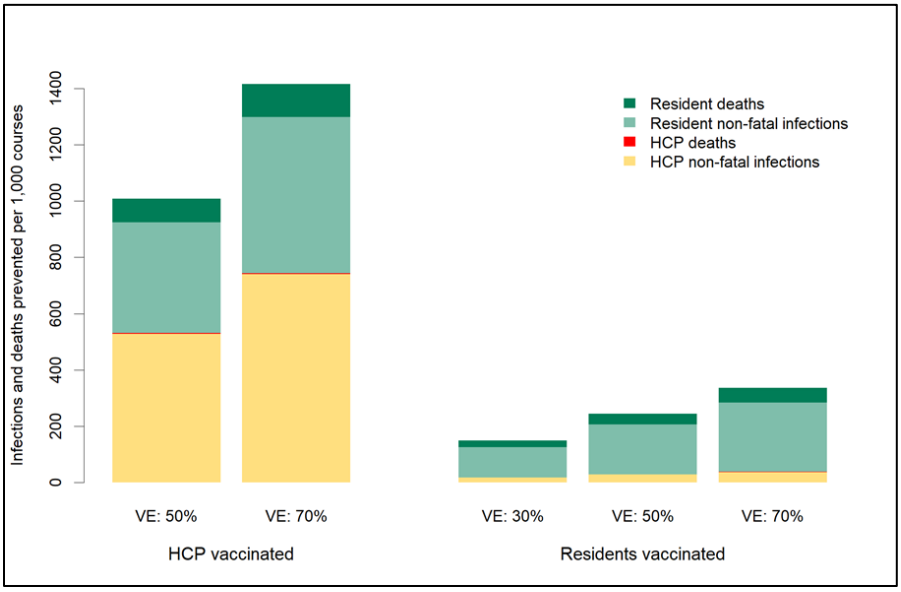
Vaccinating HCP, essential workers, and individuals with underlying conditions resulted in reductions in both infections and deaths. Vaccinating individuals ≥65 years of age resulted in smaller decreases in COVID-19 infections and larger increases in COVID-19 associated deaths. The second analysis assessed VE of 70% for all adults and found similar patterns.

The nursing home-specific model was parametrized to represent a mean nursing home set of characteristics from an analysis of CMS data. This nursing home was comprised of 87 residents with a mean length of stay of 88 days and 41 HCP who were assumed to work daily in 8-hour shifts. The model assumed that HCP interacted at work with other HCP, and at home and in non-school settings with others in the community. HCP were assumed to self-isolate on symptom onset. Prevalence of infection among admitted nursing home residents was assumed to follow the community prevalence. The first vaccine dose in these analyses was assumed to be given before the introduction of infection into a nursing home. The product assumptions for these analyses included 2 doses of vaccine given 28 days apart, with protection developing 14 days post-injection. The model evaluated VE variables of 70%, 50%, and 30% among persons ≥65 years of age. It was assumed that vaccination does not attenuate severity or transmissibility of breakthrough infections. The model assumed no waning of immunity over the analysis time horizon.

This figure represents a SARS-CoV-2 transmission among nursing home residents and healthcare staff without vaccination:



When evaluating vaccines with variable VEs and grouped by vaccinating either HCP or residents, the model estimated that vaccinating nursing home healthcare providers resulted in greater reductions in both infections and deaths than vaccinating nursing home residents. This is even when assuming that residents are at a higher risk of severe disease and death due to their older age and presence of underlying medical conditions. This is depicted in the following figure:



In summary, from the two models just presented, vaccinating HCP, essential workers, or adults with underlying conditions resulted in reductions of COVID-19 infections and deaths and vaccinating adults ≥65 years old resulted in more modest declines in infections and larger declines in deaths. Vaccinating nursing home HCP resulted in greater reductions in both infections and deaths than vaccinating nursing home residents.

Open Discussion

Dr. Hunter asked whether each additional 10 million doses of people vaccinated according to this modeling would reduce infections and deaths another 3% to 4% in a linear fashion, or if there was any reason to suspect that there would be increasing benefits or diminishing returns from vaccinating each additional 10 million people.

Dr. Slayton replied that in the initial analyses, they were considering the first allocation of vaccines that would become available, which followed more or less linear patterns. As additional doses are assumed to be part of the scenario, there may be deviation from the linear trends and additional analyses would need to be conducted with better defined parameters on expected VE and seropositivity among vaccinated and unvaccinated individuals to better discern those trends.

Dr. Hunter observed that she was providing information about the initial vaccination, but the other steps and phases might need additional information to guide those.

Dr. Messonnier observed that the model was looking at this as the unit of action being an individual getting vaccinated, but it did not model for example if vaccination of HCP prevented COVID-19 from entering a facility and therefore would have additional benefits beyond the people who were vaccinated. If the person who introduced it into the nursing home could be prevented from getting sick, then there would be an indirect benefit for everybody else.

Dr. Slayton indicated that the initial analyses of nursing homes was based upon the assumption that there had not been a prior importation into that nursing home. Dr. Messonnier was exactly right that protecting nursing home residents from those importations, which the model and epidemiologic data suggest are primarily coming in through their HCP, is important and further modeling could be done to discern some of the value Dr. Messonnier described.

Dr. Romero added that while HCW are important sources of introduction of COVID-19 into the nursing home environment, visitation is also an important route and is an added variable to this calculation. Even protecting nursing home residents by protecting the HCP will still leave a window open for those who enter from the public.

Dr. Atmar asked whether the incremental benefit of vaccinating both HCP and nursing home residents was modeled.

Dr. Slayton indicated that it is a linear model, so it would be additive for the VE values assumed for residents and HCP, respectively.

Dr. Atmar asked whether any sensitivity analyses were done in the first model in terms of what the effect would be if there was a higher seroprevalence in the community.

Dr. Slayton replied that they have evaluated some different assumptions about both the level of mitigation and the prior seropositivity. As would be expected, both of these parameters are influential in the absolute magnitude of some of the results. This iteration of the models did not include any kind of screening of individuals prior to receiving a vaccine to better represent the understanding of the current trials and strategies being considered, but those are added features that could be further explored in this iterative process. Over the parameter space that

the current data suggest, the relative reductions were relatively stable the longer the timeline for vaccines to become available and the more that the model deviates from the initial assumptions of prior seropositivity, the level of mitigation, and the contact structure employed in the model, the more that would be expected to deviate.

Dr. Szilagyi wondered if they could combine the two analyses to estimate what the population-wide impact would be on death, for example, for a nursing home vaccination program. In Los Angeles for example, 40% to 50% of all deaths were from individuals in LTCF.

Dr. Slayton indicated that the nursing home model did not include visitors from the community. Older adults in the best available data used to develop these models have a lower number of contacts than younger adults, nursing home residents in particular tend to stay in the nursing home, and the distribution of length of stay is bimodal with short-stay and long stay-nursing home residents. The impact on the broader community of vaccinating the residents would be expected to be really small. The impact of vaccinating the HCP who may work across multiple nursing homes and tend to be younger adults with higher numbers of contacts in the facilities and the communities would be somewhat larger.

In terms of the data on Slide 10 about the very large percentage of hospitalizations and ICU deaths among individuals with underlying conditions, Dr. Szilagyi said he was surprised that percentages by decreasing rate for 10 million courses was so low in vaccinating individuals with underlying conditions with a relatively high VE of 70%.

Dr. Slayton indicated that the population-wide decrease in deaths of vaccinating individuals with underlying conditions is somewhat larger because those are more of the direct effects from vaccinating that age group. The infections, which also include some of the indirect effects to a greater degree because of the age distribution of individuals with underlying conditions modeled, and the assumptions about the numbers of contacts those individuals have with other people, are more similar to the age structure and therefore the reductions in infections of vaccinating HCP and essential workers.

Dr. Frey wondered whether there are plans to consider a lower VE of 50% or 60%. It is not clear that people have completely decided what might be an acceptable VE. While they would like to see 70% or 80%, it may not be that high.

Dr. Slayton replied that they have run this analysis with VE values at 30% and 50%, but did not show all of those combinations in the interest of time. The general trends hold true looking at the differences across the first 3 groups vaccinated compared to the third, though the absolute values change as would be expected.

Dr. Maldonado (AAP) asked whether the indirect effect assumptions varied by population and how the decision was made about how to vary indirect effect size in the different populations.

Dr. Slayton indicated that the indirect effects were all coming in from the assumptions made about the contact structure. They are using age-stratified contact rates, which is a common set of assumptions that mechanistic modelers use. Additionally, because they were evaluating the occupational groups of interest, they added an assumption that workplace contacts would be reduced by 50% from baseline for individuals in all occupations except healthcare and essential

workers. Workplace contacts are one of four groups of contacts included in the model. The others were home, school, and other settings.

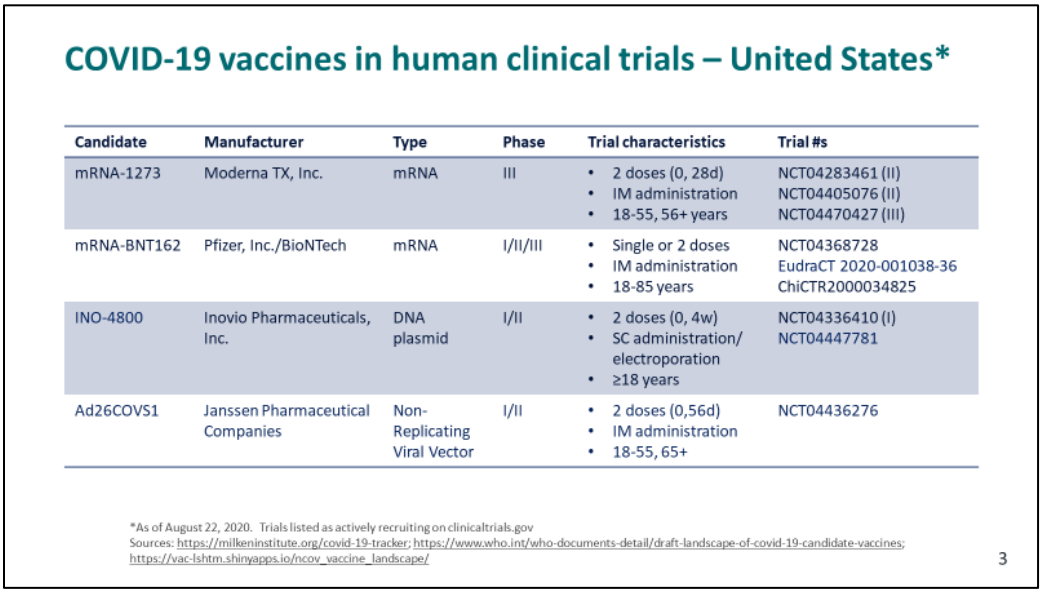
In terms of the assumption that HCP isolate as soon as they become symptomatic, Dr. Drees (SHEA) pointed out that their experience and the experience of many others is that HCP continue to work for at least a few days and sometimes longer, with the early symptoms of COVID—often because those symptoms are subtle and are not recognized as COVID until later. She assumed that this would accentuate the value of vaccinating HCP, so she wondered if there was a plan to incorporate that variable into a sensitivity or other analysis.

Dr. Slayton replied that the initial model includes HCP going to work while infectious if they are pre-symptomatic or if they are asymptomatic. The current sets of pandemic planning scenarios on the CDC website, the asymptomatic group is about 40% of the population, so there are HCP working for some period of time during their pre-symptomatic phase and a substantial minority of infections that are asymptomatic for the duration. The assumptions can be modified to show the impact that would likely occur if HCP providers worked for a longer time while infectious.

COVID-19 Vaccines: Work Group Interpretations

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

Dr. Oliver first provided a brief overview of COVID-19 vaccines in human clinical trials. This is a list of clinical trials that are actively recruiting in the US:



COVID-19 vaccines in human clinical trials – United States*

Candidate	Manufacturer	Type	Phase	Trial characteristics	Trial #s
mRNA-1273	Moderna TX, Inc.	mRNA	III	• 2 doses (0, 28d) • IM administration • 18-55, 56+ years	NCT04283461 (II) NCT04405076 (II) NCT04470427 (III)
mRNA-BNT162	Pfizer, Inc./BioNTech	mRNA	I/II/III	• Single or 2 doses • IM administration • 18-85 years	NCT04368728 EudraCT 2020-001038-36 ChiCTR2000034825
INO-4800	Inovio Pharmaceuticals, Inc.	DNA plasmid	I/II	• 2 doses (0, 4w) • SC administration/ electroporation • ≥18 years	NCT04336410 (I) NCT04447781
Ad26COVS1	Janssen Pharmaceutical Companies	Non-Replicating Viral Vector	I/II	• 2 doses (0,56d) • IM administration • 18-55, 65+	NCT04436276

*As of August 22, 2020. Trials listed as actively recruiting on clinicaltrials.gov
Sources: https://milkeninstitute.org/covid-19-tracker; https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines; https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/

3

They heard from Moderna and Pfizer earlier in the day, both of which are actively recruiting for phase 3 clinical trials. Dr. Oliver also shared lists of mRNA and DNA vaccines, protein subunit, viral vector, and inactivated vaccines that are actively recruiting globally. Novavax recently published Phase 1 data from Australia, with plans to begin Phase 2 studies in the US and Australia soon. The University of Oxford/Astra Zeneca vaccine has begun Phase 3 trials outside

of the US and plans to begin Phase 3 trials in the US soon. Several Phase 3 trials of inactivated vaccines are currently being conducted in China.

Information was reviewed by the WG, including both Phase 1 immunogenicity and safety data from the two mRNA vaccines and plans for Phase 3 studies for both mRNA vaccines. In terms of the immunogenicity data reviewed by the WG for the Moderna mRNA-1273 vaccine, neutralizing and binding antibodies were measured 7 days post-Dose 2. Responses were similar to or exceeded a convalescent sera comparison. A Th1-biased CD4+ T-cell response was noted. Based on the Phase 1 data, a dose of 100µg was selected for the Phase 3 clinical trials. Regarding safety data, local and systemic symptoms were followed for 7 days post-vaccination. Pain, myalgia, and fatigue were the most common symptoms reported. Reactogenicity symptoms were higher after the second dose. No vaccine-related SAEs were reported.

Regarding the immunogenicity data for the Pfizer/BioNTech BNT162b2 vaccine, neutralizing and binding antibodies were measured 7 days post-dose 2. Again, the responses were similar to or exceeded the human convalescent panel. CD4 and CD8 T-cell responses were demonstrated, and a Th1-biased CD4+ T-cell response was found. A 30µg dose of the BNT162b2 was selected for Phase 3 clinical trials. Regarding the safety data, local and systemic symptoms were followed after administration for 7 days post-vaccination. Fatigue, headache, and muscle pain were the most common symptoms reported. Reactogenicity symptoms were lower in the older population.

Both companies reported their plans for Phase 3 clinical trials. Both are currently enrolling large Phase 3 efficacy trials, with goals of enrolling around 30,000 individuals. The primary efficacy endpoints for both trials are symptomatic, virologically-confirmed COVID-19 disease. Both vaccines are attempting to enroll diverse populations, which includes racial and ethnic diversity, age and underlying medical conditions. Both vaccine companies discussed the current cold chain requirements for their vaccine candidates. mRNA1273 requires distribution and storage at -20ºC, with around 7 days at 2º to 8º C. BNT162b2 requires distribution and storage at -70º C, with around 24 hours at 2º to 8º C. These requirements could be updated as additional studies are completed.

Overall, the WG thought the Phase 1 data from both mRNA vaccines showed induction of neutralizing antibodies at 7 days post-Dose 2 that exceed levels in convalescent sera. Data from both mRNA vaccines support advancing to large scale Phase 3 clinical trials to assess safety and efficacy. The WG felt that the diverse cold-chain or ultra-low temperature requirements could substantially affect implementation efforts.

The WG had several thoughts regarding the current Phase 3 clinical trials. First, they emphasized the importance of enrolling diverse study participants. The also emphasized the need to allow for sufficient time post-Dose 2 to evaluate safety signals in addition to the efficacy signals. There is a need to report maternal and fetal outcomes for women who become pregnant during the clinical trials. It would be helpful to evaluate the impact on viral shedding or transmission among symptomatic and asymptomatic populations. The WG also had thoughts regarding future or additional studies, including the need to evaluate co-administration of other vaccines, especially influenza vaccines, as well as the need for studies in pregnant women and children if the initial trials are successful.

Moving to the WG interpretation of the epidemiology data, the WG reviewed COVID-19 epidemiology among the US population, various occupational settings, and individuals at increased risk of severe COVID-19 disease. Dr. Oliver highlighted a few of the important epidemiology points that influenced the WG discussion. As a reminder, healthcare personnel are defined very broadly, "Healthcare Personnel (HCP) are essential workers defined as paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials."

Hospitalized HCP within COVID-NET (N=512) demonstrate the broad ranges of occupations for infected HCP, including Respiratory Therapists: 3 (<1%), Physicians: 23 (5%), Nurses: 125 (24%), Other: 276 (54%), and Not Specified: 85 (17%). Types of HCP included in the "Other" category are identified in this table:

Hospital-based patient care support (e.g., nursing assistant)	73
Other patient care	21
Housekeeping/Environmental Services	20
Other nursing home/LTCF staff	17
Technicians	15
Management	12
Home health worker	12
Emergency medical personnel	10
Social work/counselor	10
Pharmacy	9
Food Services	8
Dentistry	6
Laboratory	6
Other	57

The LTCF workforce is comprised of disproportionately lower-wage workers. Nearly 40% are 50 years of age or older, nearly 80% are female, and 26% are non-Hispanic Black persons. Staff can be shared among multiple facilities. In many instances, COVID-19 activity increases among LTCF staff first, and then residents.

Among 14 states reporting total number of workers in affected meat and poultry processing plants from April–May 2020, COVID-19 diagnosed in 9.1% of workers. Among cases with race and ethnicity reported, nearly 90% occurred among racial or ethnic minorities. Outbreaks have been reported in many food production and agriculture sectors. There are multiple factors that increase workers' risk for exposure to SARS-CoV-2, including prolonged close workplace contact with coworkers, shared transportation and/or congregate housing, and lack of paid sick leave.

In addition, the WG reviewed data on workers in correction and detention facilities. Correction and detention staff members can introduce the virus through their daily movements between the facility and the community. In an analysis of 16 US prisons and jails, more than half of the facilities identified their first case of COVID-19 among staff members [Hagan et al. MMWR – August 21, 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6933a3.htm s_cid =mm6933a3_w].

Finally, the WG reviewed data on adults with increased risk for severe COVID-19 disease that was presented earlier in the day. Accounting for presence of individual underlying medical conditions, higher hospitalization rates were observed among adults ≥65 years of age. In addition, higher hospitalization rates were observed for adults with underlying medical conditions, with obesity, chronic kidney disease, diabetes, and hypertension having some of the strongest associations [https://medrxiv.org/cgi/content/short/2020.07.27.20161810v1].

The WG also heard presentations on modeling allocation strategies for the initial vaccine supply that were just shown to ACIP. Two different models were shown, the overall population model and a nursing home model. Regarding the population model, similar numbers of infections were prevented by vaccinating HCP, essential workers, and adults with underlying medical conditions. Vaccinating older adults resulted in more modest declines in infections and larger declines in deaths compared to other groups. Overall, the differences in impact between vaccinating different groups was small. For the nursing home model, more infections and deaths were prevented by vaccinating HCP compared to vaccinating nursing home residents. Overall, the more infection prevented now through mitigation measures, the more impact the vaccine will have.

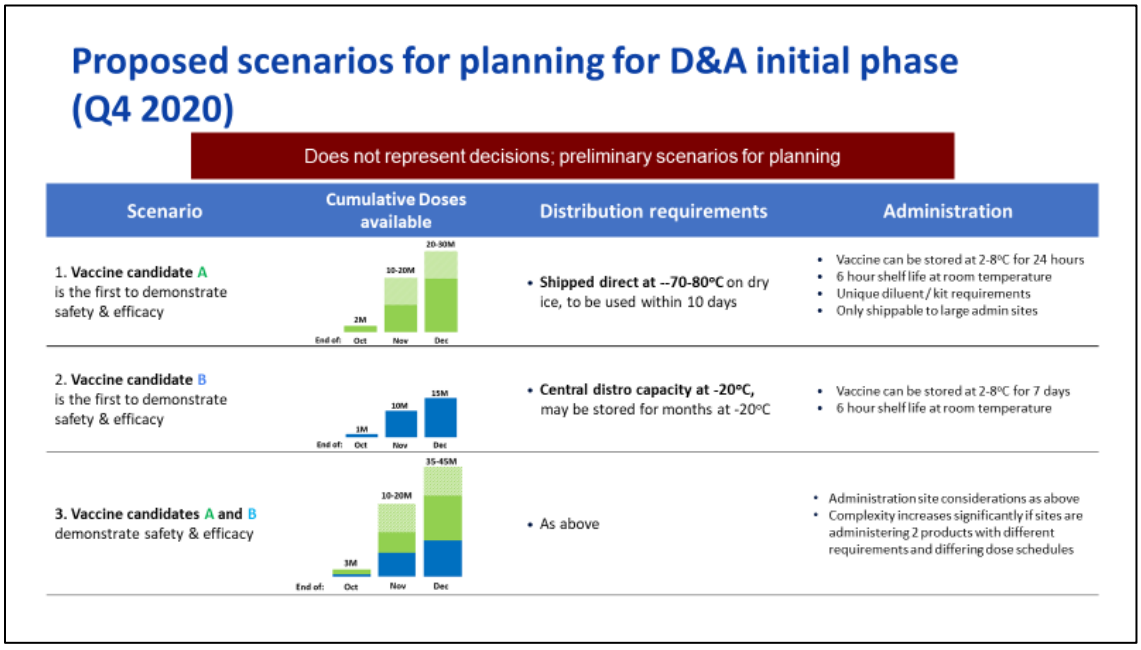
Taking into account the epidemiology and modeling data that have been presented over the past several months, the WG discussed several important points. Many occupations deemed “essential workers” are at increased risk of COVID-19 disease. The WG felt that it is important to consider these individuals who are unable to socially distance or work from home. Older adults and adults with underlying medical conditions are also at increased risk of COVID-19 disease. The WG noted that these groups are not mutually exclusive. Many essential workers are also older or have underlying medical conditions, also putting them at risk for severe COVID-19 disease. In many instances, cases increase first among staff in congregate settings such as LTCF or correctional facilities. The WG feels that it is possible that some protection could be provided to these vulnerable populations by immunity among the staff and workers. Dr. Oliver transitioned to Dr. Dooling to discuss how the data and WG thoughts could inform further discussions around allocation and distribution of the early vaccine doses.

Dr. Dooling first grounded the presentation in what the WG envisions as the overall goals of the COVID-19 Vaccine Program, which are: 1) to ensure the safety and effectiveness of COVID-19 vaccines; 2) that the vaccine reduces transmission, morbidity, and mortality of COVID-19 disease; 3) that the vaccine program helps minimize disruption to society and economy, including maintaining healthcare capacity; and 4) to ensure equity in vaccine allocation and distribution.

It is clear that identifying groups for allocation of initial doses of vaccine is critical for program planning at this juncture. Dr. Dooling took a moment to call out all of the areas of the vaccine system that will use this information. For example, distribution networks can be strengthened to reach target groups and engage key partners and stakeholders in order to accomplish that. State and local microplans need to be developed for vaccine implementation. Communications strategies need to be created to promote vaccination in target groups. Importantly, systems need to be enhanced to rapidly monitor vaccine safety, effectiveness, and coverage.

It is likely that administration of COVID-19 vaccine will require a phased approach. Once a vaccine is approved for use, there likely will be insufficient vaccine to meet demand at first. There also may be cold chain, storage, and handling requirements that require specialized equipment and high throughput at clinics. Taken together, these call for highly targeted administration in the first phase. In the second and third phases, it is anticipated that there will be sufficient supply and a broadening of the implementation strategies.

During this session, Dr. Dooling focused the ACIP members' attention on the first phase. The period during which doses are limited is projected to be short. There may be limited doses and administration may be targeted. Consideration must be given to how to best achieve the objectives of the program during this period. To help the WG think about this period, here are some proposed scenarios for planning in the initial phase:



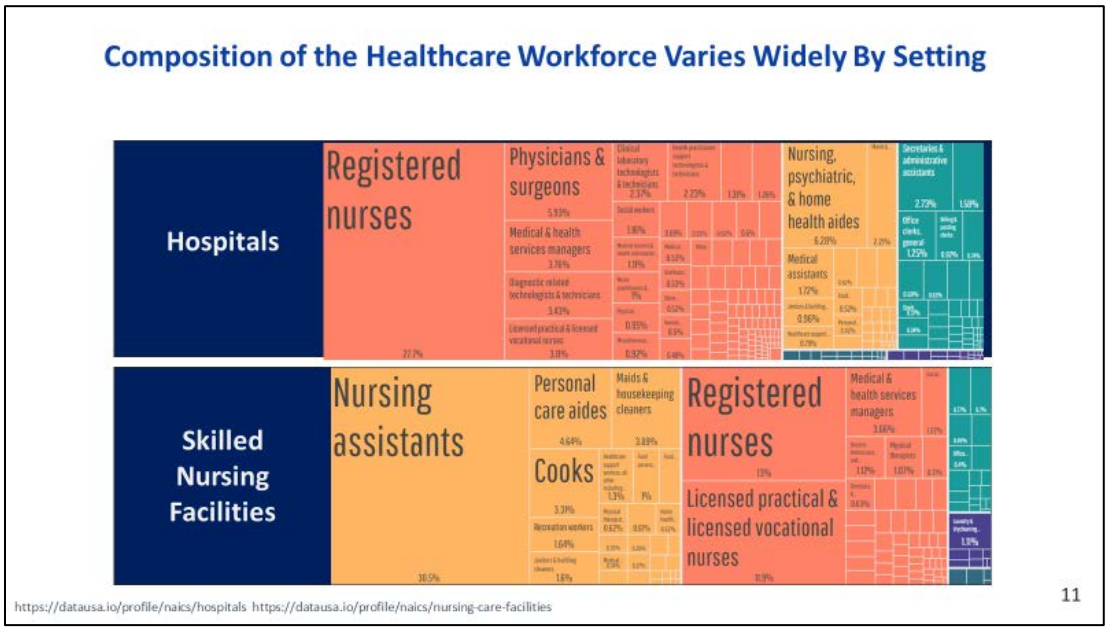
It is important to note that these do not represent decisions, but are instead a tool to assist planning. In the first scenario, Vaccine A demonstrates safety and efficacy and there could be 20 to 30 million doses available by the end of December. If such a product needed to be shipped at -70° to -80°C and could be stored for only 24 hours at standard refrigeration temperatures of -2° to -8°C, this scenario would require shipping to large, adequately equipped administration sites with high throughput. In the second scenario, Vaccine B demonstrates safety and efficacy and there could be 15 million doses available by the end of December. This vaccine could be distributed at -20°C and stored for 7 days at -2° to -8°C. In the third scenario, both Vaccines A and B demonstrate safety and efficacy and doses would ramp up with potentially 35 to 45 million doses available by the end of December 2020.

Clearly, the planning needs are immense. CDC, states, and local jurisdictions all over the country are actively working on plans. Although the implementation details were not the focus of this meeting, some of the CDC activities to support implementation planning include microplanning, critical population focus, federal entity planning, development of information technology (IT) tools, and communications and engagement materials.

Departing from implementation planning, Dr. Dooling recapped previous ACIP discussions regarding early phase COVID-19 vaccination. In June, ACIP expressed support for identification of groups for allocation of initial vaccine to aid implementation planning. ACIP recognized the disparity in COVID-19 impact on minority race and ethnic groups, essential workers, and low-income families. Also, attention was called to the need to build on existing vaccine infrastructure to meet the challenges of the COVID-19 vaccination. In July, ACIP expressed support for HCP and other essential workers to receive initial vaccine allocation.

The objective for the ACIP discussion during this session was to focus on the WG's proposed groups for early phase vaccination. Those include HCP, essential workers, persons with high-risk medical conditions, and older adults ≥65 years of age. For each, Dr. Dooling described the group, estimated size of the group, and implementation challenges. The WG wanted to hear ACIP consideration for the sequences of the group. During the September 2020 ACIP meeting, a possible vote on interim allocation of initial vaccine doses is planned.
HCP were discussed extensively during the last ACIP meeting. HCP are defined as all paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials. This includes persons not directly involved in patient care, but potentially exposed to infectious agents while working in a healthcare setting. The estimated population for this group is approximately 17 to 20 million people in the US. This estimate comes from the Bureau of Labor Statistics (BLS). Although not exhaustive, some examples include: Hospitals, LTCF (including assisted living facilities and skilled nursing facilities), Outpatient, Home Health Care, Pharmacies, Emergency Medical Service (EMS), and Public Health.

Also shown during the July ACIP meeting, the composition of the healthcare workforce varies widely by setting as shown here in the comparison between hospitals and skilled nursing facilities:



Next are essential workers other than HCP. CISA, within the DoD, is tasked with creating a list of workers who are essential to continue critical infrastructure and maintain the services and functions Americans depend on daily. CISA has recently revised their list in the context of evolving demands of the workplace during COVID-19. The guidance acknowledges that workers who cannot perform their duties remotely and must work in close proximity to others should be prioritized for mitigation measures. It is also important to recognize that sub-categories of essential workers may be prioritized differently in different jurisdictions depending on local needs. The estimated population for this group is approximately 60 to 80 million people, but it should be noted that this is a very rough estimate and may be revised as workplaces evolve and innovative ways are found to protect workers. Although not exhaustive, some examples include workers in the following industries: Food & Agriculture, Transportation, Education, Energy, Water and Wastewater, and Law Enforcement.

It is worth noting that HCP and essential worker composition by race and ethnicity is similar to the overall US population according to self-reported data from the NHIS[1]. Despite representation of Black and Hispanic essential workers that is similar to the overall population, a recent study from Utah demonstrated that Hispanic and non-White workers accounted for 73% of workplace outbreak-associated COVID-19 cases. In every industry, Hispanic and non-White workers have been disproportionately affected by workplace outbreaks[2] [[1]NHIS details: data from 2016, 2017, and 2018; Analysis: Modeling Section, COVID-19 Response, CDC; [2]Bui DP, McCaffrey K, Friedrichs M, et al. Racial and Ethnic Disparities Among COVID-19 Cases in Workplace Outbreaks by Industry Sector — Utah, March 6–June 5, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1133–1138. DOI: http://dx.doi.org/10.15585/mmwr.mm6933e3].

Next are adults with medical conditions at higher risk for severe COVID-19. Earlier in the day, details were presented of the epidemiologic risks associated with these conditions. A systematic review indicates that people of any age with the following conditions, listed alphabetically, are at increased risk for severe illness from COVID-19:

- ❑ Cancer
- ❑ Chronic kidney disease
- ❑ Chronic obstructive pulmonary disease (COPD)
- ❑ Immunocompromised state from solid organ transplant
- ❑ Obesity (BMI of 30 or greater)
- ❑ Serious heart conditions (heart failure, coronary artery disease or cardiomyopathies)
- ❑ Sickle cell disease
- ❑ Type 2 diabetes mellitus

The estimated population for this group is over 100 million adults. This is a rough estimate that may change as evidence is gained about the conditions that confer risk. For the nationally representative survey, BRFSS, a percentage of the adult population with selected medical conditions was estimated at 31% with obesity, 11% with diabetes, 7% with COPD, 7% with a heart condition, and 3% with CKD. These are not mutually exclusive.

The final group is adults ≥65 years of age. This overall group is estimated to be about 53 million by 2019 US Census estimates. Broken down by age, the estimates are 6 million ≥85 years of age, 6 million 80-84 years of age, 9 million 75-79 years of age, 14 million 70-74 years of age, and 17 million 65-69 years of age. This accounts for approximately 16% of the US population. Of note, approximately 3 million persons currently live in LTCF. The proportion of the population

with COVID-19 high-risk medical conditions is 33% among younger and 39% among older adults according to self-report data from the NHIS [NHIS data from 2016, 2017, and 2018; Analysis: Modeling Section, COVID-19 Response, CDC].

To summarize, these groups are clearly overlapping. There is significant heterogeneity between and within these groups, and this accounts for more than half of US adults. Therefore, there may be a need for additional subgrouping.

Dr. Dooling transitioned to WG considerations in terms of specific thoughts on epidemiology, feasibility of implementation, and equity and ethics. The WG has considered feasibility, including the implementation challenges and implication for distribution of initial vaccine. The following points summarize their input. A COVID-19 vaccine that requires distribution and storage at -20ºC, followed by 7 days maximum at 2º to 8ºC, will require diligent vaccine management to minimize waste. The storage, distribution, and handling requirements of a -70ºC vaccine will make it very difficult for community clinics and local pharmacies to store and administer such a vaccine. Ultimately, this will necessitate that most vaccine be administered at centralized sites with adequate equipment and high throughput. Vaccinating HCP at centralized sites with high throughput is the best allocation of initial supply.

Workers at LTCFs remain a priority among HCP and achieving high coverage is important and may be resource-intensive. Mass vaccination clinics will be difficult to conduct in the setting of social distancing. Healthcare homes, such as provider offices or pharmacies, could be better suited to provide vaccination if recommendations are based on individual risk factors such as age or underlying medical conditions. The WG also noted challenges to equitable vaccine administration. These include, but are certainly not limited to, reaching people in rural areas, reaching racial and ethnic minorities, and reaching populations with limited access to vaccines.

Clearly, as groups are considered for interim prioritization of initial vaccine supply, there are many unknowns. Vaccine performance is not yet known in terms of the magnitude of benefits, potential risks, or efficacy in older adults. It is not yet known whether there will be multiple vaccines with differing profiles. The pathway to approval also remains unknown in terms of whether it will be an EUA or full licensure. The timing of vaccine availability, number of doses available, and rate of scale-up are unknown as well. Although they are working with unknowns and incomplete information, the WG remains committed to moving forward to help ACIP lay the groundwork for evidence-informed COVID-19 vaccine policy.

The next steps for the COVID-19 Vaccine WG are to review: 1) clinical trial data for candidate vaccines as they become available and which primarily will be the safety data, including plans for post-approval safety surveillance, and the immunogenicity and efficacy data; 2) epidemiologic data for risk of COVID-19 disease and severity by race/ethnicity, which will be presented during the next ACIP meeting; 3) results of focus groups and other public engagement regarding COVID-19 vaccines; and 4) equity frameworks for allocating vaccine.

In that vein, authors at the Johns Hopkins Bloomberg School of Public Health (JHSPH) recently released an Interim Framework for COVID-19 Vaccine Allocation and Distribution in the United States. Tier 1 within that framework includes the following populations:

Tier 1:

- Those most essential in sustaining the ongoing COVID-19 response
- Those at greatest risk of severe illness and death, and their caregivers
- Those most essential to maintaining core societal functions

The WG will be considering this framework as well as that which is forthcoming from the National Academy of Sciences, Engineering, and Medicine (NASEM).

In closing, Dr. Dooling posed the following questions for ACIP consideration and deliberation and invited their feedback:

1. Given the information presented thus far (epidemiology, values, acceptability, feasibility) do you agree that initial doses of COVID-19 vaccine should be allocated to healthcare personnel?

2. If supply remains constrained, due to vaccine or distribution limitations, do you agree with vaccinating essential workers next as supply permits?

Open Discussion

Given the information presented thus far (epidemiology, values, acceptability, feasibility) do you agree that initial doses of COVID-19 vaccine should be allocated to healthcare personnel?

Dr. Atmar asked whether the WG has considered regional distribution of vaccine based on or guided by local prevalence of disease.

Dr. Dooling indicated that the WG has considered that to some extent and also has discussed vaccine allocation in an outbreak setting. Some of the factors that were discussed included the fact that all of the early vaccine candidates in development are 2 doses. Thus, the amount of protection that is conferred several weeks following the second dose administration is unknown. The timing may not be adequate to combat active outbreaks. There are still unknowns with regard to the underlying seroprevalence of any jurisdiction at the time, and ultimately how long-lasting that protection is. Those are just some of the factors that have been identified in that context in terms of allocations.

Dr. Atmar expressed concern that his answer to the question and the answer of many others may seem self-serving since they are all HCP. It is hard based on the risk stratification presented to pick one group over another. It sounds like a guiding principle may be the implementation. He agreed that the healthcare industry is probably in a better position to handle and distribute the vaccine to HCP in the circumstances outlined should it be one of the candidate vaccines that has the difficult cold chain issues to address.

Dr. Cohn added that in terms of the number of doses that may be available in the very early constrained period, they would propose halving the number of individuals who should be vaccinated because of the short timeline between Doses 1 and 2 being 21 and 28 days. They want to make sure that individuals receive both doses and that they do not vaccinate more broadly and then not have doses made available the following month, for example, to provide

people second doses in those windows. There are some considerations around the total number of individuals who may be vaccinated over time as well.

Dr. Szilagyi agreed with the dilemma of feeling somewhat self-serving because they are HCP. In terms of implementation issues in addition to the cold chain matter, he was struggling with not knowing how many doses there actually will be. He emphasized that he understood Dr. Cohn's comment about the two doses. If there will be only 20 million doses, it is not clear how they will allocate vaccine within the other groups that are much larger at 100 million, 50 million, 68 million. He also thinks there is a challenge with confidence in this vaccine for a number of reasons they have all discussed. Of even greater concern is that there is now some evidence that very high-risk populations, including some minority populations, may have more concerns about the future vaccine than other populations. Although he has been hearing anecdotes about concerns about the vaccine, his sense is that the uptake among HCP would be much higher. It could start a nice process toward increasing confidence in the vaccine if HCP get the vaccines themselves, and if the proportion of HCP who are vaccinated is very high. Particularly when there is an issue of concern about confidence in a vaccine, HCP getting it themselves is a very good demonstration for the rest of the country. In terms of the number of doses there might be, perhaps consideration needs to be given to prioritizing within these conditions if there are fewer doses.

Dr. Romero noted that his comments echoed those stated already, but that the issue that stands out most in his mind is that of the requirements for ultra-cold storage and transmission of the vaccine. In a state like his, which is primarily rural, this poses a significant problem. Without a doubt, it means that they will have to focus on HCP initially. Other populations like their high-risk essential workers, such as meat packers and agricultural workers, may have to wait until there is a more stable vaccine that can be transported and delivered more or less at room temperature. He sees this as a major issue, but one that may be out of their control depending upon the vaccines that are available. He also thinks there should be some degree of flexibility in determining these risk groups based on the limited supply within each state. His state's risk group assessment may differ somewhat from that of the WG or the ACIP. In terms of laboratory personnel in commercial laboratories who are carrying forward the diagnostics of COVID, public health officials suffer greatly when they cannot have rapid turnaround of diagnostic tests either because of supply or because of insufficient personnel to process tests. If his public health laboratory suffered a significant hit from COVID, it would be a major blow to their efforts at COVID detection, containment, and mitigation within the state. He stressed the importance of including hospital, public health, and commercial laboratories. He also championed the cause of public health personnel, who are essential to his state in controlling mitigation of outbreaks. They send these individuals out into the community to find and test individuals and make recommendations. Unfortunately, he has had several of his public health employees become infected.

Dr. Cohn clarified that Dr. Romero was speaking in his new role as the State Health Officer for the State of Arkansas. He is now officially a member of the public health community.

Ms. Bahta observed that it seemed clear in some of the modeling that there is a benefit both to the health care community and the population who they care for, especially in LTCF by vaccinating those HCP. As she has thought about this and reviewed the JHSPH document, it seemed that they need to be able to continue to provide care to the broader population who will require hospitalizations without having a huge compromise of the healthcare population. In

Minnesota, many of their LTCF HCP were ill with COVID-19 in the spring. A lot of it was because of a lack of personal protective equipment (PPE), which seems to be a persistent issue. In that respect, she supported an allocation to HCP.

Dr. Lee stressed that the WG discussions have been highly challenging for many reasons. She agreed that the distinction between where they want to be in 6 to 9 months versus where they are now is very important, in part because benefit-risk balance is going to be critical to all of the decision-making. In the first weeks of vaccines being available, implementation considerations are going to be huge. She agreed that given the current vaccine candidates they hope may come forward soon, it would make sense for them to make sure that they are reducing the complexity of implementation as much as is feasible. The more complex they make it up front, the harder it is going to be to then scale up quickly. She is supportive of the idea of prioritizing populations where the vaccine can actually be implemented. She wondered whether anyone could comment on other potential vaccine candidates that were mentioned early on. Specifically, she was interested in what the timing might of the 2 that were supposed to initiate trials later on, the Novavax and Oxford vaccines. That could be helpful for decision-making early on as well. Thinking about the potential for a very limited supply of vaccine in the early weeks, it will behoove the WG and ACIP to make sure that they are using data to drive decision-making. Obviously, they want flexibility at the local level to ensure that each local area understands the epidemiology of their disease and is getting vaccine to those workers who seem to have a high-risk of exposure. That will differ by region or local context.
Dr. Dooling responded that CDC is in communication with all of the companies that have plans to enroll candidates and conduct clinical trials in the US. The WG will hear from them and subsequently, the manufacturers will have an opportunity to present to the ACIP.

Dr. Hunter thanked all of the speakers of the day and over the 4 years that he has been a member of ACIP for serving up on a silver platter the kind of information the voting members need to provide input. He agreed that starting with HCP will prevent a large number of infections and deaths much more than in other priority groups. Therefore, it makes sense to begin with them. The implementation issues like the ability to vaccinate HCP in facilities that are most likely to utilize specialized storage and handling is a plus. In addition, he had some personal things he wanted to advocate for from his perspective as a clinician and public health person. The first is that in order to promote vaccine confidence, he would advocate for ACIP Policy Statements that encourage vaccination to be voluntary and not a condition of employment. He also would support Policy Statements that allow some flexibility in interpreting eligibility for vaccination at the point-of-administration or registration, especially as vaccine supplies increase. Obviously, early on they will need to be tight. However, they need to prepare from the beginning for the transition between the first of the 3 phases when hopefully there will be more vaccine available.

Dr. Cohn reminded ACIP members that while many HCP will be able to be vaccinated more easily given that they are in healthcare facilities, there are a number of HCP who work at LTCF and in other places where they will still have to ensure access to vaccination if, indeed, that is the first group. Based on Dr. Slayton's presentation, it is clear that LTCF staff will be an important group as well.

Ms. McNally said that speaking as the consumer representative and for the reasons that had been discussed (potential risk to HCP, implementation issues, safety monitoring), she also expressed support for prioritization of HCP.

Dr. Drees (SHEA) pointed out that if the vaccine is a condition of employment and there is an AE, that is automatically covered by Workers Compensation. However, it is not necessarily covered if it is an optional vaccine. Although an institution can choose to cover that. ACIP may want to think through the language around that to ensure that any AEs that do occur are covered.

Dr. Atmar reported that the State of Texas has a law that basically states that HCP need to be vaccinated against vaccine-preventable diseases with few exceptions. ACIP may make suggestions, but some of this is going to be guided by local laws and other considerations.

Dr. Cohn reminded everyone that under an EUA, vaccines are not allowed to be mandatory. Therefore, early in the vaccination phase individuals will have to be consented and cannot be mandated to be vaccinated.

Dr. Atmar noted that EUA versus licensure remains an open question.

Dr. Hunter clarified that he was suggesting that the ACIP recommendations are somewhat like a federal law in which there is a base of a minimum that can be done, and then local or state entities can do more with the federal law. His opinion was the same for requiring vaccine for employment. While they do not have to say it is a requirement for employment, it could be a consideration for employment. The guidance could describe the advantages and disadvantages for that.

If supply remains constrained, due to vaccine or distribution limitations, do you agree with vaccinating essential workers next as supply permits?

Dr. Bernstein asked how acceptance of vaccine by various populations was factored into the modeling allocation strategies and different assumptions regarding VE. For example, did the modeling take into consideration various percentages of acceptance. He stressed the importance of building confidence in the vaccines. He would expect that for each population, the percentage of individuals who would accept these vaccines could be quite variable by population as well as geographically.

Dr. Dooling said her understand of the modeling results was that the models did not factor in partial acceptance. They modeled X number of doses going entirely to certain groups and then let the model results play out.

Dr. Atmar agreed with the assessment that essential workers would be the next target to help maintain the society's infrastructure.

Dr. Poehling agreed that the data presented to date highlight the importance of covering HCP followed by essential workers, and that implementation is a very important component because the more vaccine that is reliably in the population with full protection (e.g., both doses) the better. The microplanning is essential because implementation and cold storage will remain an important part of this consideration.

Dr. Sanchez agreed to a point, but thought those with high-risk medical conditions should be next. Perhaps those with high-risk medical conditions could be prioritized first within the HCP recommendation. This is a huge number and vaccine may not be available for all. High-risk

medical conditions are associated with more severe disease and death, which led him to want to prioritize them.

Dr. Szilagyi said he was struggling with this one because the size of the essential worker group is about the same as the older population. If the model is correct, there would be far fewer deaths among essential workers. However, they are essential workers and are critical for societal operation. Minorities have substantially higher risks of morbidity and mortality from COVID-19, many have high-risk medical conditions, and many are essential workers. In a sense, prioritizing essential workers targets a very high minority population who are essential due to their occupation. He also thought it possibly would be easier to administer the vaccine with the cold chain vaccine, especially if mobile vans or other ways are utilized to reach essential workers.

Dr. Frey commented that so far she agreed with both of these groups for being prioritized, but thinks there has to be a strategy to prioritize people within each of these groups. She asked who will make the decisions about how many doses go to a particular region or state and who, within that region or state, will prioritize who is supposed to get vaccine.

Dr. Messonnier emphasized that this is a very important issue and that her answer would not be as succinct as she likes to give ACIP when they ask these hard questions. She thinks this is an issue that is still under discussion, and there is a complicated interplay between the question of prioritization and allocation. In other words, one might want general information about the question posed before decisions are made about prioritization. However, they think the way this is going to go is that once they have ACIP's recommendations around prioritization and there is more information about the specific characteristics of the conditions of use of the vaccine, the federal government will be in a better position to make allocation decisions. CDC is working up the technical specifications that would go with a variety of potential scenarios. She reminded those who went through H1N1 that it was very different, but certainly had similarities. She said she understood the sentiment that Dr. Romero echoed earlier in the session, which was to ask them not to try to over-engineer and to leave space for local and state public health departments to have some flexibility to deal with their own local situations. CDC definitely has heard that input and will try to take it into account in their proposals.

Dr. Lee said she also was struggling with essential workers, given that it is hard to make this decision at this point. It is assuming that the implementation considerations they know about now are going to be the same 4 weeks from now. She acknowledged that deciding whether it should be essential workers or those with high-risk medical conditions was very challenging to her. She thinks they will have to see where they are in a few weeks with regard to understanding more about implementation and having a sense of which vaccine candidates might be the most likely to come forward initially. Within the groups there is the ability to acknowledge that there are differential risks among even low-wage workers within the healthcare delivery system in terms of high-risk medical conditions and age. However, that kind of guidance even within a particular category, should not impair implementation efforts. They do need to acknowledge that risk-based recommendations are always more challenging to implement, COVID notwithstanding, than universal recommendations. It is critical to provide enough information so that local teams who are administering the vaccines can make sure they are maximizing the impact, but also not constraining them so much that they are not getting the vaccine distributed. That is the balance they are looking to strike.

Dr. Talbot reminded everyone that they are in a weird time and that there are people who still have to go to work and put themselves at risk. There are many people with high-risk conditions who can work from home, but there are many with high-risk conditions who are essential workers and who are putting their lives on the line to keep society running. It is absolutely critical to continue to think about essential workers for many reasons. Many of them are of lower socioeconomic status (SES) and many have high-risk conditions who are unable to work from home. That is the key. As vaccine becomes available in huge quantities, they can talk about the people who have the luxury of being at home. Along those lines, there is not going to be enough vaccine for everyone in healthcare and everyone who is an essential worker. It is also important to remember that not everyone is going to want the vaccine. There is an opportunity to offer it to these groups first, but not everyone is going to want to take it up. Perhaps with the limited supply, everyone will be more motivated to get it. As for the freezer comments, there are some amazingly talented and innovative people in health departments, at CDC, and in public health who will come up with incredible ways to get to essential workers. Therefore, she did not want that to limit them.

Dr. Bell thanked all of her colleagues on the ACIP for such thoughtful and helpful feedback to the WG as they move forward in an effort to make interim recommendations. This is clearly going to be pivotal to any successful vaccination program. With all of the moving parts and uncertainties, she has been struck by how much the ACIP members have adhered to the guiding principles and provided the WG with food for thought so they can work through these issues further between now and the next meeting.

Certification

Upon reviewing the foregoing version of the August 26, 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 – June 30, 2020

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Professor of Pediatrics
Horace C. Cabe Endowed Chair in Infectious Diseases Director, Pediatric Infectious Diseases Section
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Director, Clinical Trials Research
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Term: 10/30/2018-06/30/2021

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Term: 7/1/2019 – 6/30/2023

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Term: 11/27/2017-06/30/2021

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Term: 11/27/2017-06/30/2021

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Term: 7/1/2016 – 6/30/2020

LEE, Grace M., MD, MPH
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Professor of Pediatrics, Stanford University School of Medicine
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Term: 7/1/2016 – 6/30/2020

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

POEHLING, Katherine A., MD, MPH
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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

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Children and Adults Health Programs Group
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