

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

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



**Summary Report  
June 24, 2020  
Atlanta, Georgia**

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**Final - June 16, 2020****MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)**

Centers for Disease Control and Prevention

Atlanta, Georgia 30329

June 24, 2020

<b>AGENDA ITEM</b>	<b>PRESIDER/PRESENTER(S)</b>
<b>Wednesday, June 24</b>	
9:00 <b>Welcome &amp; Introductions</b>	Dr. José Romero (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary, CDC)
9:15 <b>Meningococcal</b> Introduction: Meningococcal Vaccines Session Safety and Immunogenicity of MenQuadfi MenACWY-TT (MenQuadfi): ETR, GRADE, and Workgroup Considerations	Ms. Veronica McNally (ACIP, WG Chair) Dr. Corey Robertson (Sanofi Pasteur) Dr. Lucy McNamara (CDC/NCIRD)
VFC Resolution Update: Meningococcal Vaccines	Mr. Frank Whitlatch (CDC/NCIRD)
10:15 <b>Influenza Vaccines</b> Introduction WG Considerations and proposed recommendations	Dr. Robert Atmar (ACIP, WG Chair) Dr. Lisa Grohskopf (CDC/NCIRD)
11:15 <b>Break</b>	
11:25 <b>Public Comment</b>	
11:55 <b>VOTES</b> Influenza Vaccines <b>VFC Vote</b> Meningococcal Vaccines	Dr. Lisa Grohskopf (CDC/NCIRD) Mr. Frank Whitlatch (CDC/NCIRD)
12:30 <b>Lunch</b>	
12:40 <b>Coronavirus Disease 2019 (COVID-19)</b> Overview of COVID-19 disease SARS-CoV-2 immunology U.S. COVID-19 epidemiology Routine pediatric and influenza vaccination in the setting of COVID-19	Dr. John Brooks (CDC/NCHHSTP) Dr. Natalie Thornburg (CDC/NCIRD) Dr. Sara Oliver (CDC/NCIRD) Dr. Melinda Wharton (CDC/NCIRD)
2:00 <b>Break</b>	
2:10 <b>COVID-19 Vaccines</b> Introduction COVID-19 vaccine development  Landscape of candidate COVID-19 vaccines	Dr. Beth Bell (ACIP, WG Chair) Dr. Matthew Hepburn (Lead, Operation Warp Speed Vaccines) Dr. Kathleen Neuzil (University of Maryland)
3:30 <b>Break</b>	
3:40 COVID-19 vaccine prioritization considerations Work Group considerations and next steps	Dr. Sarah Mbaeyi (CDC/NCIRD) Dr. Kathleen Dooling (CDC/NCIRD)
4:50 <b>Agency Updates</b> CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, ODP	
5:00 <b>Vaccine Supply Update</b>	Dr. Jeanne Santoli (CDC/NCIRD)
5:05 <b>Adjourn</b>	

**Acronyms**

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

### 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
AFM	Acute Flaccid Myelitis
AGS	American Geriatrics Society
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
aIV	Adjuvanted Inactivated Influenza Vaccine
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
ANA	American Nurses Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APHL	Association of Public Health Laboratories
ASH	Assistant Secretary for Health
ASPR	Assistant Secretary for Preparedness and Response
ASTHO	Association of State and Territorial Health Officers
BARDA	Biomedical Advanced Research and Development Authority
BLA	Biologics License Application
BMI	Body Mass Index
BSL-4	Biosafety Level 4
CBER	Center for Biologics Evaluation and Research
ccIIV	Cell Culture-Based Inactivated Influenza Vaccine
CDC	Centers for Disease Control and Prevention
CHC	Community Health Center
CICP	Countermeasures Injury Compensation Program
CISA	Clinical Immunization Safety Assessment
CMIA	Chemiluminescent Microparticle Immunoassay
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
COVID-19	Coronavirus Disease 2019
COVID-NET	COVID-19-Associated Hospitalization Network
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
Ct	Cycle Threshold
CTN	Clinical Trials Network
DM	Diabetes Mellitus
DNA	Deoxyribonucleic Acid

DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria and Tetanus Toxoid and Pertussis
DVA	Department of Veterans Affairs
DVD	Division of Viral Diseases
ECMO	Extracorporeal Membrane Oxygenation
ED	Emergency Department
EIP	Emerging Infections Program
EIS	Epidemic Intelligence Service
ELISA	Enzyme-Linked Immunosorbent Assay
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
EV	Enteroviruses
FDA	Food and Drug Administration
FHA	Filamentous Haemagglutinin
FQHC	Federally Qualified Health Center
FY	Fiscal Year
GAVI	Global Alliance for Vaccines and Immunisation; The Vaccine Alliance
GI	Gastrointestinal
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HAN	Health Alert Network
HCoV	Human Coronaviruses
HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers
HD-IIV	High-Dose Inactivated Influenza Vaccine
HHS	(Department of) Health and Human Services
HI	Hemagglutinin Inhibition
Hib	Haemophilus Influenzae Type B
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
ICD	International Classification of Diseases
ICU	Intensive Care Unit
ID	Intradermal
IDSA	Infectious Disease Society of America
Ig	Immunoglobulin
IHS	Indian Health Service
IIS	Immunization Information Systems
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-like Illness Surveillance Network
IM	Intramuscular
IMD	Invasive Meningococcal Disease

IQIP	Immunization Quality Improvement for Providers
ISD	Immunization Services Division
ISO	Immunization Safety Office
IVIG	Intravenous Immunoglobulin
LAIV	Live Attenuated Influenza Vaccine
LRN	Laboratory Response Network
MASO	Management Analysis and Services Office
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MIS-C	Multisystem Inflammatory Syndrome in Children
MMR	Measles, Mumps, and Rubella
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>
mRNA	Messenger Ribonucleic Acid
NACCHO	National Association of County and City Health Officials
NACHC	National Association of Community Health Centers
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
NAS	National Academy of Sciences
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
<i>NEJM</i>	<i>New England Journal of Medicine</i>
NFID	National Foundation for Infectious Diseases
NHIS	National Health Interview Survey
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIP	National Immunization Program
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NSSP	National Syndromic Surveillance Program
NVSN	New Vaccine Surveillance Network
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
NVSN	New Vaccine Surveillance Network
NYC	New York City
OASH	Office of the Assistant Secretary for Health
OID	Office of Infectious Disease
OIDP	Office of Infectious Disease Policy and HIV/AIDS
OSHA	Occupational Safety and Health Administration
PCP	Primary Care Practitioner
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis

PHAC	Public Health Agency Canada
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PIMS	Pediatric Inflammatory Multisystem Syndrome
PPE	Personal Protective Equipment
PPV	Positive Predictive Value
PRAMS	Pregnancy Risk Assessment and Monitoring System
PrEP	Pre-Exposure Prophylaxis
PRNT	Plaque Reduction Neutralization Test
PT	Pertussis Toxin
PT	Preferred Terms (MedDRA)
QIV	Quadrivalent Influenza Vaccine
RCT	Randomized Controlled Trial
RCA	Rapid Cycle Analysis
RIV	Recombinant Influenza Vaccine
RN	Registered Nurse
RNA	Ribonucleic Acid
RR	Relative Risk
rRT-PCR	Real-Time Reverse Transcription Polymerase Chain Reaction
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCR	Seroconversion Rate
SD-IIV3	Standard Dose Inactivated Influenza Vaccine
SDOH	Social Determinants of Health
SET-NET	Surveillance for Emerging Threats to Mothers and Babies Network
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Expert
SNS	Strategic National Stockpile
STEMI	ST-Elevation Myocardial Infarction
TB	Tuberculosis
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TEC	Tribal Epidemiology Center
TIV	Trivalent Influenza Vaccine
UK	United Kingdom
UNICEF	United Nations Children's Fund
US	United States
US Flu VE	US Influenza Vaccine Effectiveness Network
USG	US Government
USPHS	US Public Health Service
VA	(US Department of) Veteran's Affairs

VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VFC	Vaccines For Children
VICP	Vaccine Injury Compensation Program
VIS	Vaccine Information Statement
VRBPAC	Vaccines and Related Biological Products Advisory Committee Meeting
VRC	Vaccine Research Center (NIAID)
VSD	Vaccine Safety Datalink
WG	Work Group
WHO	World Health Organization
WRA	Women of Reproductive Age



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

**José Romero, MD, FAAP**  
**ACIP Chair**

**Amanda Cohn, MD**  
**Executive Secretary, ACIP / CDC**

Dr. Cohn called to order the June 2020 Advisory Committee on Immunization Practices (ACIP), welcomed those present, and provided instructions for the various platforms through which participants were joining the meeting (e.g., Zoom, webinar, teleconference). She announced that 2 additional virtual ACIP meetings dates have been added: August 12, 2020 and September 16, 2020. These dates are subject to change. Any changes made will be updated on the ACIP website and sent via email to all subscribers to the ACIP/CDC page. The next regularly scheduled meeting is October 28-29, 2020. At this time, it is not known whether the October meeting will be virtual or in person.

She noted that slides to be presented during this meeting were made available through a ShareFile link for liaison and *ex-officio* members and for members of the public on the ACIP website at the following URL, which eventually will be replaced with a 508-compliant version:

<https://www.cdc.gov/vaccines/acip/meetings/slides-2020-06.html>

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. Minutes from the February 2020 meeting were scheduled to be posted shortly.

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. She recognized that the virtual environment makes this especially challenging and noted that while there would be an opportunity for public comment during this meeting, they do miss seeing everyone in-person and being able to interact and connect in that way. 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 11:25 AM, prior to lunch.

To create a fair and efficient process for requesting to make an oral comment, people interested in making an oral comment were asked to submit a request online in advance of the meeting. Priority is given to these advance requests, and if more people request to speak than can be accommodated, a blind lottery is conducted to determine who will be the speakers. Speakers selected in the lottery for this meeting were notified in advance of the meeting. Written public comments may be made via [regulations.gov](https://www.regulations.gov) using the docket number ID CDC-2020-0049. Information on the written public comment process, including information about how to make a public comment, can be found on the [ACIP website](https://www.acip.cdc.gov). Regulations.gov closes approximately 24 hours following the end of the ACIP meeting. Dr. Cohn pointed out that written public comments could be made during and after the meeting as well.

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 those vaccines. Regarding other vaccines of the concerned company, a member may participate in discussions with the provision that he/she abstains on all votes related to the vaccines of that company. At the beginning of each meeting and prior to each vote, ACIP members will state any COIs.

Dr. Cohn indicated that detailed instructions for submission of names of potential candidates to serve as ACIP members is now available on the ACIP website. Applications for ACIP membership are due no later than July 1, 2020 for the 4-year term beginning July 1, 2021.

Dr. Romero welcomed everyone to the June 2020 virtual meeting of ACIP. He conducted a roll call of ACIP members, during which no members declared any COIs. He then 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 from the June 2020 ACIP meeting.

### **NCIRD Director's Welcoming Remarks**

**Nancy Messonnier, MD, Director  
National Center for Immunization and Respiratory Diseases (NCIRD)  
Centers for Disease Control and Prevention (CDC)**

Good morning, everybody. Thank you for joining us at our first virtual ACIP meeting. I'd like to thank the ACIP members, the *ex officio* members, the liaisons, and the rest of the audience who is listening to us today. I'd especially like to thank the CDC team, both our regular ACIP team and all of the folks who are supporting us today. I know this won't go off without hiccups, but we certainly appreciate the village that it takes to pull off this kind of meeting.

Before we get started today, I'd like to take a moment to speak to you about the events that are taking place in our country. Over the last few months, we've been battling a pandemic, its economic consequences, and the painful reality of racial injustices and inequities. Like many of you, I feel overwhelmed by these circumstances. However, we cannot ignore the racial injustice, systemic racism, and their impact on the longstanding racial disparities in healthcare and public health in the United States (US). The lack of diversity in organizations across multiple sectors, including scientific and medical pursuits, is mirrored in our healthcare system where significant health disparities exist in certain communities.

COVID-19 is just the latest in a long list of diseases that underscore the health inequities in the African American community. In order to close the health disparity gap, there is much more that needs to be considered when designing and implementing our public health work. There is also much more to do within our own organizations to increase diversity and provide more opportunity for our peers who are Black, Hispanic, and from other racial and ethnic minority groups. It is important to mentor, recruit, and retain the next generation of scientific leaders who reflect the communities we serve, especially in and from the communities who bear the burden of many health inequities.

At NCIRD, we are working through programs like the Morehouse College IMHOTEP program to build the pipeline of racial and ethnic minority candidates for our flagship programs like Epidemic Intelligence Service (EIS) and we are committed to improving our workplace diversity and inclusiveness so that all staff feel welcomed, fully engaged, and supported. We must also develop, enhance, and maintain strong partnerships, which are vital in implementing our public health programs. We are continuing funded partnerships with groups like the National Association of Community Health Centers (NACHC), and we're strengthening existing partnerships through improved connections between state immunization programs and state Health Equity Directors.

I want to close by saying how much I appreciate the dedication and perseverance of our CDC staff and our many partners who continue the critical daily work of protecting people and saving lives despite the extreme turbulence and uncertainty right now. We are a country founded on the ideals of opportunity and equality and as physicians, scientists, and public health professionals, we have a real responsibility to live up to those values. Let's double down on our commitment to improve health outcomes for all people. I challenge everyone in the vaccine space to listen, create opportunities for open and honest dialogue, and to do your part to support, recruit, and retain the most diverse workforce possible—especially in our scientific leadership positions. While the events happening in our country are extremely painful, they are a signal to those of us in leadership positions to chart a better path forward starting now. Thank you.

## Meningococcal Vaccines

### Introduction

**Veronica McNally, JD**  
**Chair, Meningococcal Work Group**  
**Advisory Committee on Immunization Practices**  
**President and CEO, Franny Strong Foundation**

Ms. McNally introduced the Meningococcal Vaccine WG session. A new meningococcal serogroup A, C, W, Y (MenACWY) vaccine, MenACWY-TT (MenQuadfi™), was approved by the Food and Drug Administration (FDA) in April 2020. It is approved for individuals ages  $\geq 2$  years.

The issue under consideration is whether MenACWY-TT should be available as an option for MenACWY vaccination according to currently recommended dosing and schedules in the Vaccines for Children (VFC) program. The VFC vote will address whether MenACWY-TT should be included as an option for meningococcal serogroup A, C, W, and Y vaccination in the VFC program using currently recommended dosing and schedules for MenACWY vaccines. No ACIP vote is needed as no changes to recommendations are proposed.

Meningococcal disease is a serious infection that can progress rapidly. One in 10 patients die despite antibiotic treatment. Among survivors, 1 in 5 have long-term sequelae that can include hearing loss, amputation, and cognitive deficits. The incidence of meningococcal disease is at an all-time low in the United States (US) with 0.10 cases per 100,000 population in 2018. Serogroups C, W, and Y combined currently account for approximately 50% of all cases.

MenACWY vaccines have been recommended for adolescents and persons at increased risk since 2005. Three MenACWY conjugate vaccines are currently licensed:

- MenACWY-D (Menactra®)
- MenACWY-CRM (Menveo®)
- MenACWY-TT (MenQuadfi™)

The populations currently recommended for MenACWY vaccination are adolescents with one dose at 11 or 12 years of age and a booster at age 16 years, and persons aged  $\geq 2$  months at increased risk for meningococcal disease due to specified underlying conditions or exposures.

The Meningococcal Vaccines WG reviewed data on MenACWY-TT safety, immunogenicity, persistence of immune response, and concomitant administration with other vaccines. The WG used Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) along with the Evidence to Recommendations Framework (EtR) to assess the use of MenACWY-TT as an option for MenACWY vaccination.

The agenda for this session included presentations on the following topics:

- Safety and Immunogenicity of MenQuadfi™
- MenACWY-TT (MenQuadfi™): EtR, GRADE, and WG Considerations
- VFC Resolution Language

**Safety and immunogenicity of MenQuadfi™**  
**Meningococcal (Groups A, C, Y, W) Conjugate Vaccine**

**Dr. Corey Robertson**  
**Sanofi Pasteur**

Dr. Robertson provided information regarding Sanofi Pasteur's newest MenACWY vaccine, MenQuadfi™. Invasive meningococcal disease (IMD) still poses a public health challenge given its high case fatality rate of approximately 10% to 15%. About one in five survivors are left with serious permanent sequelae<sup>3,4</sup>. Thankfully, MenACWY vaccines have been effective at preventing the disease. Since introduction of the first MenACWY conjugate vaccine (Menactra®) in 2005 followed by Menveo® in 2010, IMD caused by serogroups C, W, and Y has declined by more than 90% among adolescents and young adults<sup>5</sup>. There is still room for improvement with MenACWY vaccination, including an opportunity to expand protection at both ends of the age spectrum with a single vaccine. With this in mind, MenQuadfi™ has been developed. [References: 1. Thompson MJ, et al. Lancet. 2006;367(9508):397-403. 2. WHO. <https://www.who.int/en/news-room/fact-sheets/detail/meningococcal-meningitis> accessed March 2020]. 3. CDC. MMWR. 2013;62(RR-2):1-22. 4. Rosenstein NE, et al. N Engl J Med. 2001;344(18):1378-1388. 5. MacNeil JR, et al. Clin Infect Dis 2018; 66:1276–81].

MenQuadfi™ is a quadrivalent meningococcal conjugate vaccine intended to help prevent IMD caused by serogroups A, C, W, and Y. In April 2020, FDA approved the vaccine for use in persons 2 years of age and older. This includes adults 56 years of age and older, a segment of the US population for whom no licensed meningococcal conjugate vaccine existed. MenQuadfi™ was developed with the ambition of being used across a broad age range. Sanofi Pasteur is currently conducting ongoing trials to assess the performance of MenQuadfi™ in children as young as 6 weeks of age. In those same studies, Sanofi Pasteur is examining different dosing intervals with the hope of it being incorporated in various immunization schedules that exist worldwide. MenQuadfi™ contains tetanus toxoid as a protein carrier. Each 0.5-mL intramuscular (IM) dose contains 10 µg each of the 4 meningococcal polysaccharide antigens contained in the vaccine. MenQuadfi™ will be supplied in a single dose vial as a fully liquid formulation or solution that does not require reconstitution.

Dr. Robertson reviewed the clinical trials that comprised the development program that led to the initial licensure of the vaccine in the US, which are shown in this table:

**Robust clinical development program led to initial US licensure of vaccine**

Clinical Study Code	Phase	Title	Comparator	ClinicalTrials.gov Identifier
MET50	II	Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Healthy Adolescents (NOTE: Coadministered vaccines were Tdap and HPV4)	MenACWY-CRM (Menveo)	NCT02199691
MET49	III	Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adults Age 55 Years and Older	MPSV4 (Menomune – A/C/Y/W-135)	NCT02842866
MET56	III	Immunogenicity and Safety of a Booster Dose of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adolescents and Adults	MenACWY-D (Menactra)	NCT02752906
MET35	III	Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered in Healthy Children 2 to 9 Years of Age	MenACWY-CRM (Menveo)	NCT03077438
MET43	III	Immune Lot Consistency, Immunogenicity, and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adolescents and Adults Aged 10 to 55 Years	MenACWY-D (Menactra)	NCT02842853

Menveo is a registered trademark of GlaxoSmithKline Biologicals S.A.  
Menactra and Menomune are registered trademarks of Sanofi, its affiliates and/or its subsidiaries.

**All trials were randomized, blinded, and active-controlled**

In the first 3 trials, MenQuadfi™ was evaluated in adolescents, older adults, and as a booster. In the last 2 trials, MenQuadfi™ was evaluated in children 2 through 9 years of age and persons 10 to 55 years of age. The comparators used are shown in the 4<sup>th</sup> column of the table. All trials were randomized, blinded, and active-controlled. Due to randomization, demographic characteristics were well-balanced across vaccine groups within each of the trials. The study populations for each trial reflected the racial and ethnic diversity of the US population to varying degrees. The results of 4 of the 5 trials have been published in the medical literature, while the manuscript for the remaining trial is currently under review. Dr. Robertson described each study.

MET50 was a study of 1700 adolescents 10 through 17 years of age who were randomly assigned to 1 of 4 vaccine groups. Group 1 received MenQuadfi™ (N=503), Group 2 received the comparator MenACWY-CRM (N=501), Group 3 received MenQuadfi™+Tdap+HPV (N=392), and Group 4 received concomitant Tdap+HPV (N=296) without MenQuadfi™. The mean age of the study population was just over 11 years. In terms of safety, the frequency of solicited reactions was similar across the different vaccine groups, except for myalgia that occurred at a higher frequency in the concomitant vaccination groups that included Tdap and human papillomavirus (HPV).

Turning to immunogenicity, MenQuadfi™ induced seroresponse rates that were non-inferior to the comparator vaccines. Point estimates were consistently higher for MenQuadfi™ than for the comparator across the different vaccine serogroups, and the 95% confidence intervals were not overlapping. The same pattern was seen with respect to seroprotection rates and post-vaccination geometric mean titers (GMTs), including a pronounced response to serogroup C relative to the comparator vaccine. Concomitant administration of Tdap and HPV did not have a material impact on the immunogenicity of MenQuadfi™. Likewise, when MenQuadfi™ was given with Tdap and HPV, MenQuadfi™ did not have a material impact on the response following HPV vaccination at the specified seroconversion rates.

Looking at the Tdap component, seroprotection rates for diphtheria and tetanus following concomitant MenQuadfi™, Tdap, and HPV vaccination were non-inferior to the seroprotection rates observed after Tdap and HPV without MenQuadfi™. Non-inferiority of pertussis antibody

responses was considered met if the lower bound of the 95% confidence interval around the geometric mean concentration (GMC) ratio of Group 3 over Group 4 was greater than 0.667. Based on that definition, non-inferiority was met for the pertussis toxin (PT) antigen and not met for filamentous haemagglutinin (FHA), pertactin (PRN), and fimbriae (FIM). Lower antibody responses to pertussis antigens have been observed in trials in which other quadrivalent conjugate meningococcal vaccines have been co-administered with pertussis-containing vaccines. The clinical significance of any of these findings is unknown, since no antibody correlate of protection exists for pertussis.

Moving on to the study of MenQuadfi™ in adults 56 years of age and older, participants were assigned to received either MenQuadfi™ or the plain polysaccharide vaccine Menomune®. The mean age of the study population was just over 72 years. Solicited reactions were higher in the MenQuadfi™ compared to the plain polysaccharide group. There are likely two reasons for this, especially with regard to injection site reactions: 1) MenQuadfi™ contains tetanus toxoid as its protein conjugate whereas Menomune® does not have a protein conjugate; and 2) MenQuadfi™ is administered intramuscularly and the plain polysaccharide vaccine is administered subcutaneously. In terms of immunogenicity, MenQuadfi™ induced seroresponses that were non-inferior to those induced by the comparator vaccine. Point estimates were consistently higher. In this case, the 95% confidence intervals were not overlapping. A similar pattern was seen with seroprotection rates, with the exception of serogroup A for which the 95% confidence intervals did overlap. MenQuadfi™ induced GMTs that were higher than those induced by the comparator vaccine, especially for serogroup C.

MET56 was a study of MenQuadfi™ when used as a booster. In this trial, over 800 individuals 15 years of age and older participated. To be eligible for participation, they had to have been primed with either MenACWY-D or MenACWY-CRM. They were randomly assigned to receive either MenQuadfi™ as a booster or MenACWY-D as a booster. The mean age was 20 years. Injection site and systemic reactions were similar between the two vaccine groups when they were used as boosters. MenACWY-TT as a booster induced a response rate that was non-inferior to MenACWY-D when used as a booster. Both vaccines induced high seroprotection rates ranging from 99% to 100%. Both vaccines induced robust booster responses in terms of GMTs, but especially MenQuadfi™ and especially for serogroup C.

In MET35, MenQuadfi™ was evaluated in a trial of 1000 children 2 through 9 years of age. Half were randomly assigned to receive MenQuadfi™ and the other half to receive MenACWY-CRM. The mean age of the study population was 6 years. The frequency of solicited reactions was similar between the two vaccine groups, except that there was a slightly higher trend toward a high frequency of injection site reactions among those who received the comparator. MenQuadfi™ induced seroresponse rates that were non-inferior to the comparator vaccine. Point estimates were consistently higher for MenQuadfi™. With the exception of serogroup A, the 95% confidence intervals were not overlapping. The same pattern was seen with respect to seroprotection rates and GMTs, with the most pronounced difference for serogroup C.

MET43 was a study of MenQuadfi™ in adolescents and adults 10 through 55 years of age. Over 3300 persons participated in this trial and were randomly assigned to receive either MenQuadfi™ from one of three vaccine lots or MenACWY-D. The mean age of the study population was just over 27 years. Solicited reactions occurred with similar frequency between

the two vaccines. MenQuadfi™ induced seroresponse rates that were non-inferior to those induced by the comparator vaccine. Point estimates were consistently higher with non-overlapping confidence intervals. The same pattern was seen with respect to seroprotection rates and post-vaccination GMTs, with the most pronounced difference for serogroup C.

In closing, MenQuadfi™ was demonstrated to be safe and to induce a robust immune response against serogroups A, C, W, and Y, especially serogroup C. Immune responses were consistently non-inferior to standard-of-care vaccines across age groups  $\geq 2$  years for all 4 vaccine serogroups. MenQuadfi™ induced booster responses among persons previously primed with MenACWY-D or MenACWY-CRM. Clinical trial data show that MenQuadfi™ can be co-administered with the routinely recommended adolescent vaccines Tdap and HPV. MenQuadfi™ has been licensed for use in persons 2 years of age and older. Sanofi Pasteur will be distributing doses of the vaccine in the US in 2021 to help support meningococcal vaccination efforts. Trials are ongoing to seek expansion of the age indication down to children 6 weeks of age and to evaluate MenQuadfi™ in a number of different dosing intervals and along with other routinely recommended pediatric vaccines with the hope of MenQuadfi™ being incorporated in the different immunization schedules that exist around the world. Sanofi Pasteur believes that MenQuadfi™ has the potential to provide effective protection against invasive disease caused by serogroups A, C, W, and Y in a variety of settings.

### **Discussion Points**

Dr. Messonnier requested that Sanofi Pasteur comment on their plans for Menactra® in terms of whether that vaccine will continue to be available.

Dr. Robertson indicated that the plan is to transition from Menactra® to MenQuadfi™. Given that Menactra® is registered in over 70 countries, that transition will take some time and certainly will not occur before age indication for MenQuadfi™ is achieved down to 6 weeks of age.

Referring to slide 11, Dr. Bernstein noted that there were injection site reactions with both meningococcal vaccines and when MenACYW-TT was given with Tdap and HPV vaccines, but there appeared to be no injection site reactions at all for the group who received only Tdap and HPV.

Dr. Robertson clarified the study was designed to look at injection site reactions specifically related to the MenACWY vaccine recipient groups. Because of this, injection site reactions in the group who received only Tdap and HPV are not reported in the slide. This is not to say that this group did not have any injection site reactions.

Dr. Fryhofer (AMA) inquired as to how the tetanus toxoid component affects vaccination with tetanus vaccination and reactions among patients who also receive Tdap or Td.

Referring to slides 17 and 18, Dr. Robertson indicated that when MenQuadfi™ was given with Tdap, no impact was observed on tetanus and diphtheria responses. In terms of non-inferiority of pertussis antibody responses, non-inferiority was met for 1 of the 4 antigens and was narrowly missed for FHA and pertactin. A similar reduction in antibody response to pertussis antigens has been observed in other studies in which meningococcal vaccine has been given



with pertussis-containing vaccines. Sanofi Pasteur does not anticipate that this will be an issue clinically, given that they also assessed vaccine response with respect to these antigens and across the board they were high. The data presented have been published.

Following up on Dr. Fryhofer's comment, Dr. Hunter noted that after multiple doses of tetanus vaccine are given, there is stronger local swelling and pain at the injection site. This can be significant after 5 to 7 doses. If this is done in series over time in a person's lifetime, he wondered if they would have significant local reactions. Typically, this would not be dangerous but could be quite painful possibly in a small number of people. He asked whether that had occurred in any of the studies.

Dr. Robertson indicated that they do not have data in situations where Tdap or Td was given repeatedly for boosters along with MenQuadfi™; however, this will certainly be monitored for in the future.

### **MenACWY-TT (MenQuadfi™): EtR, GRADE, and WG Considerations**

**Lucy McNamara, PhD, MS**

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

Dr. McNamara presented a brief overview of current serogroup A, C, W, Y, or MenACWY vaccine recommendations and available vaccines; reviewed the policy question and the EtR framework for inclusion of MenACWY-TT as an option for meningococcal ACWY vaccination; briefly touched on all of the points in the EtR, but focused on the benefits and harms section including GRADE; and reviewed the considerations and conclusions of the meningococcal vaccines ACIP working group on this issue. The following table shows the MenACWY vaccines referenced during this presentation:

<b>Serogroup A, C, W, and Y meningococcal vaccines</b>				
<b>Vaccine product</b>	<b>Manufacturer</b>	<b>Trade name</b>	<b>Licensed for ages</b>	<b>Year licensed</b>
MenACWY-D	Sanofi Pasteur	Menactra	9 mos–55 yrs	2005
MenACWY-CRM	GlaxoSmithKline	Menveo	2 mos–55 yrs	2010
MenACWY-TT <sup>^</sup>	Sanofi Pasteur	MenQuadfi	≥2 yrs	2020
MPSV4 <sup>*</sup>	Sanofi Pasteur	Menomune	≥2 yrs	2014
MCV4-TT <sup>**</sup>	Pfizer	Nimenrix	NA	NA

MenACWY-D=Meningococcal groups A, C, W, and Y polysaccharide diphtheria toxoid conjugate vaccine  
 MenACWY-CRM=Meningococcal groups A, C, W, and Y oligosaccharide diphtheria CRM197 conjugate vaccine  
 MenACWY-TT=Meningococcal groups A, C, W, Y polysaccharide tetanus toxoid conjugate vaccine (<sup>^</sup>Contains 10µg each of serogroup A, C, W, and Y polysaccharides conjugated to 55µg tetanus toxoid carrier protein)  
 MPSV4=meningococcal polysaccharide vaccine, Groups A, C, Y and W combined  
 MCV4-TT=Meningococcal groups A, C, W, Y polysaccharide tetanus toxoid conjugate vaccine  
<sup>\*</sup>No longer available in the United States  
<sup>\*\*</sup>Never licensed in the United States, contains 5µg each of serogroup A, C, W, and Y polysaccharides conjugated to 44µg tetanus toxoid carrier protein

The first two vaccines in the table, MenACWY-D and MenACWY-CRM, are the vaccines currently in use in the US. Note that while MenQuadfi™ was referred to as MenACYW-TT by the manufacturer, for consistency MenACWY-TT was used in this presentation. Menomune®, or MPSV4, is no longer available in the US. and Nimenrix®, or MCV4-TT, has never been licensed

in the US. While MenQuadfi™ and Nimenrix® are both tetanus toxoid-conjugate vaccines, they have different amounts of meningococcal antigens and tetanus toxoid carrier protein.

As a reminder, the current ACIP recommendations for use of MenACWY vaccine in the US are that 2 doses of MenACWY are recommended for adolescents at 11 through 12 and 16 years of age. Other individuals at increased meningococcal disease risk due either to underlying medical conditions or to increased exposure are also recommended to receive meningococcal vaccines, including boosters for those who remain at increased risk.

The policy question and PICO (population, intervention, comparison, and outcome) addressed in this session are shown in the following table:

<b>Policy question: Should MenACWY-TT (MenQuadfi) be included as an option for meningococcal ACWY vaccination according to currently recommended dosing and schedules?</b>	
<b>Population</b>	Persons aged ≥ 2 years currently recommended to receive meningococcal ACWY conjugate vaccines
<b>Intervention</b>	Vaccination with MenACWY-TT according to currently recommended dosing and schedules
<b>Comparison</b>	Vaccination with MenACWY-D and MenACWY-CRM according to currently recommended dosing and schedules
<b>Outcome</b>	<ul style="list-style-type: none"> <li>• Serogroup A, C, W, or Y meningococcal disease</li> <li>• Short-term immune response</li> <li>• Persistence of immune response</li> <li>• Immune interference due to co-administration with other routine adolescent vaccines</li> <li>• Serious adverse events</li> </ul>

Currently, there are no data on vaccine effectiveness (VE) against serogroup A, C, W, or Y meningococcal disease for MenACWY-TT. The remaining four outcomes identified were included in the evidence profile: short-term immune response, persistence of the immune response induced by the vaccine, immune interference due to co-administration with other routine adolescent vaccines, and serious adverse events (SAEs) associated with MenACWY-TT.

The first element in the EtR framework is the problem. ACIP has recognized the importance of meningococcal disease as a public health problem through existing vaccine recommendations. The WG felt that the question of whether to include MenACWY-TT as an option for meningococcal vaccination is of public health importance given recent licensure of this vaccine in the US and to support security of the vaccine supply.

For the evidence retrieval to examine benefits and harms, a systematic review was conducted of studies in any language from the PubMed, Medline, Embase, CINAHL, Cochrane, Scopus, clinicaltrials.gov, and clinicaltrialsregister.eu databases using the search string: MenACYW-TT, MenACYWTT, MenACYW TT, MCV4-TT, MCV4TT, MCV4 TT, MenQuadfi, and “vaccin\*” and “(immunogenicity or efficacy or effectiveness or impact or safety or adverse event\*)”. Efforts were made to obtain unpublished or other relevant data and studies were included that

presented primary data on MenACWY-TT (MenQuadfi™). The database search identified 149 references. After screening the titles, abstracts, and articles or publicly available clinical trial results, 10 studies were included in the GRADE analysis. This table shows the 10 studies identified, all of which were Phase II or III clinical trials conducted by the manufacturer. All 10 studies included safety data:

Study Code	Study design	Population	Country	N (MenACWY-TT)	N (comparison)	Outcome
MET54	Phase II randomized, open-label	12-24 months	Finland	94	94	Immunogenicity, safety
MET51	Phase III randomized, modified double blind	12-23 months	Spain, Finland, Germany, Hungary	506	404	Immunogenicity, safety
MET35	Phase III randomized, modified double-blind	2-9 years	United States, Puerto Rico	480	482	Immunogenicity, safety
MET43	Phase III randomized, modified double-blind	10-17 years, 18-55 years	United States	1098, 1410**	300, 293**	Immunogenicity, safety
MET44	Phase II randomized, open label	56+ years	United States	201	100	Immunogenicity, safety
MET49	Phase III randomized, modified double-blind	56+ years	United States, Puerto Rico	448	453	Immunogenicity, safety
MET56*	Phase III randomized, modified double-blind	15+ years	United States, Puerto Rico	403	407	Immunogenicity, safety
MET50	Phase II randomized, open-label	10-17 years	United States	499, 391^	500, 296^	Immunogenicity, safety, coadministration
MET57	Phase III randomized, open-label	12-23 months	Mexico, Russia, South Korea, Thailand	294, 589^	294	Safety, coadministration
MET62*	Phase III open-label; follow-up to MET54	4-5 years	Finland	42	49	Safety, persistence

\*Safety and/or immunogenicity evaluated after booster dose \*\*N's for 10-17y and 18-55y age groups, respectively ^N's in meningococcal vaccine only and co-administration groups, respectively

The first 8 studies listed had immunogenicity data, MET62 had persistence data, and MET50 and MET57 had information on co-administration. Only MET50 included co-administration of routine adolescent vaccines. The data reviewed for GRADE did not include any data on individuals who are recommended to receive meningococcal vaccines based on underlying medical conditions, including persons with complement component deficiency or taking a complement inhibitor; persons with functional or anatomic asplenia (including sickle cell disease); and persons with HIV infection as these groups were excluded from the evaluated studies.

In terms of short-term immunogenicity assessed 30 days after vaccination with MenQuadfi™, Dr. McNamara shared an example of the immunogenicity results for the MET50 study among individuals 10 through 17 years of age. In this study, MenACWY-TT elicited higher GMTs and a larger percentage of seroresponders than the comparator for all four serogroups, with the largest difference for serogroup C, a trend observed across all included studies. For each of the 8 studies with data on short-term immune response, across serogroups, age groups, and comparator vaccines, GMTs and percentage of seroresponders were nearly always higher among individuals who received MenACWY-TT. All studies demonstrated non-inferiority of MenACWY-TT compared with the comparator vaccine.

The certainty of evidence was evaluated using GRADE. Under this approach, certainty of evidence is rated on a 1-4 scale with a 1 corresponding to randomized controlled trials (RCTs) or overwhelming evidence from observational studies; a 2 corresponding to RCTs with important limitations or exceptionally strong evidence from observational studies; a 3 corresponding to observational studies or RCTs with notable limitations; and a 4 corresponding

to clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations.

For healthy children, adolescents, and adults, the WG felt that there was no serious risk of bias, inconsistency, indirectness, or imprecision. The studies demonstrate that immune responses to MenACWY-TT are non-inferior to those induced by other licensed quadrivalent meningococcal vaccines with high certainty, so this criterion was rated as a 1. For groups at increased risk due to underlying medical conditions, indirectness was considered very serious based on the fact that the studies included only healthy individuals. The certainty for these groups was rated as a 3.

The second GRADE outcome was SAEs. All 10 studies included data on SAEs. Reported rates of SAEs were generally low and none of the reported SAEs were determined by the researchers to be related to the vaccine. The highest rates of SAEs were reported in toddlers, an age group for which the vaccine is not currently licensed in the US. The majority of these SAEs were accidental injuries or infections by pathogens not included in the study vaccines. For individuals aged 2 years and older, including booster dose recipients, rates of SAEs were similar in the MenQuadfi™ and comparator groups.

For GRADE, the 9 randomized studies with safety data were included. Risk of Bias was considered Serious because many trials were not fully double-blinded, which could lead to bias in assessing SAEs. In addition, the studies did not describe how the researchers determined that SAEs were not vaccine-related. There were no serious concerns for inconsistency, indirectness, or imprecision for use of the vaccine in healthy individuals, so overall certainty was determined to be moderate, or 2. For people at increased meningococcal disease risk due to underlying medical conditions, indirectness was very serious as the studies included only healthy individuals, resulting in very low certainty of 4 for this group.

One study evaluated immune persistence. This study was conducted in children 4-5 years of age vaccinated 3 years earlier with MenACWY-TT compared with Nimenrix®, or MCV4-TT. For serogroups C, W, and Y, GMT ratios were greater than 1 showing higher GMTs 3 years after vaccination with MenACWY-TT than with the comparator. The GMT ratio for serogroup A was less than one. However, it is important to note that serogroup A is extremely rare in the US. This was a descriptive analysis so non-inferiority was not assessed. GRADing the evidence from this one study, the risk of bias was determined to be serious because fewer than 50% of the participants who received the primary vaccine dose were included in this follow-up persistence study. There was also serious concern for indirectness because the study was conducted in Finland in individuals vaccinated as toddlers, an age group for which MenACWY-TT is not approved in the US. Finally, there was a serious concern for imprecision because of the small number of participants. Overall, this brought the certainty to a very low certainty of 4 for healthy individuals. For the groups at increased risk due to underlying medical conditions, indirectness was considered very serious because the study included only healthy individuals, but overall certainty remains the same at 4.

In terms of the data from one study on co-administration with the routinely recommended adolescent vaccines HPV and Tdap, non-inferiority was demonstrated for HPV across all 4 included HPV types when comparing co-administration of MenACWY-TT, Tdap, and HPV

vaccines to co-administration of just Tdap and HPV. MenACWY-TT responses were also non-inferior when co-administered with Tdap and HPV compared to MenACWY-TT alone. For Tdap, non-inferiority was demonstrated for both tetanus and diphtheria antigens, and for the PT pertussis antigen, but not for the pertussis FHA, PRN, and FIM antigens.

Decreased immune response to the pertussis antigens included in Tdap was demonstrated in previous studies of co-administration of Tdap with other MenACWY vaccines<sup>1</sup>. GMC ratios for pertussis antigens were similar when comparing coadministration of Tdap with MenACWY-TT or with currently recommended MenACWY vaccines.<sup>2</sup> The clinical significance of these findings is unknown as there is no accepted correlate of protection for pertussis vaccines [<sup>1</sup>Gasparini et al. (2010) “Randomized Trial on the Safety, Tolerability, and Immunogenicity of MenACWY-CRM, an Investigational Quadrivalent Meningococcal Glycoconjugate Vaccine, Administered Concomitantly With a Combined Tetanus, Reduced Diphtheria, and Acellular Pertussis Vaccine in Adolescents and Young Adults”; <sup>2</sup>Weston et al. (2011) “Immunogenicity and Reactogenicity of Co-Administered Tetanus-Diphtheria-Acellular Pertussis (Tdap) and Tetravalent Meningococcal Conjugate (MCV4) Vaccines Compared to Their Separate Administration].

For GRADE, risk of bias in this one available study was classified as serious due to the reduced number of participants evaluated for HPV immunogenicity, for which no explanation could be identified from the published article. There were no serious concerns about indirectness or imprecision for healthy individuals, so overall certainty was a 2. For the groups at increased risk due to underlying medical conditions, indirectness was considered very serious based on the fact that studies included only healthy individuals, bringing the overall certainty to a 4.

While PCV13 is not a routine adolescent vaccine and therefore co-administration issues with this vaccine were not included as an outcome for GRADE, PCV13 is also recommended for individuals who are recommended to receive MenACWY because they have medical conditions that increase risk of meningococcal disease. One study assessed co-administration of MenACWY-TT and PCV13 in toddlers and no evidence was found of immune interference between these vaccines.

To summarize the GRADE assessment, for healthy individuals the WG rated the certainty of evidence as 1 for short-term immunogenicity, 4 for persistence, and 2 for co-administration of routine adolescent vaccines and SAEs. However, for people with medical conditions increasing their risk of meningococcal disease, the quality of evidence was rated as a 3 for short-term immunogenicity and 4 for the other outcomes.

Overall, the WG felt that the desirable effects outweigh the undesirable effects, favoring inclusion of MenACWY-TT as an option for MenACWY vaccination. For the values, acceptability, and feasibility sections of the EtR framework, the WG felt that the 86.6% vaccination coverage in 2018 for at least one dose of MenACWY vaccine<sup>1</sup> among adolescents demonstrates that the target population values and accepts this intervention and that it is feasible with current vaccination platforms. However, there are limited data on uptake among other individuals recommended to receive MenACWY vaccine such as microbiologists or individuals with medical conditions that increase meningococcal disease risk. It is not expected that values, acceptability, or feasibility would differ for MenACWY-TT compared with currently available meningococcal conjugate vaccines [<sup>1</sup>Walker TY, Elam-Evans LD, Yankey D, et al.

National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2018. *MMWR Morb Mortal Wkly Rep* 2019;68:718–723. DOI: <http://dx.doi.org/10.15585/mmwr.mm6833a2>].

For resource use, the manufacturer has indicated that the projected cost of MenACWY-TT will be within 5% of the cost of currently licensed and available MenACWY vaccines, so resource allocation will not be substantively affected by inclusion of MenACWY-TT as an option for MenACWY vaccination.

To summarize the EtR assessment, the WG felt that for the question of whether to include MenACWY-TT as an option for meningococcal ACWY vaccination, the problem was of public health importance. While the desirable anticipated effects are small, the undesirable ones are minimal therefore favoring intervention with a certainty of evidence that varies from high to very low across critical outcomes and populations recommended for vaccination. The WG believes that the target population does feel that the desirable effects outweigh undesirable effects with probably no important uncertainty or variability in how much people value the main outcomes, that the intervention is acceptable to key stakeholders, that it is a reasonable allocation of resources, and that it is feasible to implement.

Overall, it was felt that the desirable consequences probably outweigh undesirable consequences in most settings. The WG's interpretation was that there was sufficient information to include MenACWY-TT as an option for meningococcal ACWY vaccination according to currently recommended dosing and schedules. This would apply only for individuals aged 2 years and up, the ages for which the vaccine is licensed in the US. The WG was in agreement on this.

Of note, several of the current recommendations for use of MenACWY are off-label for all currently licensed MenACWY vaccines, including the 2-dose primary series for groups with specified underlying medical conditions; all booster doses among persons aged <15 years; and boosters beyond the first for individuals who are recommended to receive boosters every 3 to 5 years. For MenACWY-D and MenACWY-CRM, but not for MenACWY-TT, use in persons aged greater than 55 years is also off-label.

Implementation of MenACWY-TT as an option for MenACWY vaccination does not represent a change in policy or ACIP recommendations and therefore, no ACIP vote is required. However, a VFC vote and updated VFC resolution are required to include MenACWY-TT as an option in the VFC program.

### **Discussion Points**

Because MenACWY-TT is not approved for people less than 2 years of age who are at high risk, it will be very important moving forward to ensure that there continues to be a vaccine for children 2 months to 2 years of age.

Dr. Lee recognized and appreciated that the trials incorporated racial and ethnic diversity that was representative of the population. She expressed her hope that this would become the norm, but emphasized the importance of this in current and future conversations.

Dr. Sanchez expressed concern about the lower pertussis antibody titers for certain antigens as more pertussis disease and outbreaks are seen in the US. While there are no defined protective levels, he stressed the importance of studying this in the future.

Dr. Barnett (ISTM) pointed out that while serogroup A disease may be rare in the US, it is one of the most common for travelers. She wondered whether the WG expressed any concern about the lower GMT response for serogroup A.

Dr. McNamara clarified that the lower GMT response for serogroup A that she mentioned was specifically for the persistence study in which MenQuadfi™ was being compared with Nimenrix®, which is a vaccine that is not currently licensed in the US. In all of the studies assessing short-term immunogenicity, non-inferiority was demonstrated for immune response for MenQuadfi™ compared to the vaccines currently available in the US.

Given that MenQuadfi™ is conjugated to tetanus toxoid, Dr. Fryhofer (AMA) requested clarification as to whether this would affect receiving tetanus boosters and would provide any protection against tetanus.

Dr. McNamara clarified that the vaccine is licensed for protection against meningococcal disease, but she did not believe the ability of the vaccine to protect against tetanus has been assessed.

Dr. Robertson added that Sanofi Pasteur has taken the opportunity to assess anti-tetanus responses, which are on par with levels that would be considered seroprotective. However, the vaccine is not indicated for use in prevention of tetanus.

### **VFC Resolution Update: Meningococcal Vaccines**

**Frank Whitlatch  
Immunization Services Division  
National Center for Immunization and Respiratory Diseases  
Centers for Disease Control and Prevention**

Mr. Whitlatch indicated that the purpose of this presentation was to update the resolution to reflect currently available meningococcal conjugate vaccines that can be used to prevent meningococcal disease attributable to serogroups A, C, W, and Y. He pointed out that yellow font/highlight in the presentation was used to indicate changes to the resolution in comparison to the prior approved version.

No changes were made to the eligible groups for MenACWY:

#### **Eligible Groups**

- Children aged 2 months through 10 years who are at increased risk for meningococcal disease attributable to serogroups A, C, W, and Y, including:
  - Children who have persistent complement component deficiencies (including inherited or chronic deficiencies in C3, C5-C9, properdin, factor H, or factor D)

- Children taking a complement inhibitor (e.g., eculizumab [Soliris], ravulizumab [Ultomiris])
- Children who have anatomic or functional asplenia, including sickle cell disease
- Children infected with Human Immunodeficiency Virus (HIV)
- Children traveling to or residing in countries in which meningococcal disease is hyperendemic or epidemic, particularly if contact with local population will be prolonged
- Children identified to be at increased risk because of a meningococcal disease outbreak attributable to serogroups A, C, W, or Y
- All children aged 11 through 18 years

A new table was added to cover all vaccine types covered by this section of the resolution, which the previous resolution did not include:

**Meningococcal Conjugate Vaccines (MenACWY)**

Recommended Vaccination Schedule and Intervals

The table below lists meningococcal conjugate vaccines currently available to prevent meningococcal disease attributable to serogroups A, C, W, and Y.

Vaccine Type	Brand (1)	Age indication (pediatric)	Children at increased risk			Children not at increased risk
			2 m through 23 m	2y through 18 y	Booster Doses	
Men-ACWY-D	Menactra	9m - 18 y	Initiating at 9-23 m: 2 doses, 12 wks apart	For children with persistent complement deficiencies, complement inhibitor use*, functional or anatomic asplenia, or HIV: 2 doses, ≥8 wks apart  Other children at increased risk: 1 dose	For children who remain at increased risk and completed the primary dose or series at age:  ≤7y: additional dose 3 yrs after primary; boosters should be repeated every 5 y  ≥7y: additional dose 5 yrs after primary; boosters should be repeated every 5 y	Primary: 1 dose at age 11-12 (or 13-18 y if not vaccinated previously)  Booster: 1 dose at age 16 (if vaccinated at 11-12 y) or 1 dose at 16-18 y (if vaccinated at 13-15 y)
Men-ACWY-CRM	Menveo	2m - 18 y	Initiating at 2 m: 4 doses, at 2, 4, 6, and 12 m  Initiating at 7-23 m: 2 doses, 12 wks apart			
Men-ACWY-TT	MenQuadfi	2y - 18 y	Not indicated			

\*Includes eculizumab (Soliris) and ravulizumab (Ultomiris)  
(1) Use of brand names is not meant to preclude the use of other comparable US licensed vaccines

The Menactra® and Menveo® information reflects previously published ACIP recommendations, while the MenQuadfi™ information is new.

The recommended schedules and intervals for meningococcal conjugate vaccines have not changed and can be found at the following links:

- <http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf>
- <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6324a2.htm>
- <https://www.cdc.gov/mmwr/volumes/65/wr/mm6543a3.htm>

The recommended dosage and contraindications and precautions also have not changed:

Recommended dosage

Refer to product package inserts.



### Contraindications and Precautions

Contraindications and Precautions can be found in the package inserts available at <https://www.fda.g>

For serogroup B, the eligible groups have not changed:

### Eligible Groups

- Children aged 10 through 18 years at increased risk for serogroup B meningococcal disease, including:
  - Children who have persistent complement component deficiencies (including inherited or chronic deficiencies in C3, C5-C9, properdin, factor H, or factor D.
  - Children taking a complement inhibitor (e.g., eculizumab [Soliris], ravulizumab [Ultomiris])
  - Children who have anatomic or functional asplenia, including sickle cell disease
  - Children identified to be at increased risk because of a meningococcal disease outbreak attributable to serogroup B
  
- Children aged 16 through 18 years who are not at increased risk for serogroup B meningococcal disease may also be vaccinated

The recommended vaccination schedule and intervals have not changed:

## Serogroup B Meningococcal Vaccines (MenB)

### Recommended Vaccination Schedule and Intervals

Vaccine (1)	Age Group	Dosing Schedule (Primary Series)	Dosing Schedule (Booster Dose)
MenB-4C (Bexsero, GSK)	10–18 years	Two doses, at least one month apart (0 and ≥1 month schedule)	For children at increased risk due to complement deficiency, complement inhibitor use, or functional or anatomic asplenia: A booster dose is recommended if it has been at least one year since primary series; repeat every 2-3 years as long as risk remains.
MenB-FHbp (Trumenba, Pfizer)	10–18 years	Persons at increased risk for meningococcal disease including during serogroup B outbreaks: Three doses (0, 1-2, and 6 month schedule)  Adolescents who are not at increased risk for meningococcal disease: Two doses (0, 6 months) (2)	For children at increased risk due to a serogroup B outbreak: Booster dose recommended if it has been at least one year since primary series. If recommended by public health officials, booster dose may be given if it has been at least 6 months since primary series.  Booster doses are not recommended for adolescents who are not at increased risk for meningococcal disease.

1. Use of brand names is not meant to preclude the use of other comparable US licensed vaccines.
2. If the second dose is administered earlier than 6 months after the first dose, a third dose should be administered at least 4 months after the second dose.

The recommended dosage and contraindications and precautions have not changed:

Recommended dosage

Refer to product package inserts.

Contraindications and Precautions

Contraindications and Precautions can be found in the package inserts available at <https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states>

The statement regarding updates based on published documents has not changed:

[If an ACIP recommendation regarding meningococcal vaccination is published within 6 months following this resolution, the relevant language above (except in the eligible groups sections) will be replaced with the language in the recommendation and incorporated by reference to the publication URL.]

**Motion/Vote: VFC Resolution for Meningococcal Vaccines**

Dr. Szilagyi made a motion to approve the VFC Resolution as presented. Dr. Poehling seconded the motion. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

**14 Favored:** Atmar, Ault, Bahta, Bell, Bernstein, Frey, Hunter, Lee, McNally, Poehling, Romero, Sanchez, Szilagyi, Talbot  
**0 Opposed:** N/A  
**0 Abstained:** N/A

**Influenza**

**Introduction**

**Robert L. Atmar, MD**  
**Chair, Influenza Work Group**  
**Baylor College of Medicine**

Dr. Atmar reminded everyone that during the February 2020 ACIP meeting there was an overview of early 2019-2020 season influenza activity; a presentation of early season 2019-2020 influenza vaccine effectiveness (VE) estimates; a presentation from Seqirus™ on FLUAD® Quadrivalent that was licensed by the Food and Drug Administration (FDA) on February 21, 2020; and a presentation of safety data from a comparative randomized controlled trial (RCT) of high-dose and adjuvanted inactivated influenza vaccines among older adults.

Since that meeting, the WG has been discussing development of the proposed 2020-2021 ACIP influenza statement. The agenda for this session included presentations on 2019-2020 influenza activity, VE, and safety updates; and WG considerations and proposed 2020-2021 recommendations.

### **WG Considerations and Proposed Recommendations**

**Lisa Grohskopf, MD, MPH**  
**Influenza Division, CDC**  
**National Center for Immunization and Respiratory Diseases**  
**Centers for Disease Control and Prevention**

Dr. Grohskopf began with an update of 2019-2020 influenza activity. Starting with virologic surveillance, she reviewed the results of influenza positive tests reported to CDC weekly from US clinical and public health laboratories. Based on the clinical laboratories, influenza B viruses predominated early in the season, but with time, there was an increasing presence of influenza A viruses, such that by the season taken as a whole, identified specimens were roughly divided between influenza A and B viruses. There is more information with the public health laboratories, since they generally provide subtype and lineage. Overall, the predominant virus groups were H1N1pdm09 and B/Victoria. An additional point for the clinical laboratories, the percent of specimens that were positive was decreasing steeply from about week 8 through 12 or 14 of 2020.

Surveillance data for influenza-like illness (ILI) come from ILINet, a network of providers who report weekly the percent of outpatient visits that were for ILI. For the most recent season, 2019-2020, there was relatively high ILI activity from late December through February, with two separate peaks. Then there was a third peak. Because this is ILI, which uses a symptom- or syndromic-based definition rather than laboratory confirmation of influenza, other pathogens besides influenza could be involved. By the time of the third peak, it is known from other surveillance indicators that influenza was still circulating, but activity had already begun to fall pretty dramatically. It also is known that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) activity was increasing at that time and so it was assumed that the third peak was due in a large part to coronavirus disease 2019 (COVID-19) rather than influenza. In terms of influenza-associated hospitalizations based on data from FluSurv-net for cumulative hospitalization rates per 100,000 for laboratory-confirmed influenza, between October 1, 2019 and April 30, 2020, the cumulative hospitalization rate was approximately 69 per 100,000 population. This is considerably less than the pretty severe 2017-2018 season but was higher than recent non-pandemic seasons.

Mortality data from the National Center for Health Statistics (NCHS) come from death certificate diagnoses and are reported as the percent of deaths due to pneumonia- and influenza-coded diagnoses. These are diagnostic code data, not laboratory confirmed influenza. For the earlier part of the season, values were relatively low, but then there was a large peak in pneumonia and influenza deaths in the latter part of the season. This is thought to be largely due to COVID-19.

In terms of pediatric mortality associated with laboratory confirmed influenza, which has been reportable since 2004, there were 185 pediatric deaths reported to CDC for the 2019-2020 season as of the most recent reporting week. This is unfortunately fairly close to the 188 reported for 2017-2018. Among these deaths, 71 were associated with influenza A viruses and 114 were associated with influenza B viruses. In general, for the past number of seasons with these data, among those children who are eligible for vaccination and for whom vaccination information is available, the majority were not vaccinated. Generally, around 20% were vaccinated. Thus far with the available data for 2019-2020, it appears that approximately 20% were vaccinated.

For the past several seasons, CDC has published estimates of influenza burden in the US. The preliminary estimates cover the period between October 1, 2019 and April 4, 2020. The estimates are that there were between 39 million and 56 million influenza illnesses, between 18 million and 26 million influenza-associated medical visits, between 410,000 and 740,000 influenza-related hospitalizations, and between 24,000 and 62,000 influenza-related deaths.

The next estimates come from the US Flu VE Network. As a reminder, the US Flu VE Network is a network of 5 healthcare organizations for which the locations and Principal Investigators are as follows:

- Baylor Scott and White Health: Manju Gaglani
- Kaiser Permanente Washington: Mike Jackson & Lisa Jackson
- Marshfield Clinic Research Institute: Ed Belongia & Huong McLean
- University of Michigan: Arnold Monto & Emily Martin
- University of Pittsburgh: Rick Zimmerman & Tricia Nowalk

At these sites, the network enrolls outpatients  $\geq 6$  months of age with acute respiratory illness with cough of  $\leq 7$  days duration. Dates of enrollment are between October 29, 2019 through March 26, 2020. The network uses a test-negative design, which involves comparing vaccination odds among influenza reverse transcriptase polymerase chain reaction (RT-PCR) positive cases and RT-PCR negative controls. Vaccination status is defined as receipt of at least one dose of any 2019-2020 seasonal influenza vaccine according to medical records, immunization registries, and/or self-report. VE is calculated as  $(1 - \text{adjusted OR}) \times 100\%$ . Adjustments are made for study site, age, sex, self-rated general health status, race/Hispanic ethnicity, interval from onset to enrollment, and calendar time.

Regarding preliminary end-of-season 2019-2020 influenza VE from the US Flu VE Network as of June 9, a total of 8844 patients were enrolled. Of these, 2743 (31%) were RT-PCR positive and 6121 (69%) were RT-PCR negative. Among those who were PCR positive, the breakdown by influenza virus type, subtype, and lineage was that about half (51%) were influenza A(H1N1)pdm09; 44% were B Victoria; and relatively little were H3N2 and B/Yamagata viruses.

In terms of the preliminary VE estimates, estimated VE was 39% for any influenza, 31% for influenza A(H1N1)pdm09, and 44% for influenza B/Victoria overall across age groups. All of these estimates are statistically significant. Looking at VE against H1N1pdm09 viruses by age group, there was statistically significant VE of 45% among adults 50-64 years of age. The VE point estimate was a little lower at 38% for those aged 65 and older, with the lower limit of the

confidence interval here being 0. Estimated VE was lower in the 22% to 29% range for younger adults and for children was not statistically significant for either of the pediatric age groups. For influenza B/Victoria viruses, VE point estimates were similar across age groups in the 38% to 44% percent range and were statistically significant among children and young adults. They were not statistically significant for those 50 years of age and older.

In summary for this section, preliminary results for the 2019-2020 season indicate 39% (95%CI: 32, 45) VE against medically attended influenza. Vaccine provided important protection against influenza B viruses, given the severity of 2019-2020 season for children. Protection against A/H1N1pmd09 viruses was lower than previous seasons. Investigation of contributing factors for these results is ongoing. Finally, note that preliminary end-of-season estimates use best available information on vaccination status of the participants at the time presented. These estimates will be revised as data are finalized.

An end-of-season safety update is normally presented during June ACIP meetings, so Dr. Grohskopf presented data on the 2019-2020 season influenza vaccine safety. First, two disclaimers: 1) The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of CDC and FDA; and 2) The use of product trade names is for identification purposes only.

Beginning with a brief summary of 2019-2020 influenza vaccine safety surveillance, approximately 174.5 million doses of influenza vaccine were distributed in the US through February 28, 2020<sup>1</sup>. CDC and FDA analyzed spontaneous reports to the Vaccine Adverse Event Reporting System (VAERS). No new safety concerns were identified for any influenza vaccine types. In addition, CDC conducted near real-time sequential monitoring through Rapid Cycle Analysis (RCA) in the Vaccine Safety Datalink (VSD). Approximately 5.8 million doses of influenza vaccine were administered at VSD sites through March 7, 2020. No new safety concerns were identified for any influenza vaccine types in this analysis [<sup>1</sup>CDC Seasonal Influenza Vaccine Supply & Distribution: <https://www.cdc.gov/flu/prevent/vaccine-supply-distribution.htm>].

Dr. Grohskopf also presented information about a study in progress, the Clinical Immunization Safety Assessment (CISA) Project study of the safety of quadrivalent recombinant influenza vaccine (RIV4) versus quadrivalent inactivated influenza vaccine (IIV4) among pregnant women. This is a randomized observer- and participant-blinded clinical trial. The study population consists of pregnant women aged  $\geq 18$  years who are at gestational age  $\leq 34$  weeks at the time of vaccination. Participants are randomized 1:1 to receive RIV4 (Flublok<sup>®</sup> Quadrivalent) or IIV4 (Flulaval<sup>®</sup> Quadrivalent). Maternal and infant safety outcomes are collected from enrollment through 90 days postpartum and local and systemic reaction data are collected from vaccination day through Day 8 after vaccination. Blood is collected at baseline and 28 days after vaccination for immunogenicity assessment. Participants are being enrolled from 3 sites during the 2019-2020 and 2020-2021 influenza seasons, with a total goal of 430 participants. To date, this study has enrolled and randomized 233 participants during the 2019-2020 season. A safety review was held in which a panel of three medical experts who are not study investigators reviewed the interim safety data for serious adverse events (SAEs). Each panel member concluded there were no substantial safety concerns observed. The current plan

is to continue enrollment in 2020-2021 influenza season. More information will be presented on this study at a later meeting.

Turning to WG considerations and the proposed 2020-2021 recommendations, Dr. Grohskopf outlined the proposed changes to the influenza statement for the 2020-2021 season. The core recommendation is unchanged. Annual influenza vaccination is recommended for all persons 6 months of age and older who do not have contraindications. There are two primary updates to the recommendations: 1) the US influenza vaccine viral composition, which has been updated for 2020-2021; and 2) inclusion of two recently licensed vaccines, Fluzone<sup>®</sup> High-Dose Quadrivalent and Fluad<sup>®</sup> Quadrivalent.

With regard to vaccine composition for 2020-2021, there have been updates to the influenza A(H1N1)pdm09, influenza A(H3N2), and influenza B/Victoria components. The B/Yamagata component is the same as last season. Note that for this season, a different composition is specified for egg-based versus non-egg-based vaccines, at least for influenza A viruses. These are not actually distinctly different vaccine compositions. For several years, FDA has specified different reference strains for egg- versus cell-based vaccines. It is just being explicitly stated now. Generally, the viruses are referred to as pdm09-like viruses and H3N2-like viruses. For any particular target virus that is desired to target for the coming seasons, there are several possibilities for suitable viruses. That is reflected here:

Egg-based influenza vaccines will contain hemagglutinin derived from:

- an A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like virus;
- an A/Hong Kong/2671/2019 (H3N2)-like virus;
- a B/Washington/02/2019 (Victoria lineage)-like virus; and
- (for quadrivalent vaccines) a B/Phuket/3073/2013 (Yamagata lineage)-like virus.

Non-egg-based influenza vaccines will contain hemagglutinin derived from:

- an A/Hawaii/70/2019 (H1N1)pdm09-like virus;
- an A/Hong Kong/45/2019 (H3N2)-like virus;
- a B/Washington/02/2019 (Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (Yamagata lineage)-like virus.

The second primary update is that there are two new influenza vaccines that were licensed after the publication of the 2019-2020 statement, which are expected to be available for the first time during 2020-2021. First, in November 2019, the FDA licensed Fluzone<sup>®</sup> High-Dose Quadrivalent from Sanofi Pasteur for ages 65 years and older. Like the previous trivalent high-dose vaccine, this vaccine contains 60 micrograms of hemagglutinin per vaccine virus for a total of 240 micrograms in a 0.7 milliliter dose. The 0.7 milliliter dose volume is slightly higher than that for all other injectable vaccines, including the previous trivalent version of Fluzone<sup>®</sup> High-Dose, which is 0.5 milliliters. This vaccine will replace the previous trivalent Fluzone<sup>®</sup> High-Dose for 2020-2021. Pre-licensure data were presented to the ACIP in October 2019. In February 2020, the FDA licensed Fluad<sup>®</sup> Quadrivalent from Seqirus<sup>™</sup> for persons ages 65 years and older. This vaccine contains MF59 adjuvant similarly to the previously licensed trivalent formulation of Fluad<sup>®</sup>. Pre-licensure data were presented to the ACIP in February 2020.

There are several other notable changes and clarifications. First, in the Contraindications and Precautions table (Table 2), the text of the header which previously read “Contraindications and conditions for which use is not recommended” has been changed to “Contraindications.” The original header reflected the fact that for one of the vaccines, live attenuated influenza vaccine 4 (LAIV4), there are some labeled contraindications that are listed in the package insert, and others which are not labeled contraindications but instead are situations in which ACIP recommends that LAIV4 not be used. However, following discussion of this issue in the context of the adult and pediatric schedules at the October 2019 ACIP meeting and ensuing WG discussions, the WG consensus was that it was clearer to simply to call these “Contraindications” in the table. The text of the document provides more detail concerning which contraindications are labeled contraindications in the package insert, and which are ACIP recommended contraindications.

There is another change to the contraindications and precautions table, which involves use of LAIV4 in specific populations: those with cochlear implants, active cerebrospinal fluid (CSF) leaks, and anatomic or functional asplenia. The text previously indicated in the section on vaccination of immunocompromised persons that vaccines other than LAIV4 should be used in these populations. The basis for this was the fact that LAIV4 is a live vaccine, the lack of data on use of LAIV4 in these groups, and the availability of alternative vaccines. These conditions were not explicitly listed separately in the contraindications table, however. The WG recently revisited this issue. To help inform this WG discussion, the Immunization Safety Office (ISO) conducted a targeted review in VAERS for LAIV-related reports in populations with asplenia or sickle cell disease and those with CSF leak or cochlear implant. As a reminder, VAERS is the US spontaneous reporting surveillance system which has been operating since 1990 and is co-managed by CDC and FDA. VAERS receives AE reports from manufacturers, medical providers, vaccine recipients, and the general public.

In a review of primary US reports between July 1990 and March 16, 2020, the vaccines included were LAIV (whether monovalent, trivalent or quadrivalent) with or without other vaccines. There were no age restrictions. Search methods used included Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and text string search. This search yielded two reports related to asplenia or sickle cell disease. For sickle cell disease, there was 1 non-serious report in a child. For asplenia/splenectomy, there was 1 death report in an adult. There were 3 reports related to cochlear implant, all non-serious reports in children. There were no reports for CSF leaks. In addition, a literature search developed with a librarian using terms based on “influenza vaccine” and “Cochlear implant,” “cerebrospinal fluid leak,” “CSF leak,” “anatomic asplenia,” “functional asplenia,” or “sickle-cell anemia” was performed. This yielded 141 citations, but no data related to use of LAIV in these populations. In WG discussions, it was noted that there are insufficient data reflecting use of LAIV4 in these populations. There are also alternative influenza vaccines available. In the proposed document, these conditions have been added to the list of contraindications for LAIV4 specifically in the table.

The last update concerns use of influenza antivirals and LAIV4. The statement has for several years previously indicated that use of influenza antivirals from 48 hours before to 2 weeks after administration of LAIV4 may interfere with the effectiveness of vaccine, since LAIV4 contains live virus that must replicate in the nasopharynx. This time interval is noted in the package insert for LAIV4. However, the newer antivirals peramivir and baloxavir have longer half-lives than

oseltamivir and zanamivir. Unfortunately, insufficient data are available concerning use of LAIV in the setting of influenza antiviral use. It is unknown whether and to what extent interference with the vaccine might occur. However, it seems biologically plausible that interference could occur. In discussion of these issues within the WG, the following was proposed. Based on the half-lives of the antivirals, and assuming a minimum of 5 half-lives after the last dose being needed for adequate washout of antiviral, language has been added indicating that it is prudent to assume interference might be possible if antivirals are administered within these intervals:

Antiviral	Interval
Oseltamivir and Zanamivir	48 hours before to 2 weeks after LAIV4
Peramivir	5 days before to 2 weeks after LAIV4
Baloxavir	17 days before to 2 weeks after LAIV4

Language concerning persons with a history of severe allergic reaction to egg (e.g., having had any symptom other than hives after egg ingestion) has been updated to reflect availability of two egg-free vaccines, the cell-culture based inactivated vaccine (ccIIV4) and the recombinant influenza vaccine (RIV4). For the last several seasons for individuals with a history of severe reaction to egg, the language has specified that those individuals should be vaccinated in a medical setting under the supervision of a health care provider who is able to recognize and manage severe allergic reactions. However, this season that language has been updated to indicate that for these individuals, these conditions hold if a vaccine other than ccIIV4 or RIV4 is used.

To summarize the proposed changes, principal changes include the 2020-2021 US influenza vaccine composition and inclusion of Fluzone® High-Dose quadrivalent and Fluad® Quadrivalent for adults aged 65 years and older. Other changes include that Table 2 now says “Contraindications” rather than “Contraindications and conditions for which use is not recommended.” Asplenia, cochlear implant, and active CSF leak are included as contraindications in Table 2. There is updated guidance concerning LAIV4 and influenza antivirals based on half-lives of the various agents. Updated language is included concerning vaccination of persons with egg allergy to reflect availability of egg-free vaccines.

### **Discussion Points**

Referring to Slide 16, Dr. Lee observed that there were higher estimates noted against H1N1pdm09 in adults 50 years of age and older. Given the age differences noted, she wondered whether prior receipt of influenza vaccine was assessed as a potential reason for those differences.

Dr. Grohskopf indicated that she did not have that information at this time. In a number of previous seasons, the Flu VE Network has managed to perform analysis assessing various seasons of prior vaccination history. She anticipated that they might do the same in the future and recognized this as an important question.

Dr. Szilagyi asked whether there is any updated information on LAIV use in the Flu VE Network data. He also noted that there was a difference in VE for influenza A versus B among children for both age groups with confidence intervals just barely crossing 0. He suggested that it may be



helpful in future presentations to show the VE for the combination for all influenza. Looking at the point estimates and confidence intervals, he felt sure there would be significant VE for children for both age groups if combined. Related to that overall VE, he thought it was always worth emphasizing that a VE of almost 40% means a reduction of 40% of outpatient influenza patient medically attended visits. Although lower than hoped, it is a significant reduction in morbidity due to influenza vaccine.

Dr. Grohskopf indicated that there has not been a lot of use of LAIV within the Flu VE Network facilities within the last couple of seasons. She did not think that had changed for this season, but perhaps they will know more when those data and previous receipt history are finalized. She will take the comment regarding the depiction of the VE data back to the VE group.

Dr. Bernstein asked what plans might be in place for assessing influenza and SARS-CoV2 in the Southern Hemisphere and how that might help the Northern Hemisphere.

Dr. Grohskopf recognized this as an excellent question but was not aware of any specific plans at this point. She indicated that she would seek more information about that to provide later.

Dr. Bahta expressed an interest in some of the patterns in the Spring as H1N1pdm09 was rising followed by such a precipitous fall, and wondered whether that was a decrease that was related to people ceasing testing because they were testing for COVID-19 instead or if it was a true rapid decline.

Dr. Grohskopf said it was difficult to discern. It could be a combination of variables. By the time influenza activity began to decrease, that would not have been an atypical period of time necessarily for influenza activity to fall. The peak did seem to be running from about late December into February. It would not be uncommon to see that kind of a drop, although the point is well taken that it looks somewhat precipitous. It is difficult to say what the testing patterns were during that period of time.

Dr. Sanchez suggested that comments be added at least with regard to CSF leak and Cochlear implants that data are insufficient. When providers see the contraindication, there will be heightened concern if given inadvertently. Perhaps this could be reflected in a footnote.

Dr. Kimberlin (AAP) agreed with Dr. Sanchez, emphasizing that 2 reports of asplenia or sickle cell disease and 3 reports of CSF leak and Cochlear implants in VAER hardly seemed sufficient to warrant a contraindication. At the very least, mention should be made of the weakness or the lack of data would be warranted and that this recommendation is being made out of an abundance of caution or something to that effect.

Dr. Grohskopf pointed out that it is not directly noted in the table. It is noted in the text, but perhaps consideration could be given to adding a footnote to the table. That is more or less the tenor of the recommendation. There is not much in VAERS and the recommendation is largely based on the fact that there are alternative vaccines and some biologically plausible issues to be concerned about. The other issue that has to be considered is the Table of Contraindications should be as simple, direct, and easy to interpret as possible in that table which is a point that

was raised during the October 2019 meeting. This was the best compromise the WG could come up with.

Regarding the sudden decline in influenza, Dr. Hunter wondered at the end of the season whether that was coincident with the implementation of social distancing as COVID-19 was getting started. It would be nice to know whether approaching seasonal influenza with targeted physical distancing for a limited amount of time every season might be considered for inclusion in influenza recommendations in the future.

Dr. Grohskopf said that could be plausible. The data in that network are national and things were different in various parts of the country with regard to the activity.

Dr. Atmar noted that the slide showing the decline also had a line showing the percent positive, which decreased precipitously at the same time the number of isolates decreased. He thought it was real. Anecdotally, one of his colleagues in Houston who does a lot of viral diagnostics and surveillance noted a precipitous change in the identification of all respiratory viruses as physical distancing was rolled out in their community. This probably was not unique to influenza and at least in the Houston area may have been associated with the social distancing measures instituted to try to limit the spread of COVID-19.

Given the next wave of COVID-19 anticipated in the Fall, Dr. Quach (NACI) wondered whether the ACIP Influenza WG was anticipating any changes in the vaccination administration program.

Dr. Cohn indicated that there would be an update later in the day on the influenza program implementation plans for the Fall during the COVID session.

Dr. O'Leary (PIDS) inquired as to why they continued to use the language "egg allergy" when there is accumulating evidence that shows individuals who are severely allergic to eggs are not at higher risk of anaphylaxis than the general population. He sees that as a barrier to influenza vaccination if primary care practitioners feel like they cannot administer the vaccine in their office and have to send those children to an allergist. The language is essentially identical to the language in the General Recommendations on immunization. All immunizing providers are supposed to be able to handle anaphylactic reactions. Calling out non-egg cell-based vaccines is creating an exception for those vaccines where there are no exceptions for any other vaccines to his knowledge.

Dr. Grohskopf responded that this is a topic that has been discussed for the past several years. There are existing and increasing data indicating that severe allergic reactions are unlikely. However, the current incarnation of the language before this recent change arose out of an abundance of caution, and some concern during an ACIP meeting where that language was developed and refined, that there may be settings as increasingly more people are getting vaccinated outside of their medical home, where it is possible that adequate equipment and/or personnel might not be available. The WG's thinking is more or less that it is already reasonably permissive as far as location of where to vaccinate. With regard to having exceptionalism for cclIV and RIV4, it seemed to make sense at this point that that should be noted since those vaccines are egg-free. The WG will continue to revisit this with the reviews at some point in the near future. They also continue to follow this in VAERS. They began looking at this for the

annual safety update in VAERS since the initial season after the recommendations changed to be more permissive. There have been some isolated incidences of people with a history of egg allergy who have had reactions. It is important to note that cclIV and RIV4 are not going to be for everybody. Egg allergy tends to be more of an issue in the pediatric population. RIV4 is licensed for persons 18 years of age and older and cclIV is for persons 4 years of age and up.

Dr. Fryhofer (AMA) said that speaking as a general interest in practice who sees patients, she greatly appreciates ACIP being very cautious in its recommendations, especially this year. With COVID-19 and trying to get patients immunized, influenza vaccines are likely to be given perhaps in some non-traditional locations. She appreciates erring on the side of caution to make influenza vaccination clinics as safe as possible. She thought the proposed wording would be helpful for clinicians and would keep everyone safe.

Dr. Bernstein asked whether Sanofi would make clear that the multi-dose vial should be used only for 10 doses of 0.25 ml and not more since the pre-filled 0.25 ml product will not be available this coming influenza season.

Dr. Rizzo (Sanofi Pasteur) indicated that he would follow up and report back later in the day.

Reflecting on what Drs. Sanchez and Kimberlin said about the wording, Dr. Lee thought it would be helpful to clarify how ACIP is defining “contraindication” specifically because if no other vaccines were available, the benefits might outweigh the risks of vaccination with LAIV for those who are asplenic or may have CSF leaks since there are no additional data to suggest harm. Another way to think about it is as a precaution, which is not their typical language for a preferential recommendation. That would reflect the consensus of the group without confusing people about the intent of the recommendation.

#### **Motion/Vote: Changes to the ACIP Statement for Influenza Vaccines**

Dr. Bell motioned to accept the changes recommended to the ACIP Statement for the 2020-2021 influenza season. Dr. Atmar seconded the motion. No COIs were declared. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

**14 Favored:** Atmar, Ault, Bahta, Bell, Bernstein, Frey, Hunter, Lee, McNally, Poehling, Romero, Sanchez, Szilagyi, Talbot  
**0 Opposed:** N/A  
**0 Abstained:** N/A

## Coronavirus Disease 2019 (COVID-19)

### Overview of COVID-19 Disease

**John T. Brooks, MD**  
**Chief Medical Officer, Division of HIV/AIDS Prevention**  
**Acting Chief Medical Officer, COVID-19 Response**  
**National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention**  
**Centers for Disease Control and Prevention**

Dr. Brooks noted that while he would not go over all of the slides during this presentation, they were provided in the materials and that ACIP members could reach out later with any questions they may have about those.

In terms of the basic structure, *Coronavirinae* is a single-stranded ribonucleic acid (RNA) virus with a genome of about 25 to 32 kilobases, which is relatively large among these types of viruses. Key about the structure is that it is composed of four principal proteins that all are required to produce a structurally complete viral particle. The most important of these is the spike protein that is on the outside of the virus. Inside the virus is the RNA genome surrounded by a nucleocapsid, the membrane protein, and the envelope protein.

*Coronaviridae/-virinae* belong to the order Nidovirales. Nido comes from the Latin word for nest and refers to a hallmark of Nidovirus transcription, also seen in all coronaviruses with the synthesis of the three prime co-terminals in a nested set of messenger RNA (mRNA). It is important to emphasize that coronaviruses comprise a very large family of viruses that infect a wide variety of mammals and birds. They are divided into 4 genera: Alpha-CoV, Beta-CoV, Gamma-CoV, and Delta-CoV. The alphas and betas infect mostly mammals, but these are the 2 genera that cause human disease. They also have been isolated from many land mammals, as well as those that fly like bats and those that swim like beluga whales. The gammas and deltas mostly infect birds and have been isolated from birds across an entire spectrum of size from sparrows to ostriches. CoVs cause a variety of lethal diseases in mammals and birds and for those reasons have been well-studied due to impact on the agricultural sector where they cause fatal illness in herds and flocks, usually in the form of respiratory or enteric illness.

There are 7 known human coronaviruses (HCoVs), 4 of which are generally the cause of mild illness such as upper respiratory disease like the common cold and 3 of which are all serious pathogens that can cause lethal disease:

#### Common HCoVs (Lower Pathogenicity)

- HCoV-229E (alpha)
- HCoV-NL63 (alpha)
- HCoV-OC43 (beta)
- HCoV-HKU1 (beta)

### Other HCoV (Higher Pathogenicity)

- SARS-CoV-1 (beta) (the cause of the 2003 SARS)
- MERS-CoV (beta) (the cause of sporadic clusters of MERS)
- SARS-CoV-2 (beta) (the cause of 2019 pandemic)

It is important to understand that the term “COVID-19” describes the illness that is caused by the virus SARS-CoV-2.

In terms of transmission, COVID-19 appears to have first been recognized as a human illness late in 2019. It is not known exactly when, how, or whether the virus arose. It is believed to represent a cross-species transmission from an animal reservoir, very likely bats, that may have involved an intermediary host like its cousins SARS-CoV-1 and MERS-CoV-2 that may have used the palm civet and dromedary camels as intermediary hosts. That is entirely speculative at this time. Even during the earlier phase of the recognized COVID-19 outbreak in the early weeks of January 2020, more than 35% of diagnosed persons did not report a known exposure to the market where the outbreak was believed to have started. It may be that this market was simply a location that amplified a virus that already was circulating in the community. COVID-19 had been confirmed in nearly every province of mainland China by mid-January 2020, with the greatest number of cases in Hubei centered within the province’s capital in the most populous city of Wuhan.

The spread of COVID-19 was limited mostly to China early in the epidemic, with two large increases in mid-January related to a change in the Chinese case definition. As of February 25, 2020, the daily number of new cases outside of China exceeded those within China. As of March 4, 2020, the number of daily deaths from COVID-19 outside China exceeded those within China. After a brief pause following resolution of the original outbreak in China, COVID-19 spread rapidly worldwide beginning in early March. By that point, COVID-19 had been reported basically everywhere in the world except for a few island nations, Antarctica, and the International Space Station. Unfortunately, new diagnoses are continuing to accelerate with a large expansion presently occurring in the Americas. It is important to note that the most recent high peak in daily number was 188,000 in the last 24 hours. That number exceeded in one day the total 115,000 cases reported worldwide during the 6-week period that China responded to their outbreak. This is moving at a quick pace.

Despite the close genetic relatedness of SARS-CoV-1 and SARS-CoV-2, this new SARS-CoV-2 differs from both SARS-CoV-1 and MERS-CoV in two very important ways. First, although the incubation periods are about the same, the serial interval for SARS-CoV-2 is shorter than its incubation period. This means that infected persons can be infectious to others and transmit the virus before they develop symptoms. That has not been observed for SARS-CoV-1 and MERS-CoV. In fact, it has now been observed that SARS-CoV-2 infectious risk peaks in the few days before symptoms onset and shortly thereafter. Second, it also is now known that a substantial fraction of infected persons, estimated to be about 30% to 35%, never develop illness and remain asymptomatic. Unfortunately, these asymptotically infected people can transmit the infection to others. How infectious they are to others compared to symptomatic patients is still being worked out.

In terms of what is known about which body fluids carry and can transmit SARS-CoV-2, it is very clear that infections are transmitted through exposure to respiratory particles. Although viral RNA can be readily detected in stool, efforts to isolate the virus by culture have been remarkably unsuccessful with only 2 reports suggesting possible isolation of live virus and many reports of failed attempts. Thus, if stool is a mode of transmission, it has not yet been confirmed epidemiologically. Urine, blood, and other fluids to which infants might be exposed during birth reassuringly have not been shown to contain infectious virus. Curiously, detection of RNA has been confirmed in semen, but only in men during the peak of illness. After recovery, RNA no longer appears to be present and neither isolation of live virus nor sexual transmission of SARS-CoV-2 have been reported.

People often ask how far SARS-CoV-2 can travel. There is very strong evidence that this is transmitted like other respiratory viruses through respiratory droplets and other particles to which persons are exposed in close proximity to a source patient at about 6 feet or 2 meters. Small aerosolized particles comprise a large fraction of what comes out of our mouths when we speak. Although when we shout and sing, the particles do get larger. Under highly controlled experimental conditions, virus has been demonstrated to exist for hours in small aerosolized particles. However, there is no compelling epidemiologic evidence at this time that airborne transmission outside of the 6-foot respiratory droplet zone is a substantial risk for spread of virus. Examples of transmission have not been seen across large spaces such as in restaurants or theaters, or infection in people whose only exposure was passing through the same space where an infected person had lingered but was no longer present, or transmission through air handling systems such as in office spaces or cruise ships. On the contrary, SARS-CoV-2 likes ventilation. Ventilation is one's best friend with this virus because it substantially reduces the risk of infection.

Regarding how humans respond clinically to COVID-19, viral burden declines steadily after illness onset. Whether a sample is respiratory or stool, the quantity of viral RNA is highest at illness onset and decreases steadily thereafter. As viral burden declines, the ability to recover live virus from human samples by culture becomes more difficult. After 8-10 days, replication-competent virus can no longer be recovered from respiratory tract specimens based on a number of studies in otherwise healthy persons with mild to moderate illness. A recent study suggests that in severely ill and immunocompromised persons (from organ or bone marrow transplant), shedding of culturable virus may persist up to 20 days. Within days after symptom onset and as viral burden and recovery of culturable virus decline, patients begin to develop a serologic response to infection that includes IgM, IgG, and IgA. The IgG response includes neutralizing antibodies.

In addition to a time limitation of detection of live virus and infectiousness, it also is evident that ability to culture the virus from specimens declines with decreasing viral burden. It is remarkable how across a number of studies examining how long virus can be cultured, there is almost universally some threshold of viral burden below which virus is no longer able to be recovered, usually at the range of a cycle threshold (Ct) of about 30 to 35. This also depends a lot on the primers and polymerase chain reaction (PCR) set-up being used, which differ between laboratories. The point is that there is a viral burden below which there is no evidence that the virus can be cultured. Very interesting and novel for this virus is that it has been shown and widely observed that viral RNA can be detected by PCR and remain positive for weeks long

after a person has fully recovered from illness and after people are believed no longer to be infectious. To date, the longest persistent positive has been documented out to 12 weeks or 83 days.

As noted earlier, this phenomenon was not observed with SARS-CoV-1 or MERS-CoV and has created a substantial problem for patients for whom isolation is discontinued or transmission precautions are removed based on a test-based strategy using PCR testing. Clinicians are increasingly managing patients who cannot leave the hospital, cannot return to work, or cannot return to other activities or a new normal of life because they are stuck in what Dr. Brooks is calling “persistent PCR purgatory.” He reassured everyone that CDC is actively working toward reviewing all of the available data and anticipate that they shortly will amend the current test-based strategy that requires 2 consecutive negatives to remove precautions.

Regarding the clinical epidemiology of this illness, early data from reports of hospitalized patients in different parts of China show that more than 80% developed fever during illness and over half developed cough, about 25% developed myalgia or arthralgia, and a small fraction in the 10% to 20% range had headache or diarrhea. Most people present with some acute or acute onset of cough and fever. Fever may be measurable at presentation, although many people describe a prodrome of feeling feverish but do not have a measured fever. At presentation, only 44% of people in one study had a measurable fever. Most will go on to develop a fever. There are some interesting reports of patients who presented first with gastrointestinal illness (GI) of abdominal discomfort and diarrhea that preceded the development of cough and fever by a day or two.

There is no particular set of signs, symptoms, or other related clinical findings that can reliably discriminate COVID-19 from other respiratory viral illnesses such as influenza at this time. One very interesting aspect of COVID-19 that has been of relatively high frequency are anosmia and dysgeusia or any other change in their sense of smell or taste. Sometimes, this has been the only symptom of illness. The frequencies ranged from 30% to as high as 70% in one Italian cohort. When present, this can be highly predictive of infection if SARS-CoV-2 is circulating in the community. Most people will recover spontaneously with supportive care. For those who do not, the typical complications are like those seem with other viral respiratory infections (e.g., pneumonia, respiratory failure, multi-organ system failure, and death).

Concerning the severity of illness in adults versus children from 2 large early studies in China, in general most (80.9%) adults who were symptomatic experienced mild illness and recovered without complications. However, there was a very substantial fraction who developed severe (13.8%) or critical (4.7%) illness. Among those with critical illness, about half died. In contrast, the disease was considerably less severe in children. In this cohort, less than 5% developed critical or severe disease during infection. A very large fraction (12.9%) were asymptotically infected. It is important to note that these studies were conducted before the true frequency with which infections remain asymptomatic was known. It also is now known that with increasing age, infection is less likely to be asymptomatic, the peak viral burden that a person experiences is likely to be higher, and the duration of RNA shedding appears to be longer.

In terms of high-risk groups, certain underlying medical conditions (e.g., cardiovascular disease, diabetes, chronic respiratory disease) and advancing age increase the risk for severe illness and death. Once people are over 40 to 50 years of age, there is a steady increase in the case

fatality rate. The fraction of persons who die is probably related to the age structure of the population. The higher the average age, the larger the case fatality rate. Reassuringly, emerging data for immunocompromised persons seem pretty good right now. For persons with human immunodeficiency virus (HIV), there has not been a strong signal of risk in this country. However, it is expected that people with a low CD4 cell count or who are not virally suppressed could fair worse. Likewise, there is no definitive evidence that cancer therapy worsens outcomes, including immunosuppressive cancer therapy.

There are some extraordinarily unique and troublesome complications of COVID-19. The first is that this infection seems to cause a diffuse endotheliitis in which a viral tropism infects the endothelial cells that line the arteries and veins and causes inflammatory cell injury and death. This is seen across many different tissues in autopsy series. Second is a problem with hypercoagulability that has been observed in vessels of all sizes in veins and venules predominantly, but arteries, arterials, and capillaries as well. Autopsy examinations have demonstrated that clots include both those that form locally within a vessel and clots that may have traveled into a vein as a thromboembolism. Of particular concern are pulmonary thromboemboli. Two autopsy series have shown that despite aggressive anticoagulation, this was almost universal in 24 patients and was deemed by the pathologist as contributory or as a likely cause of death, but was not recognized in life. Also of interest in terms of thinking about a vaccine are peri- and post-infectious hyperimmune reactions. In adults, one of the most severe is myocarditis with ST-elevation myocardial infarction (STEMI) without coronary artery blockage. It appears that the rise in enzymes is from a diffuse injury to the entire heart muscle. In children, multiorgan inflammatory syndrome (MIS-C) has occurred about a month after exposure or infection that looks somewhat like Kawasaki disease but is very distinct from it.

In closing, Dr. Brooks briefly discussed what is known about SARS-CoV-2 and influenza co-infection based on data from a study in Wuhan involving 307 patients. These data were collected in January and February 2020, which is typically the peak of influenza in the Northern Hemisphere. Diagnoses were made by assay and influenza IgM. These patients were from a single hospital and fell into 3 groups: SARS-CoV-2 alone (42.7%), SARS-CoV-2 + Influenza A (49.8%), and SARS-CoV-2 + Influenza B (7.5%). There were no significant differences in these 3 groups in terms of age (median 50s to 60s), sex distribution (equal men and women), or illness severity at presentation. Although the number of co-infections with influenza B was small as would be expected in a typical influenza season, the patients who were co-infected with influenza B died at 5 to 6 times higher percentage (30.4%) than either those who had SARS-CoV-2 alone (7.6%) or SARS-CoV-2 + Influenza A (5.9%). In this study, the influenza B co-infections were mostly concentrated in the first 2 weeks of January. There is the possibility that what is being observed here is people learning how to better manage COVID-19, with patients succumbing to COVID-19 rather than to the co-infection. However, if that were the case, the SARS-CoV-2 alone infections would have been expected to have had a somewhat higher percentage of death. Nevertheless, this is a very important warning to pay attention to and emphasizes the importance of getting an influenza vaccination.



While the current trends are disarming, this is what is known about SARS-CoV-2. First, this infection is nothing like influenza. Second, this virus is not like any human coronavirus seen before. Third, it is causing a unique, serious, and very disturbing set of clinical and epidemiologic problems that Dr. Brooks did not think anyone ever would have expected. Simply put, this is an entirely new and very bad disease. That is why a vaccine or some other form of effective preventive therapy is urgently needed. He wished the ACIP the very best.

### **Discussion Points**

Dr. Romero asked whether there is now a better estimate of the percentage of children with asymptomatic infection and whether anything is known about their viral loads during the acute infectious period as compared to adults.

Dr. Brooks said that in terms of the frequency with which children appear to become infected, most reports seem to show that when children are equally exposed to adults, the incidence of infection may be somewhat lower in children. However, that has not been the case universally. Some studies have suggested that the frequency may be the same, but a lot of reports suggest that children may be less prone to infection or if infected, less likely to test positive by PCR. He did not know the answer to viral load or time to resolution of PCR positivity.

Dr. Drees (SHAE) noted that early on, it was only possible to obtain a COVID-19 test if someone tested negative for influenza. Because influenza positivity rates declined precipitously, some facilities stopped testing for influenza and converted to COVID-19 testing. However, it seems that little is known about how common co-infections are occurring in this country and there has been some presumption that this is uncommon.

Dr. Brooks said that part of this is a function of timing in that influenza season was beginning to decline as COVID-19 pandemic in this country began to grow. In terms of the Chinese data, he did not expect that they would see this level of co-infection. He thought perhaps China was at the peak of their influenza epidemic and COVID-19 stepped in, creating a lot more opportunity for co-infection. He did not want to discount the possibility that co-infection exists at all. CDC's laboratory is currently developing a multiplex PCR test for influenza A, influenza B, and COVID-19. Hopefully, that will provide a much better perspective on the frequency with which co-infection occurs and enable monitoring of clinical outcomes.

Dr. Poehling asked whether Dr. Brooks has any data from China about co-infection with respiratory syncytial virus (RSV).

Dr. Brooks did not have this information readily available but added this to his follow-up list.

## **Immune Responses to SARS-CoV-2 Infections**

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Dr. Thornburg presented on what is known about immunity to coronaviruses in general, what is known so far about SARS-CoV-2 immunity, testing for immune responses, and updates on recently published data on severity of disease versus antibody response and antibody kinetics.

The various types of coronaviruses can be divided broadly into common coronaviruses that cause colds (229E, NL63, OC43, HKU1) and uncommon coronaviruses (SARS-1 and MERS). SARS-1 is no longer circulating, while MERS is circulating in a very limited form.

It is difficult to extrapolate what is known about SARS-1 and MERS to immunity about SARS-CoV-2 because they are so rare. It may be necessary to take note on what is known about the common CoVs, although it is not a lot. It is known that there is protection in common CoV infections, but it can be transient and waning serum neutralizing antibodies may contribute to susceptibility to reinfection. A study was conducted on a 229E human challenge model in the late 1980s and early 1990s by Callow et al. In this study, 15 volunteers were inoculated with HCoV-229E and challenged. The 10 volunteers with lower antibody titers became infected and only 8 of them developed colds. Presumably, these were all adult volunteers, so they probably had baseline serum antibody titers and cellular immunity against the virus. On re-challenge a year later, 9 of the 10 individuals who became infected became re-infected as assayed by virus shedding. However, none of them developed a cold. It seems like even if they did not have sterilizing immunity, many of them had some immunity that protected against symptoms. A household transmission study was published by Kiyuka et al in 2018. This study found that 2.5% of household members had an NL-63 infection. Most household subjects had only one infection in the 6-month study. The investigators looked for repeat infections of all of the common coronaviruses and found repeat infections with NL-63 (21%), OC43 (5.7%), and 229E (4%). Those were all more than 90 days apart, so there was at least short-term protection against reinfection. A minority of the repeat infections exhibited higher viral titers on the second infection (41% NL-63, 31% OC43, and 1% 229E), so most of the second infections exhibited lower viral titers.

It has been a few months now and at least short-term immunity against SARS-CoV-2 has been characterized in terms of whether SARS-CoV-2 resembles common coronavirus immunity. It has been determined thus far that most COVID-19 patients mount IgG and IgM responses to the virus, many CoVID-19 patients mount neutralizing antibody responses, and the magnitude of the antibody response correlates to disease severity. In general, the more severe the infection the stronger the antibody response. It remains unknown whether COVID-19 patients are susceptible to reinfection, whether antibodies are a correlate of immunity and of what quality if so (isotype, antigenic region, neutralizing), if there is a threshold of protection, and how long serum antibodies will last.

Two broad categories of antibody assays can be used to detect antibodies, binding and functional. The binding assays used tend to test for antibodies against spike proteins or nucleic acid proteins. Three different versions of the spike protein are used in assays. The spike is the target for neutralizing antibodies. Nucleocapsid is abundant during viral replication. Assays can test for total Ig, Pan Ig that detects any immunoglobulin, IgG, IgM, and/or IgA.

The spike antigen is a trimer. It is a massive protein that is divided into the S1 region and the S2 region. It has a receptor binding domain (RBD) and the S2 domain. It is metastable and exists in a pre-fusion and post-fusion conformation. Three forms of spikes comprise a single protomer on the virion. Three versions of the protein are used in antibody assays (RBD, S1, one protomer of ectodomain or S2P along with the S2 domain). A variant has emerged as the more dominant circulating variant that has a coding mutation in the spike protein at residue 614. The D614 residue is right at the S1 and S2 interface. It is away from the RBD but is somewhat near the fusion machinery. Thus far, individuals who have tested the ability of serum to neutralize this new variant have not found differences between the original circulating variant and the 614G variant. However, it could in theory escape some antibody responses.

Nucleocapsid protein is also a target for antibodies and is used in antibody tests. It is not the target for neutralizing antibodies. However, it is easy to produce large quantities and it is abundantly expressed during early infection. Therefore, it is a very sensitive assay. However, it is unlikely a target for neutralizing antibodies. Dr. Thornburg shared a table of enzyme-linked immunosorbent assays (ELISA) and chemiluminescent microparticle immunoassay (CMIA) with Food and Drug Administration (FDA) and Emergency Use Authorization (EUA) authorization, showing the manufacturer, isotype, antigen, % positive agreement, % negative agreement and number of specimens used to validate the assay as of 6/18/20.

In addition to the binding assays that are used to detect any antibodies that bind, there are several ways to detect functional antibodies. This is a general list of the kinds of neutralization assays that laboratories and clinics are using to detect antibodies that neutralize the virus:

- Plaque reduction neutralization titer*, which is a classical test for serum that is mixed with virus to determine how much serum is needed to stop production of plaque
- Clinical isolate microneutralization*, which uses isolates made from patients to determine how much serum is needed to completely block virus-induced cytopathic effect
- Infectious clone reporter microneutralization*, which are used in containment because they are fully infectious viruses that have a reporter gene inserted into the genome so that there is a fluorescent out read
- Focus reduction assay*, which is an immunostain for a viral protein that is somewhat faster than a plaque reduction assay
- Pseudoviruses, which are being used widely in vaccine trials now because they can be done at lower containment in Biosafety Level 2 (BSL-2) laboratories, involve putting the spike

protein on the backbone of another virus and that usually has a reporter gene, are faster and easier to do, but can be more sensitive than live virus neutralization assays

In terms of what is known about antibody responses thus far, more severe patients exhibit more robust and faster antibody responses<sup>1</sup>. A majority of hospitalized COVID-19 patients develop neutralizing antibody responses<sup>2</sup>. Thirty percent of patients with mild infection have low neutralizing antibody titers of less than 500 at hospital discharge. No major changes were observed in the neutralizing antibody responses between discharge and revisit among 47 patients<sup>3</sup>. Older patients had higher neutralizing antibody titers<sup>4</sup> [<sup>1</sup>To et al. *The Lancet*. 20: 565-574; <sup>2</sup>Suthar et al. *Cell Reports Medicine*. 2020 Jun 8; and <sup>3, 4</sup><https://www.medrxiv.org/content/10.1101/2020.03.30.20047365v2>].

Most of what is known about SARS-CoV-2 immunology is from hospitalized patients, but what about milder infections? A study was conducted of sailors on the USS Teddy Roosevelt (USS TR) in which a microneutralization was used that required full neutralization of the virus, so it is a high bar. This study found that 41% of these young, healthy adults who had antibody responses did not have detectable neutralization titers<sup>1</sup>. There was a recent study looking at asymptomatic and symptomatic patients at the acute and convalescent phases. The convalescent timepoint was at 8 weeks post-discharge. This study found a decay in the acute and convalescent timepoints in the asymptomatic and symptomatic patients in binding antibodies and neutralizing antibodies. They were mostly still above the limit of detection of binding antibodies, but neutralization titers did drop below the 50% threshold in a large number of the symptomatic patients<sup>2</sup> [<sup>1</sup>Payne et al. *MMWR*. 69: 714-721; <sup>2</sup>Long et al. *Nature Medicine*. 18 JUN 2020].

In conclusion, it is known that most SARS-CoV-2 patients mount serum antibody responses and even mild cases of SARS-CoV-2 can result in development of antibodies. The magnitude of antibody response roughly correlates with severity, which is consistent with what is known about other coronavirus infections. A portion of individuals with antibody responses may not develop serum neutralizing antibody responses. By 8 weeks after discharge, a portion of patients have dropped below the 50% inhibition neutralization threshold.

### **Open Discussion**

Dr. Frey inquired as to whether there is any reason to believe that there is an antibody-dependent enhancement phenomenon that is occurring and if so, what proteins would be the culprits. She also wondered whether there is any evidence that some of the common coronaviruses such as OC43 were once very virulent and that SARS-CoV-2 might go that same route.

Dr. Thornburg did not think there were any data yet to suggest antibody-dependent enhancement of infection. There has not been any evidence 6 months in that anyone has had an antibody response who then went on to have a more severe infection if they got a second infection. While it is still early, there is no evidence of this yet. It is likely that SARS-CoV-2 immunity will be similar to common coronavirus infections. She did not recall historically what the emergence of common coronaviruses looked like but did not think it was as severe as the

emergence of SARS-CoV-2. She suspected that when they entered the population, they were as infectious.

Dr. Lee wondered whether there were any historical data on whether the antibody responses levels for the common coronaviruses differed by age or risk conditions.

Dr. Thornburg indicated that they do not have those types of data because they are common. Common coronaviruses are like a lot of other upper respiratory infections in that those are mostly diseases of childhood, which most people acquire by the time they are 2 to 5 years of age. This is complicated by the fact that people have memory B-cells and T-cells against the virus.

## **US COVID-19 Epidemiology**

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Dr. Oliver reported on US COVID-19 epidemiology among healthcare personnel (HCP), long-term care facility (LTCF) residents, children, pregnant women, and people in congregate settings as well as serology. As of June 23, 2020, a total of 2.30 million COVID-19 cases have been reported to CDC with 120,000 deaths.

A [Morbidity and Mortality Weekly Report \(MMWR\)](#) was recently published describing COVID-19 case surveillance through May 30, 2020. Through that time, over 1.7 million cases were reported to CDC. Hospitalizations were 6 times higher among patients with reported underlying conditions, and deaths were 12 times higher. Several clinical outcomes varied by sex. Males were hospitalized, admitted to the intensive care unit (ICU), and died at a slightly higher percentage compared to females. In terms of cases by date of report to CDC, the 7-day moving average peaked on April 12, 2020. While there has been a decline since then, the 7-day moving average indicates ongoing community transmission. The 7-day moving average of deaths peaked on April 21, 2020.

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 overall percent positive was 5.5% for the past week. The number of specimens testing positive has decreased since the initial increases in April. While the number of specimens from children tested as low represented less than 5% of specimens testing, the percentage testing positive in this age group was higher than in the adult age groups. Regarding the specimens tested and percent positive among [commercial laboratories](#) reported to CDC, the overall percent positive was 6.7%. The percentage of laboratory specimens testing positive was low but increased slightly in the past 2 weeks of reporting.

Visits to emergency departments (EDs) are monitored through the National Syndromic Surveillance Program (NSSP). To track trends, visits for influenza-like illness (ILI) or COVID-like illness (CLI) are monitored in a subset of EDs in 47 states. In the week ending June 13, 2020,

1.7% of ED visits captured in NSSP were due to CLI and 0.6% were due to ILI. Levels of both ILI and CLI increased in late March 2020 and then declined.

The National Center for Health Statistics (NCHS) collects death certificate data from vital statistics offices for all US deaths. Through the week ending June 13, 2020, 7.1% of all deaths were due to pneumonia, influenza, or COVID-19. This was the 8<sup>th</sup> week of decline; however, the percentage remained above the epidemic threshold.

The [COVID-19-Associated Hospitalization Network \(COVID-NET\)](#) conducts population-based surveillance for laboratory-confirmed COVID-19-associated hospitalizations in select counties in 14 states. This covers approximately 10% of the US population. A patient must be a resident of the surveillance area and have a positive SARS-CoV-2 test within 14 days prior to or during hospitalization. Charts are reviewed by trained surveillance officers. As of June 13, 2020, the overall hospitalization rate was 94.5/100,000 population with the highest rates in people  $\geq 65$  years of age at 287/100,000. COVID-19-associated hospitalization rates by race and ethnicity are calculated using hospitalized COVID-NET cases with known race and ethnicity for the numerator and bridged race population estimates for the denominator.

The age-adjusted hospitalization rates by race and ethnicity per 100,000 were 221.2 per 100,000 among Non-Hispanic American Indian or Alaska Native (AI/AN) persons, a rate approximately 5.5 times that of non-Hispanic White persons; 178.1 among Non-Hispanic Black persons, a rate approximately 4.5 times that of non-Hispanic White persons; 160.7 among Hispanic or Latino persons, a rate approximately 4 times that of non-Hispanic White persons; 48.4 among Non-Hispanic Asian or Pacific Islander persons, a rate approximately 1.2 times that of non-Hispanic White persons; and 40.1 among Non-Hispanic White persons. Overall, 91% of hospitalized adults had at least one reported underlying medical condition. The most commonly reported were hypertension (56%); obesity (49%); metabolic disease, including diabetes (42%); and cardiovascular disease (33%). Of hospitalized children, 53% had at least one reported underlying medical condition. The most commonly reported condition among children was obesity (38%).

An [MMWR](#) was published on June 17, 2020 that evaluated the characteristics associated with hospitalization among patients with COVID-19 from 6 metropolitan Atlanta hospitals and clinics. There were 220 hospitalized and 311 non-hospitalized included. Several factors were independently associated with hospitalization, including age  $\geq 65$  years, Black race, having diabetes mellitus (DM), lack of insurance, male sex, smoking, and obesity.

Turning to COVID-19 epidemiology amongst HCP, an [MMWR](#) in April 2020 described the characteristics of HCP with COVID-19. Among the cases reported at that time, 9200 (19%) were identified as a HCP. Among 1423 HCP patients who reported contact with a laboratory-confirmed COVID-19 patient in either a healthcare, household, or community setting, 780 (55%) reported having such contact only in health care setting in the last 14 days. Most HCP were not hospitalized; however, severe outcomes occurred across all age groups, including 27 (0.6% of 4407) deaths. CDC reports and routinely updates cases and deaths among HCP on the CDC website. As of June 23, 2020, there have been 83,673 cases and 464 deaths among HCP.

Dr. Oliver indicated that for each of the at-risk populations, she would highlight next steps and ongoing research to learn more. As data are available for each of these projects, the results will be shared with ACIP to inform future policy decisions. There are several projects ongoing related to HCP. The first is Project COVID Evaluation of Risk in Emergency Departments (Project COVERED), which is a prospective cohort study of 1600 HCP working in US EDs. The objectives are to: 1) estimate attributable risk of occupational acquisition of COVID-19 infection for emergency physicians and nurses; 2) estimate attributable risk of occupational acquisition of COVID-19 infection related to endotracheal intubation; 3) identify risk factors associated with SARS-CoV-2 transmission during intubation; and 4) determine the prevalence of symptomatic and asymptomatic COVID-19 infections occurring in ED HCPs. Serial symptom questionnaires, serology, and PCR will be collected over a 12-week period.

There are also HCP projects through the Emerging Infections Program (EIP), which is a network of 10 state health departments and local public health and academic partners. The projects include surveillance for, and interviews of, HCP cases compared to HCP non-cases. As of June 12, 2020, over 1000 cases had been reported and 425 interviews were conducted. Data will be shared with ACIP as soon as it is available.

There are two additional HCP studies, the Arizona Healthcare, Emergency Response and Other Essential Workers Surveillance Study (AZ HEROES) and Research on the Epidemiology of COVID-19 in Emergency Response and Healthcare Personnel (RECOVER). Both studies are primarily cohort studies over 12 months with repeat PCR and serology collected among HCP, first responders, and essential workers to determine the incidence of symptomatic and asymptomatic infections among these individuals.

Moving to LTCFs residents, there have been several published descriptions of a facility in King County, Washington. Through March 18, 2020, there were 167 confirmed COVID-19 cases associated with that facility. Of these, 101 were residents, 50 were staff/HCP, and 16 were visitors. Overall, 86% of residents were confirmed positive and 34% died. This report, as well as experience at other facilities, show that once COVID-19 has been introduced into a LTCF, it has the potential to result in high attack rates among residents, staff members, and visitors. Many areas contribute to the vulnerability of LTCFs, including inadequate familiarity with and inadequate supplies of personal protective equipment (PPE), high prevalence of underlying conditions, atypical presentations in the elderly, and the fact that many facilities share staff and patients. This was highlighted in a journal article where numerous facilities in King County shared either staff or patients with the initial facility, potentially introducing COVID-19 into those facilities as well [McMichael TM, et al. *NEJM* 2020].

The [Centers for Medicare and Medicaid Services \(CMS\)](#) released a rule on April 30, 2020 requiring all nursing homes certified by CMS to report data through CDC's National Healthcare Safety Network (NHSN). As of the week ending June 7, 2020, almost 15,000 nursing homes are reporting through this COVID-19 module. These facilities reported over 107,000 confirmed COVID-19 cases; over 71,000 suspect cases; and almost 30,000 deaths in residents. CMS began publicly reporting data from nursing homes on June 4, 2020. CDC also tracks what states report publicly. These numbers include a broader range of LTCFs beyond nursing homes, such as assisted living facilities. As of June 11, 2020, there were at least 245,605 cumulative confirmed or probable COVID-19 cases in residents and staff from 10,708 LTCFs across 51 US



states and territories based on state health department websites and other publicly available information. Information collected through the COVID-19 modules for LTCF will be used to strengthen COVID-19 surveillance locally and nationally; monitor trends in infection rates; and help local, state, and federal health authorities get help to nursing homes faster.

Focusing next on epidemiology among children, children may have different or minimal symptoms compared to adults such as abdominal pain or GI symptoms<sup>1</sup>. They also may be more likely to be asymptomatic<sup>1,2</sup>. In addition, there is limited information to date regarding the role children play in transmission. Early in the outbreak in China while children were still in classes, school-aged children had the largest number of close contacts of any age<sup>3</sup>. The efficiency of spread in schools by children is unknown. Existing data are reassuring, but are limited<sup>4-6</sup> [<sup>1</sup>[MMWR](#) April 10, 2020; <sup>2</sup>Dong et al. *Pediatrics*. June 2020; <sup>3</sup>Zhang et al. *Science* April 2020; <sup>4</sup>Heavey et al. *Eurosurveillance* May 2020; <sup>5</sup>Johansen et al. *Eurosurveillance* May 2020; and <sup>6</sup>COVID-19 in schools- the experience in NSW April 2020 Report].

One of the more concerning aspects of the COVID-19 pandemic has been the severe inflammatory disease seen among children. It was initially called Pediatric Inflammatory Multisystem Syndrome (PIMS) and initially was described in Europe. It presented with a Kawasaki-like disease and cardiac involvement. The epidemic curve peaked 4 to 5 weeks after the peak of the COVID-19 epidemic in France, which could suggest a post-infectious process [Belot et al. *Euro Surveill* 2020].

A report from England described 58 children with fever and laboratory evidence of inflammation. Among them, 15/58 (26%) children had a positive SARS-CoV-2 PCR, 40/46 (87%) children had a positive SARS-CoV-2 IgG, and 45/58 (78%) overall had evidence of current or prior SARS-CoV-2 infection. All patients presented with persistent fever (3-19 days), 31/58 (53%) had abdominal pain, and 30/58 (52%) had rash. In addition, 29 (50%) children developed shock and myocardial dysfunction; 8 (14%) children developed coronary artery dilation or aneurysm; and 2 (3%) children required extracorporeal membrane oxygenation (ECMO) [Whittaker et al. *JAMA* 2020].

A notice through the Health Alert Network (HAN) was released by CDC on May 14, 2020 establishing a case definition for Multisystem Inflammatory Syndrome in Children (MIS-C) in the US. This case definition includes the following:

- Fever > 38.0°C

**AND**

- Laboratory evidence of inflammation

**AND**

- Evidence of clinically severe hospitalized illness with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)

**AND**

- One of the following:
  1. SARS-CoV-2 positive PCR test
  2. SARS-CoV-2 positive antibody test
  3. SARS-CoV-2 negative PCR and antibody tests but with identified COVID exposure within the four weeks prior to the onset of symptoms



Information on MIS-C in the US has been collected through the Overcoming COVID-19 Study coordinated by Boston Children's Hospital and funded by CDC. There were 213 MIS-C cases enrolled at 53 participating health centers in 26 states. Most were previously healthy, with a median age of 8.4 years. Among these children, 73% were PCR or antibody positive at admission. Cardiovascular involvement was prominent at 81%, 50% had an elevated troponin, 38% had an ejection fraction <55%, 50% required vasopressor support, and ~9% had coronary aneurysms. It is known from experience with Kawasaki disease that coronary aneurysm has long-term implications when diagnosed in children.

There are several surveillance systems CDC can use to monitor MIS-C. First, CDC recommends that HCP report suspect cases of MIS-C to local, state, or territorial health departments. These health departments can then report cases to the National Notifiable Diseases Surveillance System (NNDSS) for case counts and case report forms are submitted using other MIS-C specific surveillance systems. Cases also can be assessed through the New Vaccine Surveillance Network (NVSN), which consists of 7 pediatric medical centers conducting active surveillance for acute respiratory and gastrointestinal illness, and COVID-NET described previously.

In terms of pregnant women, there can be physiologic changes in pregnancy that may increase the risk of severe illness (increased heart rate and oxygen consumption, decreased lung capacity, shift away from cell-mediated immunity)<sup>1</sup>, and severe disease has been associated with other viral respiratory infections in pregnant women<sup>1-4</sup>. However, initial reports have been unclear regarding COVID-19's impact on pregnant women. Recent studies are helping to define this better [<sup>1</sup>Ramsey PS et al. Pneumonia in pregnancy. *Obstet Gynecol Clin North Am* 2001; <sup>2</sup>Galang RR et al. Severe Coronavirus Infections in Pregnancy: A Systematic Review [online ahead of print, 2020 Jun 16]. *Obstet Gynecol*. 2020; <sup>3</sup>Mertz D et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. *BMJ* 2013; and <sup>4</sup>Mosby LG et al. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. *Am J Obstet Gynecol* 201].

A recently published prospective cohort study was conducted from mid-March to mid-April 2020 at 5 medical centers in New York City (NYC). There were 241 women with a positive SARS-CoV-2 test. Who was tested varied by medical center and over the timeframe due to test availability, evolving epidemiology, and hospital policies. Among the 241 women in the study, 89% were admitted for obstetric indications and the remainder for GI or ILI, 148 (61%) were asymptomatic at the time of admission, and 46 developed COVID-19 symptoms during hospitalization. A body mass index (BMI) of  $\geq 30$  was associated with COVID-19 severity. Insurance type, age, race and ethnicity, and underlying medical conditions were not associated with COVID-19 severity. There were 236 liveborn neonates with documented SARS-CoV-2 test results, of whom 230 (98%) tested negative. The preterm (<37 weeks gestation) birth rate in this cohort at 14.6% is higher than in the general population at 10.2%\*, with a statistically significant linear trend between COVID-19 maternal severity and the risk of preterm birth [Khoury R et al. *Obstet Gynecol* 2020; \*Martin J et al. Births in the United States, 2018. National Center for Health Statistics].

Turning to information from an *MMWR* scheduled to be released later in the week, from January 22, 2020-June 7, 2020 there were over 300,000 cases of laboratory-confirmed SARS-CoV-2 infection in women of reproductive age (WRA) defined as 15 through 44 years of age and reported to CDC through COVID-19 surveillance. Of those, 28% (91,412) had available data on pregnancy status. Of them, 8207 (9%) were reported as pregnant. This percentage may be affected by more frequent healthcare encounters among pregnant women that increased opportunities to receive SARS-CoV-2 testing, missing pregnancy status, or increased screening among pregnant women. A number of inpatient obstetric healthcare facilities have implemented universal screening and testing policies for pregnant women upon admission. Among pregnant women, 31.5% were reported as hospitalized compared with 5.8% of non-pregnant women. After adjusting for age, the presence of underlying medical conditions, and race and ethnicity pregnant women were significantly more likely to be hospitalized with an adjusted risk ratio of 5.4. Pregnant women were 50% more likely to be admitted to the ICU and 70% more likely to receive mechanical ventilation. Among pregnant women, 16 deaths were reported in a similar portion to non-pregnant women.

There are challenges in interpretation of hospitalization as an outcome for severe COVID-19 illness in pregnant women as data are not available to distinguish hospitalization for COVID-19 from hospitalization admission for pregnancy-related conditions. Therefore, differences in hospitalization by pregnancy status may reflect a lower threshold for admitting pregnant patients or the universal screening of women admitted to a labor and delivery unit. In an analysis of outcomes among pregnant versus non-pregnant women hospitalized with lab-confirmed COVID-19 from COVID-NET, the risk of ICU and mechanical ventilation was lower among pregnant compared to non-pregnant women, and there was no statistically significant differences in the risk of in-hospital death. While the reason for admission is not specified, it is possible that non-pregnant women were predominately admitted for medical illness, whereas pregnant women were admitted for medical illness or labor and delivery. Pregnant women admitted solely for labor and delivery are likely healthier than pregnant or non-pregnant women admitted for medical illness.

In summary, this new report includes the largest US cohort of pregnant women with laboratory-confirmed SARS-CoV-2 infection. More complete data are needed to assess whether SARS-CoV-2 infection in pregnancy is associated with adverse pregnancy or neonatal outcomes. The results from this study suggest an increased risk of ICU admission and mechanical ventilation, which are distinct proxies for severity, in pregnant women compared to nonpregnant women. However, the absolute risk of these clinical interventions is still very low in this population.

In terms of next steps regarding pregnant women, cohort studies, including retrospective electronic cohorts and prospective community cohorts, will assess incidence and seroprevalence of SARS-CoV-2 in pregnancy and severity of disease. Supplemental surveillance is being implemented to collect additional data on pregnancy and neonatal outcomes through the Surveillance for Emerging Threats to Mothers and Babies Network (SET-NET), and teams are leveraging existing pregnancy surveillance systems such as the Pregnancy Risk Assessment and Monitoring System (PRAMS) and COVID-NET.

Regarding COVID-19 epidemiology among people in congregate settings, 115 meat or poultry processing plants in 19 states reported COVID-19 cases to CDC in April 2020. COVID-19 was diagnosed in 4913 (~3%) workers. By state, this ranged from 0.6% to 18.2% of workers. There were 20 deaths reported that were related to COVID-19<sup>1</sup>. In April, there were 420 correctional or detention facilities with at least 1 case of COVID-19 from 32 state and territorial health department jurisdictions, with nearly 5000 cases among incarcerated persons and 2778 staff. There were 88 COVID-19 related deaths reported among incarcerated persons, 15 of which were among staff<sup>2</sup>. There were nearly 1200 residents and over 300 staff members tested in 19 homeless shelters in 4 US cities from late March 27, 2020 to mid-April 15, 2020. Homelessness poses multiple challenges that can amplify spread of COVID-19. Among shelters associated with a cluster (meaning 2 or more residents tested positive for COVID-19 in the prior 14 days), the percent of residents who tested positive ranged from 17% to 66%. In shelters not associated with a cluster, there were much lower rates of infection at 4% to 5%<sup>3</sup> [[<sup>1</sup>MMWR May 1, 2020](#); [<sup>2</sup>MMWR May 6, 2020](#); and [<sup>3</sup>MMWR April 22, 2020](#)].

For a brief overview of some ongoing serology studies, there are numerous seroprevalence surveys underway or about to begin. These include large-scale geographic seroprevalence surveys to estimate the number of people previously infected with SARS-CoV-2 and not included in official case counts. These include specimens from commercial laboratories and blood donations. There also are community-level seroprevalence surveys that cover smaller areas such that participants can be systematically selected. There also are special populations seroprevalence surveys that are meant to answer questions about specific populations, such as HCP or pregnant women.

In summary, approximately 2 million cases of COVID-19 were diagnosed in the US through June 2020. Multiple sub-populations appear to have an increased risk, including older adults, HCP, individuals at LTCF and other congregate settings, and those with underlying medical conditions. Many projects are ongoing to better define characteristics of SARS-CoV-2 infections, which will be shared with ACIP once the results are available.

## **Open Discussion**

Dr. Romero noted that Dr. Oliver presented data through May 30, 2020. However, there was an increase in the number of cases reported in the last few weeks. He requested further information about those cases and the number of states with increases in cases.

Dr. Oliver clarified that the *MMWR* with the 7-day average was through May 30, 2020. The rest of the data were through June 13, 2020. CDC publishes a [COVIDView](#) report every Friday that includes the previous week's surveillance summary of US COVID-19 activity. These data are publicly available on the website.

Dr. Bell wondered whether Dr. Oliver could reflect on plans moving forward for sensitive surveillance at multiple levels. It seems like having a sensitive surveillance system is going to be very important for control efforts, especially in the context of influenza season.

Dr. Oliver indicated that there have been multiple efforts over the summer to strengthen surveillance systems across the US, leveraging existing influenza surveillance systems and diagnostics as well.

Dr. Szilagyi noted that there are some anecdotal reports that there is a major difference in the prevalence of MIS-C in the US on the East Coast versus the West Coast and asked Dr. Oliver to comment on that. Regarding the large study on pregnant women and hospitalizations and ICU admissions, there is clearly a strong hospitalization bias. Many hospitals test for COVID-19 immediately upon hospitalization. The ICU and mechanical ventilation data for pregnant women were concerning, and he wondered whether Dr. Oliver had any additional information about the stage of pregnancy among the women with COVID-19 in the ICU.

Regarding MIS-C, Dr. Oliver indicated that there are ongoing projects assessing incidence and numbers across the US and by region. As it is a relatively rare outcome at this point, CDC is collecting data and will continue to report the results as data become available. In terms of pregnant women, the upcoming *MMWR* to be published on June 24, 2020 will have additional data that Dr. Oliver was not able to present due to time. This includes some additional analyses. She did not know whether it was broken down by trimester of pregnancy. Given that many of them women were admitted for delivery, the data are probably skewed toward later pregnancy. Surveillance systems are being enhanced throughout the US to collect additional data on pregnant women.

In reference to the previous question asking about recent increases, CDC is reporting daily case counts, and increase has been seen an increase in cases that have been reported in the US over the previous couple of weeks across the US.

Dr. Lee noted that one curious finding that stood out for her was that the proportion of positive tests was higher among children, which was a surprise given all that had been seen and heard to date regarding asymptomatic cases. She asked whether tests are done in symptomatic and asymptomatic children, and whether Dr. Oliver thinks there may be a reason that there is an increasing trend for test-positive children.

Dr. Oliver responded that the current laboratory systems through CDC do not have the ability to distinguish between symptomatic and asymptomatic infections, though they hope to enhance that moving forward. It is less that they have been increasing in recent weeks and more that they have held steady as other things have declined. They think this is likely multifactorial, but it likely just represents that they are a very unique population. Given that they have had such a small proportion of tests done, it also could be that the pre-test probability of who is being testing is somewhat higher. They are looking into this to try to figure it out across the US.

## **Maintaining and Strengthening Childhood Vaccination During the COVID-19 Pandemic**

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

Dr. Wharton provided an update on CDC's work on routine childhood vaccination during the COVID-19 pandemic, as well as the planning being done for the upcoming influenza season.

In mid-March 2020, there was a precipitous drop in ambulatory care visits of nearly 70% as stay-at-home orders were issued around the US. Some recovery was seen in early May 2020, although the number of visits remained well below baseline. Pediatrics was among the hardest hit specialties, with a 62% reduction in pediatric outpatient visits by the week of April 5, 2020. There was some improvement by the week of May 10, 2020 in terms of increases in outpatient visits across all pediatric age groups, with the least reduction seen in visits for children under 2 years of age and the most for children 3 to 5 years of age [Ateev, M. et al., To the Point (blog), Commonwealth Fund, updated May 19, 2020].

The Vaccines for Children (VFC) program provides federally purchased vaccines for eligible children in the US. In order to assess the impact that these reductions in outpatient visits on childhood vaccination, weekly VFC vaccine orders were assessed for all childhood vaccines other than influenza vaccines in 2020 compared to the comparable week in 2019. This assessment showed a dramatic reduction in vaccine orders beginning in mid-March 2020 and extending into early May 2020. A similar pattern was observed for measles-containing vaccines, but with much greater reductions. Also during this time, many medical practices were under severe stress as patients were not being seen, staff may have been furloughed, and some practices closed temporarily or permanently.

With partners, CDC has undertaken a number of activities to support recovery of routine childhood vaccination. In addition to monitoring service delivery, CDC has developed guidance on routine vaccination, the importance of well-child visits, and safe vaccine delivery. The agency has encouraged state immunization programs and healthcare practices to encourage catch-up vaccinations through reminder/recall systems. With state partners, CDC is identifying gaps in the VFC provider network and through the budget process, planning for a potential increase in the VFC-eligible population. CDC has worked with partners to identify policy interventions to support healthcare providers. In terms of communications, CDC has supported efforts to communicate about the importance of well-child visits and routine childhood vaccination to parents, providers, and partners as well as efforts to raise awareness about the VFC program for families who may be newly eligible. Finally, it is critical to address catch-up now to allow moving on to back-to-school vaccination activities during the summer and influenza vaccination in the fall.

Initial support for healthcare providers through the [Provider Relief Fund](#) was directed to providers participating in Medicare. Since June 9, 2020, providers participating in Medicaid and the Children's Health Insurance Program (CHIP) have been included. CDC has continued to promote catch-up vaccination through dissemination of information on best practices for

reminder/recall, including refocusing of the [Immunization Quality Improvement for Providers \(IQIP\)](#) program activities on catch-up vaccination. CDC also has disseminated guidance to providers on the safe delivery of vaccines during the COVID-19 pandemic.

The “[CDC Interim Guidance for Immunization Services During COVID-19 Pandemic](#)” identifies vaccination as an essential medical service for all children and adolescents that ideally should be delivered in the medical home. All due or overdue vaccines should be administered according to the routine immunization schedule during the same visit, and strategies to catch-up patients on vaccines they missed should be implemented starting with the youngest children and extending through adolescence. The guidance also addresses safe delivery of vaccines, including the use of PPE and physical distancing. CDC’s communication efforts are focused on encouraging parents to return for well-child visits, encouraging the use of reminder/recall systems to help children get up to date as quickly as possible, and encouraging providers to share with families the safety protocols put in place to ensure patients can be safely seen in a clinic to be vaccinated.

CDC also has been working with partners to promote awareness of the [VFC program](#) among parents. Prior to the COVID-19 pandemic, approximately 50% of US children were eligible to receive free vaccines through VFC. More may be eligible now due to parents’ loss of insurance or increased economic hardship. These families who have newly eligible children may not know about the VFC program. CDC appreciates the support of partners and providers to increase awareness about this critically important program. In addition, CDC has created [resources](#) for communicating with parents about routine vaccination during the COVID-19 pandemic. The American Academy of Pediatrics (AAP) has developed a highly sharable social media campaign directed at parents using the hashtag [#CallYourPediatrician](#).

CDC was pleased to see improvement in the weekly vaccine orders from the VFC program in May 2020. In terms of individual vaccines, the recovery is greater for vaccines given to infants such as Haemophilus influenzae type b (Hib) and less for pre-teens and adolescents like human papillomavirus (HPV). This shows that there is still room for improvement, although things are moving in the right direction.

School vaccination requirements provide a critical checkpoint for children’s vaccination status. Many children need to receive vaccines during the summer to stay up-to-date and comply with school vaccination requirements. It is very important that back-to-school vaccine clinics take place this summer to provide children an opportunity for vaccination. In the event that COVID-19 circulation disrupts the back-to-school vaccination effort, CDC encourages jurisdictions if possible to allow additional time for compliance rather than suspending school requirements completely through some sort of emergency action or creating a situation in which families feel like they need to seek exemptions.

Moving on to planning for the upcoming 2020-2021 influenza season, the influenza season that just concluded was characterized by an initial wave that was predominantly influenza B followed by a later wave of influenza A(H1N1). As of June 13, 2020, a total of 185 pediatric deaths that were associated with laboratory-confirmed influenza had been reported to CDC. CDC estimates that in the [2019-2020 season](#), there were millions of illnesses and medical visits, hundreds of thousands of hospitalizations, and tens of thousands of deaths due to influenza.

Because it is anticipated that SARS-CoV-2 will continue to circulate into the fall, influenza vaccination will be an important strategy to decrease stress on the healthcare system by decreasing doctor visits and hospitalizations, as well as decreasing the number of people who will need diagnostic testing. Given the risk groups who have been identified for COVID-19, influenza vaccination will be particularly important for staff and residents of LTCF, adults with underlying illnesses, African Americans, and adults who are part of critical infrastructure. There are longstanding disparities by race and ethnicity in vaccine coverage with influenza vaccine. Based on data from the 2017 National Health Interview Survey (NHIS), influenza vaccine coverage was lower among Hispanic and Black adults compared to White adults in all age groups and among groups with and without underlying high risk conditions.

In planning for the upcoming 2020-2021 influenza season, CDC is pleased that manufacturers of US-licensed influenza vaccines are planning a record high amount of vaccine with more than 180 million doses expected. Effective outreach will be needed to persons at higher risk, planning for potential need for social distancing in vaccine delivery, and in planning to extend the influenza vaccination season until December or later for distribution of all doses that are expected. Ongoing COVID-19 prevention activities provide opportunities to share influenza prevention messages and it will be important to focus on messaging for African American and Hispanic communities, given the disparities in influenza vaccine coverage and COVID-19 morbidities that have been observed.

CDC is also pleased to have been able to provide supplemental resources for public sector influenza vaccination for the 2020-2021 season. This includes supplemental funding to support immunization program activities and purchase of additional vaccines for use in adults. In most years, CDC has purchased about 500,000 doses for adults through federal contracts. This year, the agency has been able to purchase an additional 7.1 million doses. Some of these doses will be available late in the season, so it will be especially important that the vaccination season be extended into December or later. Community Health Centers (CHCs) provide an important partnership opportunity for state immunization programs to reach adults who otherwise might not be vaccinated. CDC appreciates the support of the National Association of Community Health Centers (NACHC) in facilitating these connections with its state programs.

In conclusion, there have been substantial disruptions to routine childhood vaccination services during the COVID-19 pandemic, though signs of recovery are now being seen. Catch-up for childhood vaccination needs to be undertaken now so clinical capacity can be directed to back-to-school and influenza vaccination efforts in the summer and fall. Solutions are needed to existing disparities in influenza vaccination coverage in order to avoid these disparities if possible when there is a COVID-19 vaccine. CDC appreciates the support of immunization programs, partners, and healthcare providers in getting childhood vaccination back on track by supporting catch-up vaccination efforts and communicating with parents about safe well-child visits and vaccination during the COVID-19 pandemic.

## **Open Discussion**

Dr. Bell acknowledged the amount of effort and research focused on understanding the reasons for the ethnic and racial disparities in influenza vaccination coverage among adults. Recognizing that this is clearly multifactorial, she wondered whether Dr. Wharton could reflect on what the major drivers of this disparity appear to be.

Dr. Wharton emphasized that it is a complicated and multifactorial issue no doubt, and that she was not sure she had a very satisfying answer to Dr. Bell's question. It clearly goes well beyond access. There is strong evidence of differences in vaccine perception, acceptance of vaccination by race/ethnicity, perceptions of the need for vaccination, and trust in recommendations from healthcare providers. All of those likely contribute. One of the aspects in which CDC is very interested is that it is known that quality improvement efforts (e.g., standing orders, prompts, strong provider recommendation) work to improve vaccine coverage among both children and adults. Whether those will be sufficient to reduce disparities is the question. The agency is pleased to be doing some ongoing work in association with the NACHC to try to better understand the degree to which disparities can be addressed through quality improvement and whether additional strategies will be needed. That is a focus of a great deal of work at CDC currently.

Dr. Poehling noted that the data shown on vaccine disparities was focused on adults and requested that Dr. Wharton speak about the vaccine disparities seen in children as well.

Dr. Wharton indicated that fortunately, the disparities seen in children are much lower. They are not non-existent, but they are much smaller in magnitude than seen with adults. The VFC program and the commitment of public sector immunization programs and participating providers ensures that vaccines are available to everybody.

Dr. Rockwell (AAFP) asked whether the messaging for African American and Hispanic communities is something CDC will be working on and putting out a statement in alignment with other national organizations that might confer more trust with those communities, or if this is something individual physicians should focus on in speaking with their patients. Regarding the epidemiology for SARS-CoV-2, she noticed that higher BMI was associated with higher morbidity. With the pregnant women's study, it was specifically stated that a BMI over 30 was associated. She wondered whether a BMI number could be cited for children and non-pregnant adults.

Dr. Wharton indicated that there is some research underway to help inform communication efforts. There are external partnerships with other organizations that also are working on this. In addition, there will be other activities during the summer that are anticipated to help inform future activities.

Dr. Oliver indicated that underlying conditions, including obesity, were in the COVID-NET population with a BMI of over 35. The BMI over 30 study was conducted in NYC, not through CDC. CDC is collecting BMI data in children and adults.



Dr. Goldman (ACP) suggested an advertisement campaign and education materials for adult medicine similar to that developed for children. Adult medicine is facing the same issues of patients not wanting to present to the office due to not feeling it is safe, along with a decrease in adult vaccination rates because people are staying at home.

Regarding disparities observed during the COVID-19 pandemic, Dr. Whitley-Williams (NMA) stressed that it is not just comorbidities and social determinants of health (SDOH). During the pandemic, barber shops, beauty salons, and churches have been closed. Sometimes those places serve as a source of information and communication to the community, as well as what is posted on social media. She applauded CDC's efforts in terms of examining the various strategies to get the word out. She is very concerned about the distribution of vaccines when a COVID-19 vaccine does become available in terms of whether the structure will be in place to reach those who may be at greatest risk and who also may be more difficult.

Dr. Wharton emphasized that CDC shares those concerns and is trying to plan accordingly.

## COVID-19 Vaccines

### Introduction

**Beth Bell, MD, MPH**  
**Chair, ACIP COVID-19 Vaccines Work Group**  
**Clinical Professor, Department of Global Health**  
**School of Public Health, University of Washington**

Dr. Bell explained that there are a number of considerations about COVID-19 vaccination in the US that formed the foundation for the ACIP COVID-19 Vaccine WG's work. First, there was recognition of the need for equitable access to safe and effective vaccines and evidence-based vaccination policy. As part of that, preparing for implementation of safe and effective COVID-19 is a critical next step to protect the public and reduce the impact of COVID-19 on society. The increased risk of severe COVID-19 in vulnerable populations and racial/ethnic minority groups highlight the need for diverse representation in clinical trials and for ensuring equitable access to vaccines, regardless of the specific vaccination strategy or identified priority groups. The ACIP COVID-19 Vaccines WG was established to help inform evidence-based approaches to COVID-19 vaccination policy.

The WG was established in April 2020 and has met weekly or bi-weekly since then. The WG's role is the collection, analysis, and preparation of information related to COVID-19 vaccines for presentation, discussion, deliberation, and vote by the ACIP using an open and transparent process. The WG is comprised of 41 members, including ACIP voting members, liaisons, *ex-officios*, and expert consultants. Areas of expertise of COVID-19 WG members include:

Communications	Immunology
Emergency Preparedness	Infectious Diseases
Epidemiology	Obstetrics
Ethics	Pediatrics
General Medicine	Public Health/Surveillance
Geriatrics	Vaccine Administration/Delivery
Health Equity	Vaccine Safety
Immunocompromised Hosts	Vaccinology

Among the 41 WG members are 4 ACIP voting members, with Dr. Bell serving as Chair; Drs. Dooling and Mbaeyi serving as CDC Co-Leads; CDC experts; and the following consultants, liaison representatives, and *ex-officio* government members:

#### Consultants in Several Areas

- Vaccinology
- Microbiology/Immunology
- Safety
- Ethics
- Health Equity

#### Liaison Representatives

- American Academy of Family Physicians (AAFP)
- American Academy of Pediatrics (AAP)
- American College of Obstetricians and Gynecologists (ACOG)
- American College of Physicians (ACP)
- American Geriatrics Society (AGS)
- Association of Immunization Managers (AIM)
- American Medical Association (AMA)
- American Nurses Association (ANA)
- American Pharmacists Association (APhA)
- Association of State and Territorial Health Officers (ASTHO)
- Council of State and Territorial Epidemiologists (CSTE)
- Infectious Disease Society of America (IDSA)
- National Association of County and City Health Officials (NACCHO)
- National Advisory Committee on Immunization Canada (NACI)
- National Foundation for Infectious Diseases (NFID)
- National Medical Association (NMA)
- Society for Healthcare Epidemiology of America (SHEA)

#### Ex-Officio Government Members

- Biomedical Advanced Research and Development Authority (BARDA)
- Centers for Medicare and Medicaid Services (CMS)
- Department of Defense (DoD)
- Food and Drug Administration (FDA)
- Indian Health Services (IHS)
- National Institutes of Health (NIH)

One of the first tasks undertaken by the WG was to develop terms of reference. The policy topic under consideration by the WG is use of COVID-19 vaccines in the US population. The WG activities are to: 1) review the safety and immunogenicity data for COVID-19 vaccines; 2) review the epidemiology of COVID-19 disease and identify potential target populations for vaccination; 3) discuss potential vaccine prioritization plans in the event of early insufficient early COVID-19 vaccine supply; 4) identify areas where additional data are needed to inform COVID-19 vaccine recommendations; and 5) develop COVID-19 vaccine policy options that ACIP may consider for recommendation. When considering the terms of reference, the decision was made to establish a Vaccine Safety Technical Subgroup in recognition of the importance of vaccine safety and the highly technical nature of the data that would be incoming. The role of the Vaccine Safety Technical Subgroup is to advise the main WG on the safety of COVID-19 vaccines, both during clinical development and post-licensure.

The WG has been dealing with a number of factors related to decision-making in the context of many unknowns and uncertainties. The WG must stand for the principles of evidence-based decision-making, equity, and transparency in the process and recognizes the tension between the need to provide guidance and the limited available science base. The WG strives to develop a robust understanding of what is known, making sure that diverse voices are heard in this process. The WG makes decisions based on the knowns at the time, recognizing from the start that revisions will be needed as more information becomes available. This means that the WG must advocate for implementation of the essential strategies and systems to ensure that pivotal data for decision-making are collected. The WG strives to continue to promote a feedback loop to evaluate the impact of recommendations and commit to revising accordingly.

Dr. Bell indicated that the agenda for this session would include presentations on the following topics:

- COVID-19 Vaccine Development
- Landscape of COVID-19 Vaccines in Development
- COVID-19 Vaccine Prioritization Considerations
- WG Considerations and Next Steps

### **COVID-19 Vaccine Development**

**Dr. Matthew Hepburn**

**Lead, Operation Warp Speed Vaccines**

**Department of Defense/Department of Health and Human Services**

Dr. Hepburn said it certainly was a privilege to share a few minutes of time with the ACIP and noted that he would like to make 3 general points. He indicated that he did not have any slides available for this presentation, part of which was because Operation Warp Speed (OWS) is still a work in progress and is still figuring out how they work together. As the work of the government can certainly attest, OWS is still figuring out its own clearance process for messages and materials that can be available publicly. OWS as group or entity may have been coming together over the past month or so, but it feels like they are a brand-new organization. As such, he requested ACIP's latitude in terms of his lack of ability to provide a lot of specifics about what OWS is doing. OWS also wants to engage, talk, and discuss what they are doing

with ACIP as an entity and also with the experts who were part of the call and dialogue during this meeting.

With the understanding that OWS is a work in progress, Dr. Hepburn said he wanted to explain a couple of things. The first would be to talk through the OWS organizational structure and how they came about, and second to talk about some of the conceptual themes or compare and contrast of what OWS is and what it is not. OWS is a newly formed entity about which there has been a lot written in the public media and press which he thinks, unfortunately are misconceptions and they will have the chance to get that message out publicly to discuss some of those misconceptions and notions in the coming days and weeks. For the purpose of this meeting, he thought it was helpful to note that he sees OWS as an integration of some of the best efforts in the US government and resources available to accelerate a few products in order to have a safe and effective vaccine to respond to the pandemic.

Dr. Hepburn indicated that he is an infectious disease physician who served 23 years as an Active Duty Army Officer, retired, ran some vaccine antibody development programs in the DoD, and then was asked to be part of OWS as a DoD and HHS integrated effort. One of the key take home points is that OWS is not a secret organization that is working with unknown people and no one really understands what they are doing. He really does think it is just the opposite. They are taking advantage of the best in terms of expertise and capability within both HHS and DoD. It is nice because they actually are integrated, and he thought most of them could appreciate that. One of the things the federal government often struggles with is the ability to integrate across the different departments and agencies. He thinks OWS is a case in point on how they can and should integrate, and he is happy to be more specific on that.

As part of the Vaccine Team, each of the vaccines they plan to engage with has a Product Team that is composed of about 10 to 12 individuals. Those individuals are drawn from throughout HHS and DoD, including NIH, CDC, and a significant component from their colleagues at HHS BARDA, especially regarding contracting and program management. They also have Functional Leads. The first Functional Lead that cuts across all of their products is in the pre-clinical and clinical space. This is Chaired by John Mascola at the Vaccine Research Center (VRC) and is populated with what Dr. Hepburn thinks are some of the best scientists in the government from the NIH, DoD, and elsewhere. The second cross-functional area is in manufacturing taking advantage of the best in government, but mostly from HHS BARDA. The third is led by Dr. Messonnier who leads a remarkable team in the distribution and administration category. This was put together in the previous 2 to 3 weeks, and Dr. Hepburn likes how they are working very well together. He expressed his hope that everyone could appreciate the advantage of taking a lot of different components in the government and putting them together for this common focus.

Dr. Hepburn said they could argue about the name OWS and how it may lend itself to misconceptions, but he did not think that was the point of this conversation. Why he is very excited about this is that it does entail putting in significant resources for multiple vaccines to be developed, and to be developed on an accelerated schedule. One of the key points they make when they talk about acceleration is that this is not acceleration in terms of cutting corners and this is not acceleration in terms of compromising safety standards. Rather, they are looking at accelerating where they might otherwise do things in parallel because of resources and financial

risk. For example, one of OWS's main goals is to make sure that they can manufacture at scale. He thinks everyone appreciates that one of the key components of manufacturing and scale is starting early. In a typical vaccine product development pipeline, some of the large-scale runs might be done after there are more proof of concept data. In this case, they said they are going to take more financial risk and start larger scale manufacturing operations earlier. He thinks it is a really good example of that approach. There may be a few vaccines for which they make a lot of doses and those vaccines may not pan out in clinical trials. That is lost financial resources, but really does not compromise the safety and effectiveness of the vaccine. OWS is following product development expectations that would be expected.

While Dr. Hepburn said that he was not going to go into which products they are/are not funding, OWS has broadly looked at funding sources and resources across the US government. They have not said to cut things to be part of this program or said that those who do not get picked will be cut and do not get any US government funding anymore. Rather, OWS is going through a continuous assessment process of which vaccines they think are most promising to deliver significant doses by the end of the calendar year 2020 or within the first quarter to half of 2021, and looking at different ways they can accelerate those. One of the big things that is coming up soon, that OWS's NIH colleagues in particular have been working on quite a bit, is thinking through the large-scale clinical trials that would be associated with this. These are going to be individualized and case-by-case, but one of the things most of the members have seen is a [Science article](#) by Lawrence Corey, John Mascola, Anthony Fauci, Francis S. Collins recently that advocated for harmonization wherever possible, especially for the large-scale Phase 3 clinical efficacy trials. That is OWS's intention and Dr. Hepburn thinks their colleagues at the NIH are well-positioned to take an active role in that. Further, OWS is aiming to partner with the NIH Clinical Trials Network (CTN) where it makes sense and not necessarily exclusively, to be partners in some of the large Phase 3 clinical trials that they anticipate will be coming up in the coming months.

Finally, Dr. Hepburn said that where OWS's CDC colleagues have been absolutely critical in playing a leadership role, fingers crossed, is if there is a scenario in which there is a safe and effective vaccine and that vaccine is ready for distribution, is with working through all of the complexities and challenges with distributing that vaccine. He thought a very fair question from the ACIP would be, "How far along are we in that process?" He could defer to Dr. Messonnier and CDC to comment further, but he thought from an OWS standpoint, in their first few weeks they focused on the earlier product development and making some of those important decisions to accelerate the product development pipeline. OWS does have an eye toward how these vaccines would be distributed based on their indications, which populations would benefit most from vaccination, where side effects would be anticipated—all of those complex issues. Those are critical issues that need to be addressed, which he acknowledged that most of those on the phone are expert in. OWS's intention is to address those in the coming weeks. As they address those challenges, as was outlined in the previous conversation and that he thought would be discussed throughout the day, OWS needs ACIP's help and hopefully has made clear that they are leveraging a lot of expertise in the US government. More formally from an OWS standpoint, they sincerely welcome the dialogue, input, and future conversations with ACIP. In closing, Dr. Hepburn said that he would be happy to field questions and would stay on the line for as much of the meeting as possible.

## **Discussion Points**

Dr. Romero said that ACIP looks forward to working with OWS as COVID-19 vaccine development moves ahead. He asked how OWS sees the role of the ACIP in determining risk populations and making recommendations for distribution of available vaccines in the future. He pointed out that the ACIP has a nearly 60-year experience in making recommendations regarding the use of vaccines for the control and prevention of disease in the US.

Dr. Hepburn said that simply put, OWS sees the ACIP's role as essential in helping to think through the challenges and essential for ACIP's input, advise, and expertise. For him personally, he is happy to engage with ACIP as frequently as needed. Because of ACIP's close relationship with the expertise at the CDC, he is also making the assumption that he thinks is very valid, that that dialogue occurs and the ACIP is informing the OWS team through the dialogue that they have with the CDC on a routine and informal basis. OWS is happy to include ACIP where it is appropriate and ask for ACIP's advice. In terms of right now, as ACIP could appreciate, OWS is still in the early stages for these vaccines. If they are successful with resources to accelerate the timelines on these, in the coming weeks and months, they will welcome the dialogue once they have a little more understanding of how these products work and a little more understanding of which products they think may be able to achieve Emergency Use Authorization (EUA).

Dr. Cohn thanked Dr. Hepburn and clarified one point that he made, which is that all discussions between ACIP and CDC occur in a public, open setting. She wanted to ensure that the audience understood that.

Dr. Hepburn thanked Dr. Cohn for that clarification and said that he thought this was a great forum to dialogue. OWS is happy to share information, let ACIP know what they are doing, and also be inspired by ACIP's input, suggestions, and guidance.

Dr. Frey emphasized that a lot of the timelines are being compressed with the Phase 3 studies. She inquired as to who/how a final decision will be made, at what point OWS will decide to say that a vaccine is efficacious and launch it, and how they will work with FDA and others to make these decisions.

Dr. Hepburn said that in terms of the product development that would be expected for this, they are going to follow the process that vaccine product development usually follows in terms of the clinical trials process under good manufacturing—all of those things that would normally be expected for any vaccine development. OWS is going to do all of that. That is the expectation and that will include frequent dialogue with the FDA at every step where it is appropriate and ultimately, if there is a situation where the safety and efficacy are good enough, to apply for EUA. OWS's role is to fund the companies. The vaccine development companies under contract will receive resources to do a lot of these functions. When the DoD funds a vaccine project, they fund the company to do this. With HHS BARDA, it is the same thing. OWS is funding the companies to do that and they are responsible for many of these steps in product development. What he is excited about is that by leveraging the expertise in the government as they think about clinical trials, clinical trials design, and running these clinical trials at sites, OWS can leverage all of that expertise from the NIH, CDC, and BARDA to ensure that a clinical trial is run

not just by a vaccine company, but a very high quality clinical trial that has harmonization, meaning that there are common endpoints that may offer an opportunity to look at different vaccines to have some comparability. It also will allow them to leverage trying to answer these critical scientific questions such as correlates of protection. Again, it is resources through contracts to drive a vaccine process that will follow the typical steps. But in that program management and leveraging OWS's US government team, Dr. Hepburn thinks that they can not only accelerate products, but they can actually learn a lot too about those products.

Dr. Fink (FDA) reiterated that in the clinical development of all of the COVID-19 vaccine candidates, the FDA will continue to perform independent review and oversight of the development process and will make the final determination based on the data available as to the safety and appropriateness of any progression in clinical development and providing the vaccine, even in the context of clinical study, whether that is first a human study or advancing to Phase 3 efficacy studies, and wider availability of vaccine candidates through licensure.

Dr. Talbot said that as an adult immunologist and vaccinologist, this is incredibly exciting and she is looking forward to all of the collaboration that is ongoing. She is also very excited because this gives them some time to prepare as they wait for data. As someone who conducts viral respiratory disease surveillance and vaccine effectiveness is that there is not a very good way of tracking adult immunizations in the US. The state registries vary greatly. One thing that can be done in preparation for a new vaccine or vaccines is to strengthen and enhance state registries so that adult data can flow into them, and then as time goes on, real-time vaccine effectiveness and safety data can be provided much more quickly and thoroughly than is possible at this time.

Dr. Hepburn agreed and thought they could recognize the benefit of the OWS integrated approach having the CDC on their team and part of this entire process. He has heard this from them and he deferred to their expertise in terms of the how, but he could not agree more that this is an opportunity to do this right—not minimizing the challenges. He recognized that there are enormous challenges in developing a vaccine against this virus. But, if they are successful, now is the time to think through those latter phases in terms of distribution and tracking as Dr. Talbot correctly pointed out.

Ms. Finley (AIM) said that one thing which caught her attention was integration of the best efforts in government. She encouraged OWS to build on the existing plans and infrastructure. In working with CDC, they are probably aware that there are 67 immunization awardees that address enrolling providers, distributing vaccine directly to them, overseeing storage and handling, working for the Immunization Information Systems (IIS). Many of them worked closely with CDC through the 2009 pandemic, so she encouraged building upon the effective systems that were developed.

Dr. Hepburn said he agreed 100%, noting that everyone could appreciate that what is going to happen in the fall is inherently unpredictable in and of itself and in terms of the effectiveness of a vaccine or multiple vaccines. It would be great if there are choices and options. Regarding how effective they will be and how effective they will be in what populations and scenarios raises a lot of complexity right now. The only thing that is certain is uncertainty, meaning that they are going to have to plan ahead but also be very flexible. They need to utilize the expertise

and mechanisms for vaccine distribution that are currently in place, but also pivot and be flexible to respond to the unique scenarios in which they might find themselves. Vaccine tracking would be a good example, but he thinks there are many others. OWS will rely on ACIP's expertise to inform them of the best way to get this done.

Dr. Lee expressed her hope that there continues to be a real-time connection between OWS and ACIP, especially as they continue to review evidence in real-time as a picture emerges. This particular process offers the opportunity to have openness and transparency about the process of ACIP's decision-making. There is a critical nature of a COVID-19 vaccine in general to the health and welfare of the general population, but also she sees this vaccine as being critical to ensuring that public trust and engagement can be maintained in immunizations in general. She expressed her hope that this might be an opportunity for early engagement and partnership. In the pre-distribution phase, knowing that certain vaccines may be targeted for certain populations because of their benefit/risk profile, it would be extremely helpful to think about targeted educational and engagement efforts with those priority populations in the pre-distribution phase. Even more critical and incredibly important is to ensure that in the post-distribution phase, tracking can be done. Vaccine safety surveillance in the post-distribution phase will be critical to continuing to inform decisions in real-time. She anticipates that they will have to adapt as they go, because there are so many uncertainties, but being able to link more tightly between distribution, tracking, monitoring, and particularly who is getting the vaccine in terms of risk populations, occupational risk exposure, age, et cetera will be incredibly important for ACIP as they are monitoring vaccine safety after distribution occurs.

Dr. Hepburn agreed 100%. He feels like it is a privilege to be part of a US government team that includes the CDC that has a lot of experience and thoughtfulness in terms of how to accomplish that mission, leveraging experience from a lot of other issues and incredible challenges in communicating effectively about vaccines. He was glad that their FDA colleagues were able to chime in about some of the tenants they had talked about during this meeting, such as transparency and ensuring that the vaccine is safe and effective, to make it clear about their independence in the review process. OWS has to do a better job of communicating that as an institution, but he thinks they will. They certainly will value ACIP's help in this. One thing he would ask ACIP, the people on the phone, and the government team is to learn the lessons of the past in terms of how they communicate about vaccines and also think about how to stay one step ahead of the misinformation. He said that since he is not an expert in communication, he will rely on others to be thoughtful about that. OWS anticipates that there will be a lot of misinformation and how deleterious that can be. He wants them to collectively be creative about how they stay one step ahead of it. He agreed that clear communication and transparency is a great first step.

Dr. Bell took this opportunity to reiterate a few of the points made. She was very happy to see and hear that OWS and ACIP share many common principles of transparency, integration, and using science-based policy. She reiterated that the ACIP is comprised of experts who have been appointed by the HHS Secretary, and that the ACIP has been in existence for decades. As Dr. Hepburn mentioned, OWS is a new organization. ACIP stands ready to help OWS in its efforts. They need to work together to succeed. The ACIP has developed a very well-oiled and high respected process for taking scientific information as it becomes available and using it to develop policies that are evidence-based and look to have the largest impact in terms of



preventing morbidity and mortality and reducing spread, and which are designed to strengthen and continue to inspire confidence of the public in the way in which ACIP make decisions about vaccine policy in the US. As Chair of the COVID-19 Vaccine WG, she invited Dr. Hepburn to engage with them early and often. ACIP feels that they have quite an important role to play and that they can help with many aspects of this process as it develops.

Dr. Hepburn said that he greatly appreciated Dr. Bell's comments and is certainly in favor of continuing the dialogue.

### **Landscape of Candidate COVID-19 Vaccines**

**Kathleen Neuzil, MD, MPH, FIDSA**  
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In terms of what is known about SARS-CoV-2 pathogen and immunity, Dr. Neuzil emphasized the importance of the spike glycoprotein. In terms of vaccine development lessons from other coronaviruses, looking at sequence comparison, the MERS Spike S protein is about 30% homologous to SARS-CoV-2. The SARS Spike S protein is 80% homologous. It is known that both of those prior coronaviruses had good vaccine responses to several vaccine constructs in animals. There were vaccines that made it to Phase 1 human for both SARS and MERS. They showed broadly neutralizing antibodies. MERS development continues. Unfortunately, SARS investments were re-allocated. Therefore, SARS vaccine development did not get very far.

The SARS-CoV-2 Spike protein is important for viral entry. Everything mentioned earlier from Dr. Thornburg about immunity is exactly what makes this spike protein a target for vaccine development. As Dr. Thornburg very nicely explained the characteristics of this protein, so Dr. Neuzil did not repeat them. She pointed out that in the context of vaccine development, they would hear a lot about the type of spike protein used in terms of whether it is the full length protein, receptor binding domain, and whether it is the prefusion or post-fusion form. Similarly, a lot of Dr. Thornburg's explanation was about why certain antibody tests are also relevant to vaccine development. The spike protein is a metastable protein that undergoes a major structural rearrangement to fuse the viral membrane with the host cell membrane. The idea with vaccines is to try to disrupt that binding. Some people are using the wild-type confirmation, but there also has been a prefusion confirmation and stabilization of the prefusion form of the spike protein described by investigators at the VRC at NIH where they inserted two stabilizing proline mutations that have been effective for other betacoronaviruses.

In terms of what is known about immunity in humans, attempts are made to try to parrot vaccine development on what works with natural infection. Unfortunately, little is known. There is an immune response post-infection. Neutralizing responses are seen post-infection. They do not cross-react with the SARS virus. What is not known that would be helpful to vaccine development is the level of antibody needed to prevent reinfection, the duration of protection from natural immunity, or how important T-cell immunity is to prevent infection or reinfection.

There are some hints from animal models. In fact, there are two non-human primate (NHP) models that show that if rhesus macaques are infected and an attempt is made later to re-infect them, the initial infection does protect against re-challenge. This is a positive for developing a vaccine. However, it is known that these experiments are done with relatively small numbers of animals and the re-challenge was done fairly close in time to the initial challenge at 28 days in one study and 35 days in the other. Though this is still an unanswered question, animal models are supportive.

It is known that vaccine development is a lengthy, risky, and expensive process. Generally, an accelerated timeline might mean 6 to 7 years compared to the usual 15 to 20 years. It is important to understand that these timelines are being compressed with investments in finances and resources with at-risk manufacturing and other at-risk choices. Compromises are not being made in terms of safety or safety follow-up. Nevertheless, one target being estimated for COVID vaccines is 12 to 18 months. This would represent a quite rapid timeline for initial identification of the organism almost to vaccine development.

In terms of vaccine platforms and attributes, all of the platforms that are licensed for another vaccine target are also slower to initially mix. When people ask Dr. Neuzil why it is the unproven technologies the government is currently testing, it is because they have the advantage of speed of manufacture. The tried and true licensed platforms will be coming along in the next month and also will be tested. That being said, the reason that these new platforms have not been licensed does not necessarily mean that they do not work. While this is a scientific endeavor, vaccine development is also business- and market-driven. Many of the DNA and RNA vaccines have been used for emerging infections in which the market then went away, such as SARS in which the vaccines were stopped, and the investments were reallocated to something else. Or perhaps they were used for a vaccine such as influenza for which there is a quite competitive market in which a new vaccine may not be able to compete. The fact that there is not yet a licensed platform should not imply that these are inferior vaccines that could not be safe, immunogenic, and effective.

In terms of dosing, a single dose would be nice in an outbreak situation. It is highly unlikely in a naïve population for most of these platforms that there will be efficacy after a single dose. However, most of the platforms will require multiple doses. Scale is also important. This is a pandemic and there are 320 million people in the US and 8 billion people in the world. If each of them needs 2 vaccines, it is clear that having platforms that are able to be scaled will be necessary and it would be nice to have multiple wins with 3, 4, or 5 licensed vaccines on the market in a short timeframe.

Regarding the COVID-19 vaccine candidates that are in clinical development, one of the furthest along is the non-replicating viral vector that is in a Phase 1/2/3 study in the United Kingdom (UK). This is an adenovirus vaccine. There were similar but small numbers of people in these trials for MERS, influenza, tuberculosis (TB), chikungunya, and Zika vaccine. This vaccine will enter clinical trials in the US hopefully in the next month and a half or so. There also is a non-replicating viral vector based on an adenovirus Type 5 by a Chinese manufacturer that has entered Phase 2. The second clinical trial in the US was with an mRNA vaccine by Moderna. While there has never been a licensed platform with the mRNA vaccine, the same platform has been used for influenza, Zika, and chikungunya. Novavax has a protein subunit

vaccine that has started Phase 1 testing in Australia. Pfizer in collaboration with BioNTech has 3 different formulations of an mRNA vaccine currently in Phase 1 in the US and Europe. There is a DNA vaccine by Inovio. Multiple Chinese developers have inactivated vaccines, plus or minus alum, in Phase 1/Phase 2 development. The ChAdOx1-S, mRNA, a protein subunit vaccine, and a DNA vaccine should be expected soon in the US.

One reason the nucleic acid vaccines can make it to clinic a lot faster is that what is needed is the genetic sequence. Then the genetic sequence can just be substituted for whatever genetic sequence was in the prior formulation of the vaccine. That is, a COVID RNA replaces an influenza RNA. No fermentation or optimizing cell cultures are required, so these can move very quickly. A DNA vaccine has to make it to the nucleus of the cell and needs some help with that, which is why either electroporation or devices are used to deliver DNA vaccines. Similarly, RNA vaccines only need to make it into the cytoplasm. They are encased in a lipid coat that helps them to enter cells. An individual's myocytes make the viral proteins and then the body makes the immune response.

In terms of the Moderna vaccine, a peer-reviewed publication is expected soon with the Phase 1 results. Phase 1 began in healthy adults 18-55 years of age in March 2020. As announced on May 18<sup>th</sup>, after 2 doses all participants evaluated at the 25 µg and 100 µg dose seroconverted with binding antibody. Because there is not a level of binding antibody known to be protective, they are being compared to convalescent sera. The convalescent sera can be quite diverse in the responses. Nonetheless, these participants had binding antibody levels at or above the levels seen in convalescent sera. Similarly, neutralizing antibody titers (the ability to stop the growth and spread of the virus) reached or exceeded neutralizing antibody titers seen in convalescent sera for patients who had recovered from COVID. These vaccines were generally safe and well-tolerated and provided full protection against viral replication in a mouse challenge model. It is anticipated that Phase 3 will begin in July 2020.

The viral vector vaccines are another example of gene-based vaccines for which a protein does not need to be made, so these can be manufactured faster and get into clinics sooner. This may be a replicating viral vector such as a weakened measles vaccine for which the coronavirus spike gene is inserted or a non-replicating viral vector vaccine such as the adenovirus vaccine. The myocytes make the proteins and the body hopefully will make an immune response. A [publication](#) by Feng-Cai Zhu et al in May 2020 discussed the safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored vaccine. Regarding adverse events at a low, medium, and high dose, there was reactogenicity of pain at the injection site in about 50% or more participants at all 3 dose levels. For adults, Grade 3 fever was lower. Any fever was about 40% to 50%, so there is some reactogenicity with these vaccines. Immunogenicity was seen with the enzyme-Linked Immunosorbent Assay ELISA antibody and the neutralizing antibodies in the lower, middle, and high dose. The antibody peaks at Day 28. There is a dose-dependent response for both the ELISA and neutralizing antibody. As has been seen with other adenovirus vaccines, a high pre-existing Ad5 neutralizing antibody response compromised the neutralizing antibody to COVID post-vaccination, regardless of vaccine dose.

All of these trials go through full FDA review and full ethics review and safety is taken very seriously every step of the way. In addition to the reactogenicity measures, animal studies are being done in multiple animal modes to look for any vaccine-enhanced illness. The question was asked earlier about antibody-dependent enhancement of viral replication. This has been shown primarily by viruses with an innate macrophage tropism such as Dengue. In the case of COVID, there may be more concern with a vaccine-enhanced respiratory illness. So what is being looked for in the animal studies are the inflammatory cytokines, a Th1 versus Th2 response, and looking at neutralizing antibodies versus non-neutralizing antibodies. In terms of what this means for human studies for a vaccine-enhanced respiratory illness, one might worry about that occurring a little bit later in time at perhaps 1 to 2 years after getting a vaccine when the functional neutralizing antibodies start to wane. In all of the Phase 3 trials with the government, participants are being followed out to 2 years.

In summary, safe and effective vaccines are needed that are accessible, affordable, and globally available for COVID-19. There is a robust pipeline of promising candidates in clinical development, and multiple wins are needed. There are many challenges. This is a new disease with poorly understood immunity. As these large Phase 3 trials are planned, there is an uncertain trajectory of the outbreak and whether there will be sufficient attack rates to show efficacy. Vaccine safety will be meticulously assessed. If enhanced disease occurs, it will be carefully assessed, and immune mechanisms will be investigated.

### **Discussion Points**

Dr. Atmar observed that while some of the safety concerns suggested may not show up for 1 to 2 years after vaccination after neutralizing antibody wanes, an efficacy signal may be evident earlier, at least for short-term protection. In consideration of rolling out vaccines as expeditiously as possible, he wondered how to balance early signals of potential efficacy against unknown risks of safety that may not appear until later during the follow-up.

Dr. Neuzil replied that depending on the vaccine construct, she did not know that they would expect antibody-dependent enhancement for this particular disease based on what is known about the immunology. Likewise, enhanced respiratory disease has been seen primarily in children. That may be partially due to the anatomy and the small airways. Nonetheless, because with the original SARS and MERS there was a lot of discrepancy in terms of some animal models showing disease enhancement and some not, this will be very carefully explored in animal models. In the interest of time, she did not show the animal models that have been conducted, but there are quite extensive studies being done in animals to look for any signals. There is a risk-benefit ratio in terms of development, evaluation, and use of vaccines. In the midst of this pandemic, there is unprecedented morbidity and mortality in high-risk groups and unprecedented economic consequences. The benefit side of these vaccines must be considered. It would be fantastic if a vaccine is licensed sooner and has to be given to the control group, the original participants would continue to be followed. She welcomed comments from the FDA as well.

Dr. Fink (FDA) added that FDA is looking at many potential sources of data to inform the risk of enhanced respiratory disease throughout the clinical development of COVID-19 vaccine candidates. These sources of data include characterization of immune response in the animal models and early phase clinical study participants, neutralizing and antibody responses, Th1 versus Th2 polarization, the ability of the vaccine to protect animals against challenge in appropriate animal models, and looking for histopathological evidence of enhanced respiratory disease to the extent that those types of studies are feasible. As Dr. Neuzil mentioned, there will be careful follow-up of study subjects for the long-term of 1 to 2 years at least to continue to assess vaccine safety for participants in early studies and Phase 3 efficacy trials, even if there is a signal for efficacy or at least demonstration of efficacy sufficient to support wider distribution of the vaccine before longer-term follow-up has been completed for all of the subjects.

Dr. Baker (IDSA) asked whether there would be a single-dose arm evaluation in the US trials or if all arms would be 2 doses to begin with.

Dr. Neuzil replied that this depends upon the vaccine. The furthest along are the RNA vaccines. Everything that is known about mRNA vaccines is that it is likely to take more than one dose, so those will be 2-dose vaccines. The adenovirus vaccine that is being tested in the UK is being tested as a single dose vaccine. Some subjects are receiving 2 doses, but the majority are receiving 1 dose. It is possible that some of the viral vector vaccines will be single dose or there will be both a 1- and 2-dose arm as part of the trial.

Dr. Poehling observed that there is a tension when thinking ahead about the compressed timeline and RCTs. One is to make sure what is going to happen in healthy persons, but it is known in COVID-19 that people with obesity and other underlying conditions have more disease. Consideration must be given to balancing the need to represent them and other age groups.

Dr. Neuzil indicated that the Phase 1 trials and the data she was able to show so far were in young and middle-aged healthy adults. In fact, all of the Phase 1 trials quickly expanded to older adults 65 to 85 years of age or even older. People are aware of the epidemiology and where it is important to be sure to understand where these vaccines work. Most of the clinical trials with which she has been involved are including older age groups, people with chronic diseases, and are targeting a relatively modest to high percentage of people by setting benchmarks for getting at least X percent of people in some of the high-risk categories.

Dr. Szilagyi inquired as to when Dr. Neuzil thinks there will be trials with children and whether she had any sense about the different platforms that might suggest whether the efficacy would vary across the platforms for children, older adults, and/or race and ethnicity.

Dr. Neuzil indicated that there will be trials in children, though she could not indicate timing, plans, or how quickly. One of the first vaccines and the further ahead, the ChAdOx1-S at Oxford, already has plans to age deescalate relatively soon. While she did not have the exact timeline, it is part of the clinical development plan. In the US, there is a team thinking carefully through this, how it should be done, and preparing for these trials when they feel it is safe to do so. In terms of a construct, just getting back some of the Phase 1 data, which they do not have yet, in the different age groups will be very helpful to look at the difference. It is known that for many vaccines, immunogenicity starts declining as early as in the 40s. This is seen with

influenza vaccine as early as in the 50s. It is known that immunosenescence is real. Looking at some successes in the older populations, higher doses of antigen are used for influenza vaccine and adjuvants with protein subunits that have been successful for zoster and influenza. There are vaccines that can work better in children. What is not known is whether that is because they are naïve or because they are children. It is a great question and it may well be that if there are multiple constructs, there will be formulations that are better for different age or risk groups. They also should not forget that monoclonal antibodies are being tested in terms of whether that could be used for post-exposure prophylaxis (PEP) in, for example, very debilitated elderly or immunocompromised individuals who may not be able to mount an immune response to any of these vaccines.

Dr. Bernstein wondered about how adequate sample sizes are being established as they move through the phases of vaccine development and they want to use them in multiple populations, especially those at high risk, for each of the platforms and for multiple populations.

Dr. Neuzil indicated that the initial trials will probably be close to 30,000. Part of the reason for that is that the attack rate is unpredictable, and speed and timing are important. They can either increase power by increasing sample size or the trial can go longer. In a pandemic, it is preferable not to have the trial go longer. She believes that these will be well-powered efficacy studies.

Dr. Frey observed that mouse and NHP models are frequently used to study responses to experimental COVID vaccines, but she wondered what the best animal model is for studying SAEs, specifically enhanced disease, to these vaccines or whether they really know.

Dr. Neuzil said she was not sure what she would use as a gold standard for that. If the gold standard is human disease, that is not yet understood.

Dr. Fink (FDA) added that the NHP model is probably the best at this time based on prior experiences with other coronavirus vaccines. His understanding is that there has been work more recently on other models such as hamster models. There is ongoing work to identify, develop, and characterize animal models that potentially could serve to evaluate the potential for enhanced respiratory disease.

Dr. Cohen indicated that they could try to include a brief update on animal models and studies during the next virtual ACIP meeting.

Ms. Bahta asked what is being done to ensure that the cohorts being studied are representative of the US population, particularly among communities of color where a higher proportion and more severe disease are occurring.

Dr. Neuzil acknowledged the recognition that Native Americans, African Americans, and Hispanic populations are suffering disproportionate morbidity and mortality. The rapid timeline is working against investigators because it is known that trust is built over time, which there is not a lot of. They are trying to capitalize on already established mechanisms to reach these communities. CDC is involved in some of these committees in terms of outreach and identifying

the leaders of some of these minority communities as quickly as possible so that they are well-represented in the research efforts.

### **COVID-19 Vaccine Prioritization Considerations**

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**Co-Lead ACIP COVID-19 Vaccine Work Group**

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Dr. Mbaeyi review the WG's considerations for COVID-19 prioritization. Although the goal is to offer vaccine to the entire US population, identifying priority groups for COVID-19 vaccination is essential to support vaccine implementation planning. This planning needs to begin prior to vaccine approval so that vaccine can be distributed without delay once available. However, vaccine prioritization is challenging due to incomplete information on COVID-19 epidemiology and vaccines, including characteristics, timing of vaccine availability, and number of anticipated doses. Regardless, it is essential to start identifying priority groups now with the information available to date, with continuous reassessment as data become available. Identifying priority groups for COVID-19 vaccine will allow for strengthening vaccine distribution networks to reach the target group, develop state and local micro plans for vaccine implementation, create communications strategies to promote vaccination in priority groups, and plan evaluations to rapidly monitor vaccine safety, effectiveness, and coverage.

Although there are important differences between COVID-19 and influenza, reviewing the pandemic influenza experience and lessons learned is useful in planning for COVID-19 vaccine prioritization and implementation. Preparing for vaccination during a pandemic has long been a priority of CDC and the US government. Prior to the 2009 H1N1 pandemic, multiple efforts were undertaken to outline the initial vaccine prioritization strategy, gain public and stakeholder input on priority groups, and develop guidance for allocating and targeting influenza vaccine during a pandemic. Following the emergency of the pandemic H1N1 virus in April 2009, vaccine first became available in October 2009 during the second wave of disease. ACIP recommended priority groups for initial vaccination, including certain persons at increased risk for severe disease and HCP, followed by vaccination of the general population. Other essential workers were not among the initial priority groups as that pandemic was not deemed to threaten the critical infrastructure and societal function.

However, several challenges were encountered during the vaccination response. Public demand for vaccine was highest during the period when a large number of cases were still being reported and vaccine supply was low and targeted toward the priority groups. Once vaccine was widely available, the pandemic had started to wane in the US and public demand for vaccination was low. By late January 2009, vaccine coverage was 20% among the US population. The challenges of vaccine supply and demand were noted to have shaped other aspects of the response. Notably, the overly optimistic vaccine supply projections led to raised expectations that were identified initially, leading to logistical and communication challenges. In addition, restrictive enforcement of priority groups paradoxically led to a vaccine surplus in some places. Additional challenges were encountered when expanding vaccination beyond the priority groups, including when to do so and how to communicate it effectively to the general public. The

importance of population values and vaccine prioritization was also noted. For example, the exclusion of older adults in the initial priority groups led to overall reduced acceptance of vaccine in AI/AN populations because of the important role the elders play in those communities. Finally, while it is necessary to have national guidance, state and local flexibility in vaccine implementation is important due to the varying needs in infrastructure despite challenges that may arise when challenges vary across jurisdictions. While these lessons learned from the H1N1 experience are valuable, the complexity of the COVID-19 pandemic likely will lead to new challenges.

Based in part on lessons learned from the H1N1, guidance for allocating and targeting pandemic influenza vaccines was revised in 2018. In this revised guidance, occupational and high-risk populations are grouped into tiers for vaccine prioritization. This guidance serves as a useful framework for adaptation to COVID-19 vaccine prioritization. As mentioned before, the prioritization framework is a roadmap for vaccine program planning. The tiered priority groups to be adapted for COVID-19 vaccination would need to be adapted based on the burden of disease and severity in risk groups, the pandemic's impact on society and critical infrastructure, characteristics of the vaccines, and the number and timing of doses that will be available.

Taking these factors into account, the WG discussed considerations for identifying COVID-19 vaccine priority groups. ACIP provides advice to the CDC Director and HHS Secretary on use of vaccines in the US civilian population in a transparent, evidence-based process. To help inform ACIP deliberations around use of COVID-19 vaccines, including the identification of priority groups for vaccination, the work group reviewed the epidemiology of COVID-19; characteristics of vaccine candidates under development; and evidence-based vaccine recommendation, ethics, and equity frameworks. The WG first developed proposed objectives for the COVID-19 vaccine program, which are to: 1) ensure the safety and effectiveness of COVID-19 vaccines; 2) reduce overall transmission, morbidity, and mortality in the population; 3) help minimize the pandemic's disruption to society and economy, including maintaining healthcare capacity; and 4) ensure equity in vaccine allocation and distribution. The objectives formed the basis for developing considerations for priority groups for vaccination.

Because of the current gaps in the understanding of COVID-19 disease and vaccines, the WG made a number of guiding assumptions when considering priority groups for vaccination. In light of the evolving understanding of COVID-19 epidemiology and immunology, the WG assessment is that prioritization should occur based on the information available to date and be continually defined as new data become available. The WG also assumes that a substantial proportion of the US population, regardless of age, location, or occupation remains susceptible to COVID-19. Second, there are currently no data on the safety and efficacy of COVID-19 vaccines under human clinical development in the US that are publicly available. Vaccines will not be administered until safety and efficacy have been demonstrated. However, the WG feels that concerns for reduced efficacy in certain populations such as older adults and immunocompromised individuals should not preclude them as priority groups while data are pending. Finally, the timing and number of vaccine doses that will become available are still unknown. The WG assumes that the number of initial doses is still unknown. The WG assumes that the number of initial doses may not be sufficient to vaccinate everyone in the priority groups, necessitating sub-prioritization. In addition, the WG assumes that vaccine doses will become available in incremental quantities over several months.



The WG then used principles for multiple frameworks to guide discussions on priority groups. The WG reviewed the pandemic influenza framework in which vaccine allocation decisions are made on the basis of burden of disease and severity, pandemic severity and impacts on society, and vaccine supply. Building off of this, the WG reviewed principles from the Evidence to Recommendations (EtR) Framework that ACIP uses to make evidence-based vaccine recommendations, including the burden of disease and severity, benefits and possible harms, values of the target population, acceptability to stakeholders, and feasibility of implementation. Finally, the WG reviewed ethics and equity principles, including the desire to minimize death and serious disease; preserve functioning of society, including the protection of individuals who are relied upon to fight the pandemic; and reduce disproportionate burden on those with existing disparities. As part of this, the WG affirmed that consideration should be given to maximizing benefits and minimizing harms, utilizing a transparent and fair process, assuring the just and fair stewardship of vaccines, and removing barriers to vaccination.

The discussions guided by these frameworks led to a proposed general approach for prioritization primarily to help with operational planning for vaccine implementation. The WG recognizes that this is an iterative process with priority groups to be refined as more information becomes available. The WG's assessment is that healthcare and other essential workers and high-risk populations should be vaccinated first, followed by general population. In this proposed highest priority group, persons at increased risk for severe COVID-19 include adults aged  $\geq 65$  years, long term care facility (LTCF) residents, and persons with high-risk medical conditions. Among the initial target group, the WG proposes that a subset of critical healthcare and other workers should receive the initial doses. This includes the highest risk medical, national security, and other essential workers in order to protect the healthcare infrastructure and other critical societal functions. Given the large population size of the remaining groups, further tiering of target groups may be necessary based on vaccine supply and program planning needs. There are several remaining information gaps in certain population subgroups, including the risk of disease and severe outcomes, vaccine safety and efficacy, and transmission dynamics and level of population immunity. These additional data would be helpful to inform prioritization, though decisions may need to be made in the setting of unknowns in order to proceed with vaccine implementation planning and avoid delays once a vaccine is available.

In summary, identifying priority groups for initial COVID-19 vaccination prior to the approval of a vaccine is critical for implementation planning. Lessons learned from the H1N1 influenza pandemic highlight importance of national guidance while allowing for state and local flexibility in implementation. The WG proposes priority groups for COVID-19 vaccination, including healthcare and other essential workers and persons at increased risk for severe disease. The prioritization will need to be refined as more information becomes available.

ACIP's feedback was requested on the following questions regarding key population groups in order to support vaccine program planning:

- Does ACIP agree that critical healthcare and other workers should be in Tier 1 for vaccination?
- What are ACIP's thoughts on prioritization for residents of LTCF, other congregate settings, children, and pregnant women?

- How should racial and ethnic groups at high risk for severe COVID-19 be prioritized? Should race and ethnicity be a criterion for vaccine prioritization?
- Are there other data that ACIP would like to review to help inform prioritization?

In terms of next steps, the proposed priority groups to be further refined based on ACIP's feedback with a goal to have a completed draft prioritization framework at the next meeting.

### **Discussion Points**

Dr. Ault noted that ACIP went through the process shown on Slide 5 specific to pregnancy with the 2009 influenza pandemic. There is plenty of good information, white papers, and experience from that exercise that would help with this process as well.

Dr. Hunter expressed concern that it may be necessary to distribute and administer vaccines for COVID within a narrow window of time, and wondered whether it is necessary to achieve enough immunity and enough people simultaneously in order to slow or end the pandemic. Immunity after COVID illness appears to be short-lived, which raises concern that the peak immunity also may be short-lived. Therefore, it may be necessary to vaccinate everybody at the same time to achieve herd immunity. He asked whether these concerns had been discussed within the WG.

Dr. Mbaeyi indicated that the WG has discussed issues pertaining to transmission and levels of immunity. The plan is to address this further as the WG meetings progress and during a future ACIP meeting. There are still some data the WG would like to review to help inform some of those decisions. At this time, the WG feels that the subsets of HCP and other essential workers should be the first to be vaccinated.

Dr. Szilagyi said he thought the reason they were not seeing hands raised is because this is so tough. He does think there will be a need for prioritization and appreciated mention of "critical healthcare workers." He is a healthcare worker but would not consider himself to be a critical healthcare worker, so he thinks there will need to be differentiation even in Tier 1. He thinks they have to follow the data as much as possible for LTCF and Native Americans, for whom the data are profound. The data about children not being affected as much by the coronavirus and being largely asymptomatic are also pretty strong. He is struggling about what to do with race and ethnicity. It is clear that African Americans, Native Americans, and Latino populations are at higher risk and that a large part of that has to do with underlying conditions and access barriers. There should be a focus on underlying conditions, eliminating barriers, and inversely increase the level of intervention for people who have barriers to access (low-income populations, people who have difficulty reaching healthcare). Interventions should be optimized for those groups. He is still struggling with which tier to put that last group in.

Dr. Romero commented that if they fail to address the issue of racial and ethnic groups as a high risk in prioritization, whatever comes out of ACIP will be looked at very suspiciously and with reservation. Dr. Szilagyi suggested improving healthcare access to these groups, but this will not address the problems that exist now. These individuals already have significant comorbid conditions that will not be reversed in a matter of months. Therefore, this issue must

be dealt with at this time with the information available. These groups need to be moved to the forefront in his opinion, which can be further discussed within the WG.

Dr. Sanchez agreed that this is a very difficult process and that there are racial groups that are at highest risk. Mandatory vaccination of HCP as is done with influenza is also going to shift numbers. There has not been success with prioritization of groups with influenza vaccination. He recalled that when high risk groups were targeted initially with influenza vaccines, children who were seen in clinics were not in high risk groups and were expected to return to get vaccinated. He thinks they will have to be accepting of some lower risk groups as vaccine supply becomes more abundant, because they may end up not being able to provide a sufficient immunity length to curb the pandemic. Strict prioritization could result in many high-risk people not wanting to get the vaccine for whatever reason. He has seen estimates in some surveys of 50% to 60% for a potential vaccine.

Dr. Mbaeyi clarified that CDC does not make mandates for vaccination, including for HCP. This typically would be determined within a hospital system. Any sort of recommendation made by ACIP would not imply a mandate for vaccination.

Dr. Poehling said she also was struggling with race and ethnicity because of the numbers they saw earlier. She lives in a state where there are multiple poultry factories with profound impact, which also overlaps with race/ethnicity. She asked whether the “other” category would include poultry workers and other areas that have been particular hotspots.

Dr. Mbaeyi said that what the WG had discussed thus far was identifying not only critical healthcare, but also essential workers. A number of potential groups could be considered in the highest tier. The next steps would be to drill down to identify which particular groups would be the most critical to go in the first tier, given that there are many people who provide essential and helpful services, understanding that the others would follow in subsequent groups for prioritization. They welcome any thoughts on that as well.

Dr. Frey emphasized the importance of putting the topic of racial/ethnic groups squarely on the table, which appeared to be what most people preferred. It is very important to put the groups into a high tier—maybe not the whole population, but parts of those populations such as urban poor and working poor. Disadvantaged populations have a lot of comorbidities because they do not have access to healthcare because they cannot afford it, but they also are living in crowded conditions compared to other people in which there are multiple family members living in small apartments for example. Also, the working poor have to work. They cannot take off like some people do because they have to feed their families, so they also are disadvantaged in that way. She is a big proponent of prioritizing some of these groups in some areas, certainly to address people living in urban areas in crowded conditions.

Dr. Atmar asked whether “other congregate settings” includes prisons. Regarding one of the decisions the WG made about including or not excluding from the prioritization those groups who have historically had poor immune responses but might not be included in vaccination studies. Certainly, the LTCF and nursing home residents represent populations that are at extreme risk based on data that have been presented. They also are populations who have been less well-protected against influenza. It is important to vaccinate the HCP taking care of

the residents or the personnel working in the facility to provide protection. From his understanding, this population is not being targeted for active immunization, but instead would be targeted for passive immunization, at least in a lot of initial studies. As an at-risk group, he wondered whether they should be targeted for vaccination studies as well. He said that while he understood the rationale for why that might not happen initially, he was conflicted by recognizing that they are a group at particular risk and also that they may be a group less likely to benefit from vaccine when there are other groups that might benefit to a larger degree. He wondered what the WG thought about those questions.

Dr. Mbaeyi clarified that “other congregate settings” could include prisons, homeless shelters, or other areas where people are in close quarters with one another where there have been outbreaks. The WG has discussed LTCF residents at length and recognizes that they are at extremely high risk, but currently there is not any evidence either way regarding their levels of protection in terms of efficacy. Therefore, the WG in general felt that they should continue to be considered a high priority group and if data emerge that suggest otherwise, this can be re-evaluated continuously. Given their high-risk and high death rates, they continue to be viewed as a high priority group. In addition, the WG discussed the workers and HCP at these facilities and also felt that they should be considered highly for vaccination given their role in taking care of this vulnerable population. When there are data on vaccines, these decisions can be reassessed.

Dr. Atmar asked whether this also could be reassessed if passive immunization strategies are effective.

Dr. Mbaeyi indicated that this is not something the WG is evaluating.

Dr. Cohn reminded everyone that these are still very early discussions at ACIP and among the WG. The reason they wanted to have this public meeting was to acquire ACIP’s input on where they should go with some of these discussions. These things will evolve as they get more data and continue to think these issues through, and they will be discussed again at future meetings.

Dr. Bernstein agreed about how difficult this discussion is. He expressed interest in knowing how the 5 tiers were established. It seemed to him that there was a huge overlap of the populations within each tier and also between the tiers. He also wondered what role the success of vaccine development would play in perhaps shuffling the different populations into different tiers.

Dr. Mbaeyi indicated that this was derived from the 2009 pandemic influenza guidance. The tiers were developed based on the recognition that there would be a need for not only vaccine supply reasons, but also for vaccine implementation reasons to have tiers of priority groups identified based on their population size, risks, et cetera and recognizing that it would be unlikely that the entire population could be vaccinated at the same time. That was the genesis behind the proposed tier structure for COVID-19. If an adult HCP is in Tier 1, they would not also fall into another tier where healthy adults are addressed. There should not be a lot of overlapping populations between the tier groups.

Dr. Messonnier added that the 5 tiers do not represent a magic number. This last came out in 2018. The initial process to develop this took multiple years and involved a lot of stakeholder and public outreach. Because so much groundwork already had been done, the WG began with the same framing knowing that unfortunately they do not have 2 years to figure it out. This is not meant to hold ACIP to 5 tiers. Of course, when more data become available on the different vaccines, the tiers will be adjusted. If the first vaccine available is less immunogenic in older adults, that would change the tiering. The issue now is that they need to start planning and some of these early considerations have significant impact on operational planning for the fall. They recognize that they are asking ACIP to do an insurmountable task in the absence of sufficient data. Yet, this is the situation in which CDC finds itself. As always when faced with tasks that seem insurmountable, CDC seeks advice from ACIP. CDC recognizes that ACIP does not have perfect information, yet the agency has never needed ACIP's guidance more than now.

Dr. Szilagyi asked whether the WG considered combining underlying conditions (cardiopulmonary, obesity, diabetes, access problems) as an example of a group of patients.

Dr. Mbaeyi referred to Slide 17, indicating that the WG did place persons with underlying conditions in the priority group to be vaccinated. That would include the people to whom Dr. Szilagyi referred.

Dr. Cohn clarified that the slide that was up for discussion was to address some additional groups who were not defined as specifically in the proposed priority groups.

In thinking about return to school, Ms. McNally asked whether there had been discussions about teachers.

Dr. Mbaeyi indicated that the WG has been discussing teachers. The WG views the next task to drill down to be more specific to define certain types of workers. Teachers have been discussed and the WG wants feedback on that as well.

Dr. Poehling pointed out that closure of schools has had profound impact on some adults throughout communities, so they probably should talk about teachers and children. The negative impacts on their educational attainment are becoming quite clear.

Dr. Hunter wondered whether they were looking at the groups in the wrong way. As a local public health representative, he was thinking that the venue and mechanism of getting the vaccine out as quickly as possible to as many people as possible may be more about targeting particular venues, areas, and groups of clinics like Federally Qualified Health Centers (FQHCs). This is definitely not the time for shared clinical decision-making between the patient and physician. Maybe it should be about whomever wants it gets it now in order to get as many of the shots out as quickly as possible. If they are setting it up to be an individual patient-by-patient decision between a clinician or healthcare system trying to set up a decision tree that each clinician or clinic has to decide, that might be the wrong way to do it.

Dr. Messonnier stressed that what Dr. Hunter just said is the key point. CDC's plans to operationalize this are to target groups rather than individuals. She can visualize approaches for the essential workers and others in the Tier 1 groups to easily access them by going through the places they work, such as hospitals and poultry plants, to take the vaccines directly to them. They still will leave room for individual decision-making for folks who are not in these higher risk groups. They do think that FQHCs represent a key group, which CDC is working with now in terms of influenza vaccination. If ACIP says they want CDC to prioritize minority groups, they would look to see where they could best access those groups. That might be partly through FQHCs, beauty salons, or other places where people tend to congregate. One of the reasons CDC wants this discussion early about how ACIP recommends the agency prioritizes is because then they want to turn it into operational planning with state and local health departments. They learned from H1N1 not to over-engineer it, but until ACIP articulates to CDC how the agency should prioritize, they cannot get to the next step of microplanning in each location. It is not just a top-down federal strategy. It is going to take the entire immunization infrastructure, including state and local health and local partners, to determine how to access priority groups.

Dr. Talbot thought it would be essential to know how the virus is transmitted and who is transmitting it. They learned a lot from pneumococcus in that is spread by children in whom very good vaccine responses are achieved.

Dr. Oliver indicated that the Epidemiology Task Force group at CDC has been working on some household transmission studies in some of the early outbreak areas throughout the country. As those data come in, they are helping inform to some extent who the primary index case and secondary case were in the household. Hopefully, they will be able to present those data to ACIP soon.

Dr. Frey suggested that it would be interesting to understand estimates for availability of product, production capabilities of the manufacturers, and in what countries products will be available from those manufacturers. Consideration may have to be given to different models based on the number of vaccines there actually are.

Dr. Messonnier agreed and indicated that information becomes available, they will be transmitting it. She stressed that it is likely that some of these discussions they are having will be in the absence of complete data. That being said, they have a general sense as always that they need to be flexible. In vaccine development, there are many potential areas where things can turn out differently than expected. The goal is to have enough vaccine by next year to vaccinate everyone in the American public. They are not talking about an end goal of 1 million doses of vaccine a year. They are talking about a goal of enough vaccine for everybody. However, it is unknown when those quantities of vaccine will be available or which vaccines it will be.

Dr. Romero pointed out that having increased numbers of vaccines and different products also adds another layer of complexity. What if a vaccine is efficacious but is not as efficacious as all of the vaccines? That also falls into the prioritization issue of the vaccine. It is great to have more vaccine, but they probably are not all going to be the same with regard to efficacy and

protection. That is going to lead them to having to think about more issues in terms of prioritization.

Dr. Bernstein noted that in the initial influenza recommendations, they were earmarking high-risk people and then over time transitioned to universal recommendations. He wondered with such a large percentage of the population being susceptible if they might need to be considering the family unit or something along those lines. It would be difficult to separate a mother/infant dyad. Taking a group approach, it was not clear how to separate that within families in a local community.

Dr. Frey asked how much discussion there has been around efficacy of these vaccines, what is going to be considered acceptable, and if it will be similar to influenza vaccine that has a rather limited efficacy compared to many other vaccines.

Dr. Messonnier said she thought it was premature to try to guess. The likelihood is that this vaccine will first be used under an EUA, but that is still under discussion. Like any vaccine, once it is licensed, the process will continue to be that CDC will come to ACIP for recommendations. It was a good question to ask whether ACIP would be routinely recommending a vaccine that has an efficacy more similar to influenza. There are a variety of groups at CDC and in the US government broadly who are working on modeling. They certainly can request a presentation to the WG to provide some input into the potential impact of a vaccine at different effectiveness levels so that ACIP can get a head start on thinking through how that might impact its recommendations.

Dr. Foster (APhA) emphasized pharmacy's major role in the distribution process of vaccines. One of the problems they had with the H1N1 process was that pharmacy was at a low priority for receiving the vaccines. One advantage is that they are distributed through almost every area, plus a lot of pharmacies have the ability to put a sign out front saying, "Get your vaccine here." He requested that they keep in mind that sooner distribution to pharmacies may be beneficial to getting the vaccine distributed.

Dr. Mbaeyi recognized that being more inclusive of pharmacies was a major lesson learned from H1N1.

Dr. Drees (SHAE) indicated that SHAE is very interested in how this vaccine would be distributed among HCP. SHAE has endorsed a policy for mandatory influenza vaccination for HCP and was in the process of expanding that to all vaccines recommended for HCP, though that got sidelined with COVID-19. Obviously, it would still be a local decision. Even within the smallest group of critical HCP, there will still need to be some prioritization. One struggle with H1N1 vaccine regarded whether to prioritize people who were most likely to come in contact with the disease versus those who were most likely to have severe consequences of the disease or some combination of the two. She assumed that being vaccinated would not change the PPE recommendations in any way. They are seeing the lowest infection rates on their COVID units because those personnel know that they are always dealing with COVID patients. The people not dealing with COVID all of the time are the ones getting infected. It just adds more complexity.

Ms. Hayes (ACNM) pointed out that in the entire conversation about vulnerable populations, they have to remember how many people are uninsured in people of color communities. They also must talk about who will be subsidizing this vaccine when it becomes available, because the vast majority of people who are uninsured are not going to want to pay out of pocket for it.

### **Work Group Considerations and Next Steps**

**Kathleen Dooling, MD MPH**

**Co-Lead ACIP COVID-19 Vaccine Work Group**

**Medical Officer, National Center for Immunization and Respiratory Diseases  
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Dr. Dooling summarized the considerations and discussions of the ACIP COVID-19 Vaccine WG, as well as the intended next steps. The WG looks forward to ACIP's feedback in order to achieve its work plan. The WG's proposed objectives of the COVID-19 Vaccine Program are to: 1) ensure the safety and effectiveness of COVID-19 vaccines; 2) reduce transmission, morbidity, and mortality of COVID-19 disease; 3) help minimize disruption to society and the economy, including maintaining healthcare capacity; and 4) ensure equity in vaccine allocation and distribution.

The WG is engaged with experts in several disciplines to ground its discussions in the best available science. There are a number of knowns and key unknowns that will be important for vaccine policy. With regard to COVID-19 immune response, it is known that most people with SARS-CoV-2 develop antibodies, usually within 2 weeks, and most patients mount neutralizing antibody responses. Key unknowns about the immune response regard the duration of immunity following SARS-CoV-2 infection, whether neutralizing antibodies protect against viral infection, and whether there are immunologic correlates of protection.

In terms of epidemiology in the US, it is known that there are multiple populations with evidence of high risk of COVID-19 disease or severity. Those include occupationally defined categories, such as healthcare or agricultural workers; people who have individual characteristics that put them at higher risk, such as older age or underlying medical conditions; inequities and social determinants of health (SDOH) resulting in disproportionate impact on people belonging to American Indian, Black, or Hispanic race/ethnic groups; and people living in congregate settings, such as those in long-term care, correctional facilities, and the homeless. People in congregate settings have been especially hard hit, and dramatically so when the individuals living within them are already at high risk. Outbreaks in long-term care, correctional facilities, and homeless shelters have demonstrated high attack rates of disease that are frequently accompanied with tragic case fatality rates.

Some of the key epidemiologic unknowns important for vaccine policy pertain to the proportion of viral transmission contributed by children; the risk of disease and severity in pregnant women; the true incidence of multisystem inflammatory syndrome in children (MIS-C) and the long-term sequelae; and the current level of population immunity and heterogeneity by factors such as geography, occupation, race, and ethnicity.



Of course, COVID-19 vaccine policy will depend on detailed understanding of the vaccines that are proven safe and effective in clinical trials. Multiple platforms are being utilized to develop COVID-19 vaccines. Multiple approaches increase the chances of developing safe and effective vaccines to meet national and global needs. Vaccines must meet stringent safety standards in clinical trials. Otherwise, they will not be used in the population. Some of the key unknowns regarding COVID-19 vaccines that will be necessary for policy include vaccine characteristics such as number of doses, route of administration, and storage temperatures required. It is also necessary to understand vaccine performance. For example, it is important to understand immunogenicity and efficacy by age and risk groups. It also would be helpful to know the interval from vaccination to protection. To understand the role of a future vaccine in controlling the pandemic, it is necessary to know the vaccine's effect on acquisition of infection and transmission. It also is necessary to understand any AE profile by age and risk groups. Finally, it is important to know the FDA approved populations.

To elaborate on that process, Dr. Dooling provided an overview of the path of a vaccine from clinical development to recommendation. The purpose of clinical development is to generate safety, immunogenicity, and efficacy data. Enhancements facilitated through OWS, which have been introduced to achieve the goal of a safe and effective COVID-19 vaccine, include close coordination and cooperation within government (OWS, DHHS, CDC, NIH, ASPR, and DoD), as well as the manufacture of vaccine during this early period which could save months if a vaccine is approved.

FDA's role is to apply stringent requirements to ensure the safety, purity, and potency of licensed vaccines where potency is understood to mean effectiveness. In specific circumstances, FDA may grant EUA for the use of an unlicensed vaccine or for the use of a licensed vaccine for an indication that has not yet been approved for labeling, such as the case of anthrax vaccine adsorbed (AVA) that received EUA for post-exposure prophylaxis (PEP). Additionally, it is possible to make unlicensed vaccines available outside of clinical trials through Expanded Access under Investigational New Drug (IND) such as in the case of MenB vaccine used to address college outbreaks of meningitis.

ACIP reviews the evidence generated and using the EtR, provides advice and guidance to CDC and the Secretary of DHHS on the optimal way to prevent vaccine-preventable disease in a civilian population. Once a CDC recommendation is in place, it becomes the standard of clinical practice for vaccination in the US and post-approval monitoring is initiated. This is a critical next step in the integrity of the national vaccine program and provides important checks on the safety and effectiveness of the vaccines used in the real-world. These data are fed back to FDA, CDC, and ACIP.

The EtR is the tool used by ACIP to provide transparency and consistency when developing evidenced-based recommendations. The framework examines evidence in multiple domains, as well as the uncertainty of that evidence to weigh whether or not a vaccine should be recommended and to whom. The first domain asks whether the disease is of public health importance. The WG has achieved consensus that the morbidity, mortality, and societal disruption caused by COVID-19 is of extreme public health importance. Next, the framework focuses on the expected benefits and possible harms of the vaccine. The WG will focus more on that domain as data become available. The next domains pertain to values, acceptability,

and feasibility of a vaccine policy recommendation. Through published evidence and community engagement, the WG will examine if the target populations value COVID-19 vaccination and the expected benefits therein. Separate but related the WG will assess whether the vaccine is acceptable to key stakeholders or if there are barriers to acceptability, such as uncertainty or lack of trust. Importantly, feasibility of implementing the program is assessed. The COVID-19 vaccine program will undoubtedly involve unprecedented creativity and innovation in implementation. The feasibility must be considered at every step.

The ACIP COVID-19 Vaccine WG developed several guiding principles for the COVID-19 vaccine program that have broad support among WG members. First, safety is paramount. Vaccine safety standards will not be compromised in efforts to accelerate COVID-19 vaccine development. The ACIP COVID-19 Vaccine WG supports inclusive clinical trials. Study participants should reflect groups at risk for COVID-19 to ensure that safety and efficacy data are generalizable. The WG values efficient distribution. During a pandemic, efficient, expeditious, and equitable distribution and administration of approved vaccine is critical. Finally, the WG supports flexibility. Within national guidelines, state and local jurisdictions should have flexibility to administer vaccine based on local epidemiology and demand.

The next steps for the ACIP COVID-19 Vaccine WG are to: 1) define the critical and important outcomes; that is, the benefits and risks that will feed into the EtR framework; 2) review clinical trial data for candidate vaccines, as it becomes available; 3) advance the understanding of safety issues with each vaccine platform and safety studies in Phases III & IV; 4) further refine Tier Groups for allocation of early vaccine, based on ACIP feedback; and 5) review proposed implementation strategies.

In closing, Dr. Dooling posed the following questions for ACIP's consideration and feedback:

- Do you agree with the proposed guiding principles?
- Do you agree with the next steps?
- What topics would you like to see presented at the next ACIP meeting?

### **Discussion Points**

Ms. Bahta observed that the guiding principles seemed to match and support a lot of the comments made throughout the day.

Dr. Hunter wondered whether there is a way to present modeling data about his concern that if everyone is not vaccinated in a narrow window of time, there will be people with declining immunity who become re-susceptible to some degree or not. This sounds very difficult to model, but if there is any way to provide some data about that in the future it would be helpful.

Dr. Dooling said she thought the impetus behind the question that vaccine should be distributed expeditiously was captured in the guiding principles. The WG can take the specific question about modeling of the potential to be re-infected following vaccination to the modeling team. The WG eventually will present modeling results to ACIP and will add that to the list of questions.

## Agency Updates

### **Centers for Disease Control and Prevention (CDC)**

Dr. Messonnier said she thought it was incomplete to talk about the impact of COVID-19 without at least acknowledging the impact of COVID-19 on global immunization. Global immunization activities have indeed become challenging during the COVID-19 outbreak similar to what is occurring in the US. There are concerns that millions of people globally could miss routine immunizations this year due to the COVID-19 response. GAVI (Global Alliance for Vaccines and Immunisation; The Vaccine Alliance) has estimated that at least 13.5 million people will miss their routine immunizations. HCP and other health resources have been diverted to the COVID-19 response, leaving immunization programs under-staffed. Parents are reluctant to take their children to healthcare clinics. Vaccines may not always be available. For example, global polio vaccine distribution has been impacted by reductions in air transport. CDC has been working with the United Nations Children's Fund (UNICEF) and the World Health Organization (WHO) to assess the reduction in overall immunization in polio vaccination caused by the pandemic. WHO has issued interim guidance to help countries continue to plan and catch up with their routine immunization once the COVID-19 crisis eases. It is essential to maintain a global focus on routine immunization to prevent vaccine-preventable disease outbreaks and to help ensure the delivery of a COVID-19 vaccine once one becomes available.

## Vaccine Supply

**Dr. Frank Whitlatch**  
**Immunization Services Division**  
**National Center for Immunization and Respiratory Diseases**  
**Centers for Disease Control and Prevention**

During this session, Dr. Whitlatch presented an update on the HepB vaccines supply and discontinuation of ZOSTAVAX®.

Merck will be returning to the US market the week of July 20, 2020 for adult and dialysis formulations of RECOMBIVAX HB®. Merck will have sufficient supply to cover its historical demand for both vaccines. Both formulations will be available in vial presentation only.

Effective July 1, 2020, Merck no longer will sell ZOSTAVAX® in the US. Merck does not have a specific date as to when the supply of ZOSTAVAX® will be depleted. All remaining product has an expiry date of no later than November 2020. Merck communicated this information directly to their customers in early June 2020.

As a reminder, CDC has a vaccine supply page that is kept updated in sync with all of the updates made during ACIP meetings. The Vaccine Supply/Shortage Webpage can be found at: <https://www.cdc.gov/vaccines/hcp/clinical-resources/shortages.html>.



## Certification

Upon reviewing the foregoing version of the June 24, 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.

A 3D-style header graphic with a blue bar containing the text "ACIP Membership Roster".

## 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**

**CHAIR**

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

**EXECUTIVE SECRETARY**

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

**MEMBERS**

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

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

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

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

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

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

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

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

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

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

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

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

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

**EX OFFICIO MEMBERS****Centers for Medicare and Medicaid Services (CMS)**

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

**Department of Defense (DoD)**

SCHUMACHER, Bryan, MD  
Department of Defense Liaison  
Centers for Disease Control and Prevention  
Atlanta, GA

**Department of Veterans Affairs (DVA)**

KIM, Jane A., MD, MPH  
Deputy Chief Consultant for Preventive Medicine  
Office of Patient Care Services  
National Center for Health Promotion and Disease Prevention  
Durham, North Carolina

**Food and Drug Administration (FDA)**

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

**Health Resources and Services Administration (HRSA)**

RUBIN, Mary, MD  
Chief Medical Officer  
Division of Injury Compensation Programs  
Rockville, MD

**Indian Health Service (IHS)**

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



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

KIM, David, MD CAPT,  
US Public Health Service Director Division of Vaccines  
Washington, DC

**National Institutes of Health (NIH)**

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

**LIAISON REPRESENTATIVES****American Academy of Family Physicians (AAFP)**

ROCKWELL, Pamela G, DO  
Associate Professor, Department of Family Medicine,  
University of Michigan Medical School  
Medical Director, Dominos Farms Family Medicine Ann  
Arbor, MI

**American Academy of Pediatrics (AAP)**

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

**American Academy of Pediatrics (AAP)**

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

**American Academy of Physician Assistants (AAPA)**

LÉGER, Marie-Michèle, MPH, PA-C Senior  
Director, Clinical and Health Affairs  
American Academy of Physician Assistants  
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**American College Health Association (ACHA)**

CHAI, Thevy S, MD  
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**American College Health Association (ACHA) (alternate)**

MCMULLEN, Sharon, RN, MPH, FACHA  
Assistant Vice President of Student & Campus Life for Health and Wellbeing  
Cornell Health  
Ithaca, NY

**American College of Nurse Midwives (ACNM)**

HAYES, Carol E., CNM, MN, MPH Lead  
Clinician  
Clinical Quality Compliance and Management  
Planned Parenthood Southeast  
Atlanta, GA

**American College of Nurse Midwives (ACNM) (alternate)**

MEHARRY, Pamela M., PHD, CNM  
Midwifery Educator, Human Resources for Health  
In partnership with University of Rwanda and University of Illinois, Chicago

**American College of Obstetricians and Gynecologists (ACOG)**

ECKERT, Linda O., MD, FACOG  
Professor, Department of Obstetrics & Gynecology  
Adjunct Professor, Department of Global Health  
University of Washington  
Seattle, WA

**American College of Physicians (ACP)**

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

**American Geriatrics Society (AGS)**

SCHMADER, Kenneth, MD  
Professor of Medicine-Geriatrics  
Geriatrics Division Chief  
Duke University and Durham VA Medical Centers  
Durham, NC

**America's Health Insurance Plans (AHIP)**

Vacant

**American Immunization Registry Association (AIRA)**

COYLE, Rebecca, MEd  
Executive Director, AIRA  
Washington, DC

**American Medical Association (AMA)**

FRYHOFER, Sandra Adamson, MD  
Adjunct Associate Professor of Medicine  
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**American Nurses Association (ANA)**

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

**American Osteopathic Association (AOA)**

GROGG, Stanley E., DO  
Associate Dean/Professor of Pediatrics  
Oklahoma State University-Center for Health Sciences  
Tulsa, OK

**American Pharmacists Association (APhA)**

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

**Association of Immunization Managers (AIM)**

FINLEY, Christine, RN, MPH  
Immunization Program Manager  
Vermont Department of Health  
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**Association for Prevention Teaching and Research (APTR)**

McKINNEY, W. Paul, MD  
Professor and Associate Dean  
University of Louisville School of Public Health and Information Sciences  
Louisville, KY

**Association of State and Territorial Health Officials (ASTHO)**

SHAH, Nirav D, MD, JD  
Director  
Maine Center for Disease Control and Prevention  
Augusta, ME

**Biotechnology Industry Organization (BIO)**

ARTHUR, Phyllis A., MBA  
Senior Director, Vaccines, Immunotherapeutics and Diagnostics Policy  
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**Council of State and Territorial Epidemiologists (CSTE)**

HAHN, Christine, MD State  
Epidemiologist  
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Department of Health and Welfare  
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**Council of State and Territorial Epidemiologists (CSTE) (alternate)**

LETT, Susan, MD, MPH  
Medical Director, Immunization Program  
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**Canadian National Advisory Committee on Immunization (NACI)**

QUACH, Caroline, MD, MSc  
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Medical Lead, Infection Prevention and Control Unit  
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**Infectious Diseases Society of America (IDSA)**

BAKER, Carol J, MD  
Professor of Pediatrics  
Molecular Virology and Microbiology  
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Houston, TX

**National Association of County and City Health Officials (NACCHO)**

ZAHN, Matthew, MD  
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**National Association of County and City Health Officials (NACCHO) (alternate)**

DUCHIN, Jeffrey, MD  
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Public Health - Seattle and King County  
Professor in Medicine, Division of Allergy and Infectious Diseases  
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**National Association of Pediatric Nurse Practitioners (NAPNAP)**

STINCHFIELD, Patricia A., RN, MS, CPNP  
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Children's Hospitals and Clinics of Minnesota  
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**National Foundation for Infectious Diseases (NFID)**

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**National Foundation for Infectious Diseases (NFID) (alternate)**

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**National Medical Association (NMA)**

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**Pharmaceutical Research and Manufacturers of America (PhRMA)**

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**Society for Adolescent Health and Medicine (SAHM)**

MIDDLEMAN, Amy B., MD, MEd, MPH  
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**Society for Healthcare Epidemiology of America (SHEA)**

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